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Medical Writing



Generics and biosimilars

Also in this issue...

- ICMJE requirements for sharing individual participant data from interventional clinical trials
- Collecting metrics in medical writing – the benefits to you and your business
- Document management systems for medical writing



EUROPEAN MEDICAL WRITERS ASSOCIATION



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Medical Writing

Generics and biosimilars

When I first stepped into the biosimilar world as part of my medical writing career development, I was both excited and surprised. I was entering this fascinating setting with an originator mindset, as many of us do, and discovered that there are many aspects to be considered for biosimilar documents, not all of which are entirely obvious.

Later, from chats with other writers during coffee breaks at EMWA conferences, it became clear to me that more conversations across different areas of development (originators, biosimilars, and generics) were needed. While general information on biosimilars and generics is increasingly available, there aren't many hands-on resources for medical writers who have broad medical writing experience but who don't have any experience specifically in these areas.

This MEW issue aims to bridge this information gap. The nine feature

articles included here address both the 'bigger picture' and provide hands-on tools for developing fit-for-purpose documents throughout a biosimilar/generic product's life cycle.

Regulatory pathways in the EU and the US in the generic and biosimilar industries are critically discussed in detail by **Yousuf Mohiuddin Mohammed**, with real-life examples when available. He focuses on clinical development requirements for generics and biosimilar in order for region-specific regulatory requirements to be met, but also covers the impact of such requirements on other parts of the respective submission dossiers.

The particulars of biosimilar development are further developed by me (**Diana Radovan**). My feature article provides information about biosimilar-specific terminology, addresses the typical challenges of writing biosimilar dossiers and how medical writers can provide strategic support in overcoming them, and summarises future directions in biosimilar development in the context of a changing competitive landscape.

Statistical considerations for biosimilar development are outlined by **Alison Balfour** and **Susanne Schmitt**. These considerations include clinical trial design, covering choice of endpoints, types of required analyses, choice/justification of equivalence margin (based on statistical and clinical considerations), and imputing missing data for efficacy.

Katharina Brauburger and **Sabrina Heisel-Stöhr** provide best practices for developing clinical biosimilar documents, paying close attention to a number of typical challenges, and how fundamental biosimilar concepts, such as immunogenicity and extrapolation, must be used in writing fit-for-purpose documents. The authors also run the only EMWA workshop on biosimilars, which is always fully booked in no time; so keep an eye out for it when registering for the next EMWA conference!

While general information on biosimilars and generics is increasingly available, there aren't many hands-on resources for medical writers who have broad medical writing experience but who don't have any experience specifically in these areas.



Sandra Götsch-Schmidt gives a broad and detailed overview of the types of generic-specific documents that medical writers can contribute to and elaborates on how such contributions may look. She also presents general information about the development of generics and gives pertinent information about cases where specific types of documents may not apply for certain products.

Tiziana von Bruchhausen, Kerstin Prechtel, and Stefanie Rechtsteiner provide best practices for developing pharmacovigilance documents for generics and biosimilars throughout a product's life cycle, with a focus on writing Drug Safety Update Reports, Periodic Safety Update Reports, and Risk Management Plans. They show us how regulatory considerations need to be interpreted by document and by product in order for safety concerns to be appropriately addressed.

David McKinn, Craig Scott, and Baxter Jeffs offer their insights into best practices for writing lay summaries for generics and biosimilars. They provide example language that can be used when developing layperson-orientated materials for generics and biosimilars.

Krithika Muthukumaran offers her views on the development of biosimilar insulins and how their availability (from different competitors) will impact treatment options in patients with diabetes. She addresses the topic from various perspectives, including a discussion of regulatory and market aspects by region, and what the introduction of biosimilar insulins may mean in practice for patients and healthcare industry professionals.

Martin Mewies critically summarises changes, successes, and challenges in biosimilar development from multiple perspectives: a regulatory perspective, a market perspective, and a healthcare industry acceptance perspective (by doctors and patients). He examines the progress made to date in establishing the biosimilar market, challenges in bringing biosimilars to patients, the impact biosimilars have had so far, and potential future trends.

To sum up, I hope that I have passed on some of my excitement for the field of generics and biosimilars through this issue, and that you'll find all nine articles helpful and will enjoy them as much as I have! If this turns out to be the case, please help us spread the word about the articles in the wider medical writing community and beyond and let us know which of them you found most useful in your daily practice.

GUEST EDITOR



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For the last 6 years, James Visanji has volunteered as EMWA's Treasurer and as a member of the Executive Committee. James stepped down from this role at the conference in Vienna this past May, so several of us on the Executive Committee wanted to personally thank him for his many years of service, not to mention his friendship.

James was already well into his treasurership when I joined the Executive Committee and was introduced to the wide range of topics that the committee has to consider. I really appreciated his skill at succinctly outlining the facts and the decisions to be made about EMWA's finances. It was clear that the whole committee benefited from his business knowledge and pragmatic advice on a wide range of issues, and his good humour could lighten the moment and make the long meetings more enjoyable. I will very much miss him on the Executive Committee but, as Education Officer, I'm very pleased he's got no plans to give up as a workshop leader – and who knows, maybe the time freed up might prompt ideas for new workshop topics! Thank you James.

Marian Hodges
Education Officer

When I started serving on the Executive Committee 4 years ago, it felt as if James had been on the EC for ever. While not visible centre stage, he was not only paramount for EMWA's finances, but also when things got turbulent and waters got rough, he was there, solid as a rock; when there were heated discussions, everybody listened when he spoke; and when there were important decisions to be made, everybody was happy to count on him and his knowledge. It is amazing what he has accomplished in the past 6 years. On a personal level, James has always been helpful and fun to be around. He certainly is a character, and this is what makes him so special and likeable. I will sadly miss him on the EC but am looking forward to meeting him as a "private person" at conferences and to continuing our discussions such as on environmental issues (James will know what I mean...). All the best, James, for your "EMWA sabbatical"! Best wishes,

Beatrix Dörr
Honorary Secretary



Before my time in the Executive Committee (EC), what I associated with James' name were financial reports in the Annual Meetings and cheerful ties – what a great hallmark! When I started working on the EC, I strongly felt that James held a large bit of the historical memory of EMWA: regardless of the issue we had to address, he would know whether EMWA had encountered a similar one in the past, the lessons learnt, the do's and don'ts. We all have great respect for James' experience and competence beyond his role as treasurer, and more than once his advice on tricky issues saved time and costs. In my experience, James has been a great person to work with: very firm in his positions, but also open to be convinced by well-grounded arguments. I benefited very much from his advice and learnt a lot from his attitude; although I was not always in agreement with his views, I truly respected and acknowledged them – his arguments were solid, his explanations thoughtful and sensible. The interaction with James has strengthened my ability to convey my point or come to a common agreement. Since he decided to step down from the EC, I think that he has become more laid-back, which added some hilarity to the most intensive meetings. However, dear James, be reassured that even though you have left the EC, you will remain a reference point for all of us – this is a threat that we will put into practice at the bar!

Best wishes,

Tiziana von Bruchhausen
President 2018–2019
Vice President 2017–2018

I had the pleasure of working with James throughout his tenure on the EMWA Executive Committee. All I can say is that the EMWA membership was blessed to have someone with such a laser-sharp mind serving their interests over the past 6 or so years.

Not that I expect you to(!), but anyone who looks at the improvements in our accounts in recent years can clearly see where James had a very positive effect. The organisation is in a much more secure place than it previously was – financially as well as non-financially – and the two are more intertwined than most people realise. Speaking personally, I was happy to have James on my side in the early days of my role as we tackled the labyrinthine internet arrangements (two platforms for one website anyone?) and quickly managed to cut the website-related costs down to a fraction of what they once were. But his impact was not only financial, he also exuded a professionalism which benefited the committee as a whole. (For those of you not in the know, as committee members we also have an input into all areas affecting the organisation). Most of all though, James also brought a fun element to the role. Many's the time his good humour and pleasant company helped to get us through a difficult meeting or to decompress after one. I will miss having him on the committee but am sure that once he has sorted out Brexit(!), he will return to his natural home at EMWA.

Good luck, James, and enjoy your (hopefully short) retirement.

Diarmuid De Faointe
EMWA Website Manager

Like Diarmuid, I have had the chance to see James in action over several years as a volunteer for the Executive Committee. What I have most appreciated is his ability to cut through the BS and rapidly make wise, clear-headed decisions. At the same time, he's always been willing to change his mind when presented with a cogent opposing argument. To add to this, his knowledge of business and legal issues has come in handy and saved us on many occasions. One story that sticks out in my mind was how he negotiated us out of a contract with a former vendor who was not performing (and making my life miserable). He visited them at their offices and laid things out very simply, as in "Let me make you an offer you can't refuse". They were left with no option than to agree to our demands. I could not have accomplished this myself, so I thank him for taking an enormous burden off my shoulders. James will still be around EMWA as a workshop leader and friend, but I will miss his no-nonsense approach and humour, which have been a key part of the smooth functioning of the Executive Committee over the past several years.

Best wishes,

Phil Leventhal
Editor-in-Chief

President's Message

From EMWA President 2018–2019

Our association has been growing at a steady pace, facing the challenges of a fast-moving professional and regulatory environment. I am delighted to provide below an overview of some of the major achievements during my term on the Executive Committee (EC).

A healthy, dynamic organisation run by members, for members

Thanks to the excellent work and high commitment of our volunteers, EC members, and Head Office, we have been able to run successful conferences in Cascais, Barcelona, and Warsaw, to broaden the offer to members of different degree of experience, to improve governance, and to maintain healthy finances.

- We have increased the number of workshops offered by the EMWA Professional Development Programme (EPDP) and the number of webinars, with the ambitious goal of at least 10 webinars per year.
- We have been able to impressively broaden the programme of our conferences beyond the EPDP, including various opportunities for our members to network and share expertise.
- Our social media team has established effective communication to our members and outside of EMWA.
- The newsblast has been streamlined and improved.
- The journal has maintained its high quality and excellent contents, while offering, in addition, the opportunity for volunteers to serve as guest editors.

Besides offering **52 EPDP workshops at the Vienna conference** (30 at the foundation and 22 at the advanced level), we are addressing various hot topics through other conference events outside of the EPDP, such as the **EMWA Symposium**, the **Expert Seminar Series** (ESS), and **Lunch Seminars**, offering a valuable platform for discussion with stakeholders and regulators. These initiatives strengthen the role of EMWA in public discussions and have a great potential to further our members in their profession.

The volunteers of the **Special Interest Groups** (SIG) on pharmacovigilance, regulatory public disclosure, and medical devices have been actively contributing to expand the EPDP offer and plan ESS sessions. Their commitment reflects the interest in new areas of medical

I would like to thank EMWA for the great opportunity to serve as President and commit to these exciting projects. I have learnt a lot for my professional and personal growth, and hope to have adequately represented and supported our association.

writing and shows how our members can actively tailor EMWA to their need. An example: following a webinar on veterinary medical writing, there has been growing interest in addressing this area at EMWA over the last few months. The March issue of *Medical Writing* now hosts a dedicated section on veterinary medical writing; together with some members working as veterinary writers and communicators, we have established a first network within EMWA. A new SIG dedicated to this writing area was launched in Vienna. This new group will have the opportunity to explore how to expand the training offer in their field and to open the dialogue with stakeholders and regulators through EMWA.

Networking and sharing

At the beginning of my term, I focussed on the unique value that the **Nick Thompson Fellows** (NTFs) and the past Presidents represent for EMWA. Due to their expertise, their long-lasting commitment at EMWA, and their knowledge of topics and structures of our association, these volunteers represent a valuable resource for the EC in terms of providing advice and suggestions related to conference initiatives and to EMWA in general. Particularly, the EC has requested the NTFs to explore the needs of more experienced writers and to suggest ways to provide advance opportunities, as well as to retain experienced members. In addition, the NTFs have recently proposed to share their overall “couple of hundred years of experience” by providing informal brainstorming or networking sessions at conferences – a unique opportunity to discuss medical writing problems and advance in the



profession, thanks to the sharing spirit of EMWA.

With the aim to support people interested in a career in medical writing, EMWA have reshaped this year the **Internship Forum** (IF) to further develop its potential. The experience with the IF so far and valuable considerations of the IF's volunteers have led to a new format which aims, starting in Vienna and upon further development, to offer a comprehensive career-focussed day (“**Getting into Medical Writing**”, GIMW). At the GIMW, interested people will have a unique opportunity to attend excellent lectures, participate in open discussions, network, and benefit from the exchange with experienced medical writers.

External activities

The **Ambassador's Programme**, recently created to raise awareness on the medical writing career and EMWA, has held, as of today, 20 presentations at career events, professional academies, and universities in various locations in Europe. Thanks to this initiative, EMWA has gained insight into the current training needs and trends in medical writing, with the potential for further development and cooperation. In addition, the Ambassador's Programme has started collaborating with the GIMW to provide speakers for future events and advertise these within universities close to the conference locations.

EMWA has continued playing an active role in the medical writing community to further our profession. We have maintained our collaboration with the MedComm Network, and the Board of Editors in the Life Sciences (BELs) offered again the BELs exam in Vienna.

The **AMWA-EMWA CORE reference** has been widely used within the industry, with over 14,500 downloads since its launch in 2016, and its relevance has been acknowledged by pharmaceutical companies and contract research organisations.

The **AMWA-EMWA-ISMPP Joint Position Statement** (JPS) on the role of medical writers in the preparation of manuscripts for publication has been translated by our volunteers in further languages, and 11 translations are currently available on the EMWA website.

Following a suggestion made by one of our experienced members, **EMWA is addressing the issue of predatory publishing** through the MedComm SIG, which was launched in Vienna. The members of this group are supporting internal and external activities, such as the planning of conference events, trainings, research, and preparation of a new AMWA-EMWA-ISMPP JPS. EMWA have raised the discussion on this issue with AMWA and ISMPP and are leading this initiative. I am proud to have had the opportunity to support this project on behalf of EMWA as the staff liaison for the subject matter experts of the involved professional associations.

As a last point, I would like to mention our relationship with The Organisation of Professionals in Regulatory Affairs (TOPRA), which I could strengthen during my term on the EC. Thanks to this cooperation, we have obtained valuable contacts from the TOPRA network for symposium speakers and authors of articles. This type of collaboration has the potential to expand our network in specific areas, as well as to complement the offer to our members – another way to grow through sharing and cooperating.

I would like to thank EMWA for the great opportunity to serve as President and commit to these exciting projects. I have learnt a lot for my professional and personal growth, and hope to have adequately represented and supported our association. Many thanks to the EC members and the Head Office team for their great support and the constructive atmosphere – it was a great pleasure and an enriching experience for me to work with all of them! –, and to all volunteers for making EMWA a unique association. I wish Barbara, Bea, and the next year's EC members all the best!

Tiziana von Bruchhausen
EMWA President 2018–2019



No idea is too small ... just look what happened when a few people met informally back in 1986 ...

To reiterate the message from Tiziana, EMWA's President for the past year, thank you to all EMWA volunteers, from those with a visible role such as the workshop leaders and webinar presenters to the countless people working quietly in the background, making EMWA the well-respected organisation it is today; for example: members of the Editorial Board supporting Phil Leventhal as the journal is produced each quarter, those on the Public Relations Team and in the SIGs, and the Website Team.

In particular, I would like to thank:

- James Visanji, who stepped down as Treasurer at the May 2019 conference after 6 years. During this time, he and the Finance Committee carefully examined the finances to ensure that EMWA's money is spent as effectively as possible for the benefit of members. Although he will be missed, James has handed over the baton to Sarah Choudhury with EMWA's finances in a very healthy position.
- Tiziana for leading and guiding the EC over the last year, for her enthusiasm, and for patiently steering me in the right direction. It's been a pleasure to work with her and the EC.
- Everyone involved in building EMWA's backbone: our professional development activities. These include not only the education committee, led by Marian Hodges, which maintains and grows the workshop and

webinar programme, but also everyone who has been involved in planning and presenting the expert seminars and symposia. Thanks also go to those providing additional support and resources for freelancers and people considering a move to medical writing as a career.

- And last but not most definitely not least, my thanks to Lynne Fletcher, Claire Whittingham, and their team at the EMWA Head Office.

I look forward to working with Bea (the new Vice President) and the new EC, and most importantly with YOU – EMWA's members. My aims are to respond to YOUR needs, to maintain the progress we've made and keep EMWA moving forward, and to represent EMWA as we continue to forge links with other associations. If you have any suggestions, for the running of EMWA or improving our links with the wider medical writing and communications community, please do contact me. No idea is too small ... just look what happened when a few people met informally back in 1986: <https://www.emwa.org/about-us/about-emwa/history-of-emwa-1992-2008/>

Barbara Grossman
EMWA Vice President 2018–2019
EMWA President, 2019–2020
president@emwa.org

EMWA News

Last month, EMWA members had the pleasure of attending another successful spring conference, this time in the picturesque city of Vienna. We had 442 attendees from 34 countries, with 167 people attending their first EMWA conference. There were 52 workshops, including 6 new additions to the EMWA Professional Development Programme (EPDP). The theme of the symposium was “Real-World Evidence: A Central Role for Medical Communicators”. The Freelance Business Forum was a huge success, with 85 attendees and a long, fun after-event. Various social events were offered, and no fewer than 97 attendees joined the double-blind randomised dinner. The air at the InterContinental Vienna was filled with networking opportunities, new ideas, and collaborations.

We want to congratulate and welcome the new Executive Committee (EC) members: Barbara Grossman (President), Beatrix Doerr (Vice President), Sarah Choudhury (Honorary Treasurer), Claire Harmer (Honorary Secretary), and Maria João Almeida (PR Officer). James Visanji received the “EMWA Hero” mention, a way to acknowledge and thank him for his many years of dedication to EMWA. We also want to take this opportunity to encourage all members to actively participate in EMWA activities, including EC elections, as this is a core part of how we will be represented.

The scholarships committee decided to award the 2018 Geoff Hall Scholarship to Abbie Fearon for her essay on the topic “The Medical Writer: Partner or Servant?” For those of you inspired by Abbie’s success, the 2019 competition is now open. The essay title this time is “How would you go about identifying a predatory journal?”, a perennial hot topic. The deadline for entries is September 30, 2019. You can find more information on the EMWA website.

We also have some interesting, practical news from our Website Manager. The Pharmacovigilance, Regula-

tory Public Disclosure, and Medical Devices Special Interest Groups (SIGs) now have their own tab on the EMWA home page. SIGs allow EMWA and its members to contribute to important conversations around topics that will affect our industry in the coming years.

Additionally, two new SIGs were created during the conference in Vienna: the Veterinary Medical Writing (VMW) and the Medical Communications (MedComm) SIG. The VMW SIG is co-chaired by Karim Montasser and Cemile Jakupoglu. Other committee members are Jessica Lin, Jennifer Freymann, and Miyuki Tauchi. The committee members, and other volunteers such as Marianna Ricci, Vera Faigl, and Sandra Goetsch-Schmidt, are veterinarians by education and founded this group to support the visibility of veterinary medical writing. Details on the new MedComm SIG are available in the column on the next page.

You will find more EMWA updates in the next issue of *Medical Writing*. Stay tuned!



We had 442 attendees from 34 countries, with 167 people attending their first EMWA conference. There were 52 workshops, including 6 new additions to the EMWA Professional Development Programme (EPDP).



Photo by Ana Goies



EMWA Ambassador's Programme

The Ambassador's Programme is continuing to reach out to students and young scientists at career events across Europe.

Walther Seiler represented EMWA at JobWonder, an annual career event held at the Technical University in Berlin. He shared his knowledge in the field of medical writing and the benefits of joining EMWA, which was highly appreciated.

Abe Shevack attended a career event organised by the SciMed medical writers' group at the OBA library in Amsterdam. The event was attended by 15 writers and young scientists. The group, organised by EMWA members Sally Hill, Jackie Johnson, Gabriela Plucinska, and Mariella Franker, meets regularly to share information on topics of interest to medical writers and scientific editors. Abe spoke about careers in medical writing and the benefits of joining EMWA. He also participated in a panel discussion that included 6 in-house and freelance writers, who answered questions from the audience about how they got started in the field of medical

writing. Sally held a short training session on editing, which was followed by refreshments and a networking session. It was an informative and highly enjoyable meeting.

On 6 June, Amy Whereat and the French medical writers' group held a careers meeting in Paris. John Carpenter will be attending a NetworkPharma event at the University of Westminster in London on June 20. Last but not least, Tiziana von Bruchhausen is planning to give a talk on medical writing and EMWA at the Dr Notghi clinical training academy in Berlin. The date of Tiziana's talk will be announced soon.

We are always looking to find out about forthcoming career events at universities and elsewhere where EMWA Ambassadors might attend and speak about EMWA. If you know of such an event or if you are an experienced EMWA volunteer interested in becoming an Ambassador, please contact Abe Shevack at aspscientist@gmail.com.

Abe Shevack

A new Special Interest Group on medical communications!

The MedComm SIG was established at the spring conference in Vienna. The intent is to support publication activities of EMWA members by acting as a source of affordable and updated information.

To date the following topics have been identified:

- Predatory journals/conferences
- Medical journalism
- Writing for patients/lay audiences
- Big data disclosure

The group will be co-chaired by Slavka Baronikova and Andrea Rossi. Andrea Bucceri, Julia Donnelly, and Thomas Schindler are members of the committee, and Evguenia Alechine, Tiziana von Bruchhausen, Lisa Chamberlain-James, Diarmuid De Faoite, Martin Delahunty, Beatrix Doerr, Art Gertel, Phil Leventhal, and Miyuki Taichi have confirmed their willingness to act as supporting members.

The first activity of the MedComm SIG will be to finalise and ensure higher visibility of the AMWA-EMWA-ISMMP Joint Position Statement (JPS) on predatory publishing. Several activities have been planned to maximise the impact of the JPS. These include a seminar, a webinar, and related articles in *Medical Writing*, development of further educational materials, and liaising with AMWA and ISMPP to maximise educational activities within these associations.

Articles and EMWA presentations on different topics will be presented in the soon-to-be created MedComm SIG section of the EMWA website.

As EMWA is an organisation of members for members, we look forward to establishing the programme of the MedComm SIG group based on unmet needs of EMWA members working in medical and scientific communication. Therefore, we welcome your suggestions for topics to be addressed and seek your support based on your know-how and expertise in this field.

Andrea Rossi and Slavka Baronikova

Regulatory pathways for development and submission activities

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Abstract

This article discusses how different regulatory requirements for a dossier requesting marketing authorisation for a medical drug affect the deliverables from development functions and the submission groups including medical writing. The content of the dossier submitted is strongly interlinked to the legal basis selected for a regulatory filing. This drives the requirements of data from different areas of development as well as of dossiers that can be summarised mainly into the general categories of Chemistry, Manufacturing and Controls (Common Technical Document (CTD) dossier Module 3), non-clinical (CTD dossier Module 4), and clinical (CTD dossier Module 5) reports. This article addresses different types of regulatory pathways in the EU and the US with case examples where possible. The pathways used in the generic and biosimilar industries are discussed regarding expectations of authorities in an application type. Although this article focuses on clinical research and clinical data requirements within the generic and biosimilar industries, it also addresses how other parts of the dossiers are affected.

Introduction

A thorough understanding of different regulatory pathways is indispensable from a regulatory perspective, as the regulatory submission strategy is a key decision before proceeding to development and submission activities. The focus on this area is self-explanatory in the broader sense, given that the effort invested in development and submission activities for any given medical drug can typically take as long as 15 years depending on whether it is a new active substance, a generic, a differentiated product such as a value added medicine, a biosimilar, or a combination of digital and/or device and/or medicinal product. The legal framework that lays out these regulatory pathways is comprehensibly different

in the EU and the US. Energy and focus are needed early on to decide upon the legal basis, and where necessary, scientific advice and discussion with regulators need to be initiated in order to reach understanding and agreements on the project. This is the most important step as it determines the data needed for any successful regulatory submission. In turn, the data produced during development activities are placed in allocated slots in the Common Technical Document (CTD) structure supported by medical writing, development, and regulatory teams into the respective clinical (Module 5), non-clinical (Module 4), and quality (Chemistry, Manufacturing and Controls (CMC))(Module 3) components. Module 2 covers summaries of

Table 1. Different regulatory pathways in the EU^{2,4,5}

Legal basis	Application Type	Needed clinical studies	Development and submission timelines
Art. 8(3)	Full application	Yes	8-15 years
Art. 8(3) mixed application	Full mixed application	Yes	8-10 years
Art. 10(1)	Standard Generic, abridged application	Mainly BE studies; may include PD/clinical endpoint studies for some products	2-5 years
Art. 10(3)	Hybrid Application, abridged application	Yes, in rare cases only BE also possible.	3-7 years
Art. 10(4)	Biosimilar Pathway, abridged application	Yes	5-8 years
Art. 10a	Well established use	No, generally only bibliographical references	1-2 years
Art. 10b	Fixed dose combination	Yes, depending on application.	2-5 years
Art. 10c	Informed consent (duplicate)	Reference to Modules 2 to 5	None

NB. Development and submission timelines above were collected through available public information and projected accordingly.^{40, 41} Irrespective of the submission pathway, duration of regulatory procedure is always 210 days. In addition, national phase must be calculated for DCP/MRP procedures, which last between 4 weeks and 1.5 to 2 years.



Applicability	European reference medicinal product needed for submission	Data/ Market Exclusivity	Once approved can act as RefMP	SmPC	Need for PIP
New active substance	No, active comparator/placebo	Yes, 8+2+1 years (DP+ ME+ exclusivity for add indication)	Yes	New	Yes
No RefMP, no reference to any data from 8(3) dossier, may apply to differential products like VAMs	No, active comparator/placebo	Yes, 8+2+1 years.	Yes	New	Yes
Generics (mono and combos)	Yes, innovator of the same molecule, RefMp	No	No	1:1 similar to the RefMP	No
Strictly not generic	Yes, RefMp needed	No, only in case of orphan drugs 10 years ME.	No	Slight changes in SmPC compared to RefMP	Generally no, except for PUMA
Biosimilar product	Yes, innovator biologic as RefMp	No	No	1:1 to the RefMP possible	No
Old molecules /BCS I	None	Yes	No	Based on well-established use within EU	No
Fixed dose combination	Not needed	Yes	Yes	New	No
Duplicate of originator product	NA	No	NA	NA	No

Abbreviations: Add, Additional; Art, Article; BCS, biopharmaceutical classification; BE, Bioequivalence; DCP, decentralised procedure; DP, data protection; RefMP, reference medicinal product; ME, marketing exclusivity; MRP, mutual recognition procedure; NA, not applicable; PD, pharmacodynamics; PIP, paediatric investigation plan; PUMA, paediatric-use marketing authorisation; SmPC, summary product characteristics; VAM, value added medicines

development activities and Module 1 the administrative information. In this article, all development, submission activities, and dossier writing (considering also individual study planning and reports) will be covered under the term *development and submission activities*.

European Union (EU)

Situation in the EU

In the EU, the legal basis to seek an approval of a medicinal drug product is under the European Directive 2001/83/EC as amended.¹ Table 1 summarises different regulatory pathways within the EU along with some general development and submission timelines and other regulatory requirements. All tables in this article provide an overview, and not all conditions and exceptions are considered.

There are two approval pathways within the EU irrespective of the legal basis used for submission. The first category is called national authorisation procedures, which include the Mutual Recognition Procedure (MRP), Decentralised Procedure (DCP), or national submission. The second category is the Centralised Procedure (CP), whose main objective is to provide: one marketing authorisation that is valid in all EU and European Free Trade Association countries, one invented name and one common product information, and centralised safety monitoring. Alternatively, DCP can be used for an approval within selected countries of the EU depending on the applicants seeking approval.

The scope and eligibility for the CP is defined in Article 3 of Regulation (EC) No 726/2004 as *mandatory, optional or generic/hybrid scope*. In a nutshell, *mandatory* includes biosimilars, advanced medicinal products like gene therapy, somatic therapy or tissue engineered products, medicinal products developed through biotechnological processes, and new active substances. *Generic/hybrid scope* products are in practice authorised through the DCP review procedure. However, the CP is also open for generics in case the originator product has been registered centrally. In addition, certain applications for Paediatric Use Marketing Authorisation can also be eligible for the CP.^{2,3,4}

As shown in Table 1, there are specified regulatory pathways. The EMA and other national Health Authorities (HAs) advocate effective planning and discussions with authorities to facilitate development and submission

activities.⁴ It should be noted that data collection and presentation for illustrating the cases have been performed randomly, and no systematic review was done. This overview is intended for the sole purpose of informing.

A summary of collected information from different regulatory submissions is presented as case examples to illustrate how different regulatory pathways could be used to plan the development and submission activities within given financial budgets and timelines.

Directive 2001/83/EC Article 8(3) full application

Article 8(3) within the Directive No 2001/83/EC as amended requires a complete full and independent application. A complete full application means that the development and submission activities run over a period, which is longer than for any other regulatory pathway; an independent application here means that there is no European reference medicinal product required. Such an application or submission contains all administrative information, complete CMC and quality data, non-clinical and clinical data supported through own studies. Minimal amount of literature is used to support and substitute certain tests or studies that are already well established. These kinds of submissions and filing applications under Article 8(3) are generally used for new active substances.⁶

An applicant that has received an approval under Article 8(3) can later apply for a line extension application and such applications can differ in several ways. One example is leuprorelin acetate (Prostap® 3 DCS), which was approved as a line extension under mentioned Article. The difference between the current application as line extension (Prostap® 3 DCS) with the previous authorisation of Prostap® 3 was on the use of dual chamber pre-filled syringe (DCS) instead of prolonged release powder for injection. The approval of Prostap® 3 DCS was granted without changes in the proposed indications or route of administration. The aim of such submissions is to establish that the difference

between the newly introduced product and the already authorised product has no impact on the quality, non-clinical, and clinical data, with the overall aim of achieving similar patient efficacy and safety. In the case of Prostap® 3 DCS, required quality data have been provided and given the slight change in its new product, there was no need to perform any additional non-clinical and clinical development activities. Normally, this kind of application may not require similar development and submission activities compared to a full-blown Article 8(3) application. This kind of line extension application is part of the same Global Marketing Authorisation; therefore, no new data exclusivity period applies. In case of leuprorelin acetate DCS, generic applications that intend to manufacture and/or market leuprorelin acetate DCS can establish similar quality and bio-equivalence directly to Prostap® 3 DCS rather Prostap® 3.⁷

Directive 2001/83/EC Article 10(1) abridged application

Article 10(1) is generally known as the generic pathway. Submission of a generic product requires a European reference medicinal product with expired 8-year data exclusivity. Requirements for generic applications are highly standardised and several guidelines have been issued to guide generic applicants in the planning, development, and submission activities.^{8,9,10}

The latter two still require effective planning, and in the case of unique scenarios, discussions with HAs and scientific advice are recommended. One example is the prasugrel product-specific guideline, which has been revised, and new comments have been collected to define the clinical requirements for generic applicants.^{11,12,13} The updated guideline requests an additional clinical study under elevated gastric pH conditions in case of differences in salt or free base compared to innovator of prasugrel hydrochloride. As it can be understood, any change in the requirements of data from the development side may lead to a delay in submission and increase development costs.

A thorough understanding of different regulatory pathways is indispensable from a regulatory perspective, as the regulatory submission strategy is a key decision before proceeding to development and submission activities.

Therefore, depending on the uniqueness of the product, certain discussions with HAs should be a part of development and submission activities. To better plan for these, EMA has issued general guidelines on clinical pharmacology and pharmacokinetics and in addition provides product-specific bioequivalence guidance on their website.^{9,10}

Directive 2001/83/EC Article 10(3) abridged hybrid application

Article 10(3) as legal basis provides an opportunity for applicants to apply if their products are slightly different from existing innovator products that do not fall under the generic product category of 10(1). Buvidal[®] (Buprenorphine) subcutaneous injection, for example, was submitted under Article 10(3) and was granted marketing authorisation on 20 September 2018 by the Committee for Medicinal Products for Human Use. The application of Buvidal[®] was submitted for review under the CP per Article 3(2)(b) of Regulation (EC) No 726/2004. As required for any Article 10(3) submission, a reference to a European medicinal product was needed; in the case of Buvidal[®], reference was made to Subutex[®] (Buprenorphine sublingual tablets) which were previously approved in Denmark and the UK using the DCP/MRP. Buvidal[®] subcutaneous depot injection differs from the reference medical product (Subutex[®] sublingual tablets) in terms of pharmaceutical form, strength, and route of administration. Therefore, this regulatory submission fits in the legal basis category of hybrid application 10(3). In terms of development activities and effort in preparing the dossiers, the major advantage of the 10 (3) is that it can still bridge the data to the European reference medical product. Given the possibility of bridging, the effort to produce non-clinical or clinical data is reduced (see Table 1 for overview of development timelines).¹⁴

In the case of Buvidal[®], non-clinical and clinical data were supported by bibliographic information from the public domain to the extent feasible. Five clinical pharmacology studies were also conducted to support the proposed dosing of Buvidal[®] and for bridging data to Subutex[®]. Non-inferiority to Subutex[®] was established via a Phase III pivotal study. Overall, the development and submission plan was in line with the regulatory strategy of using a hybrid application



10(3), significantly reducing the development and submission activities compared to a full 8(3) application.¹⁴

Directive 2001/83/EC Article 10(4) abridged application

Article 10(4) is meant to be used for biosimilar products within the EU and is coordinated through a centralised review process. A *biosimilar* is a successor to a biological medicine known as the *reference product*. It matches the reference medicine in terms of safety, efficacy, and quality. Using this regulatory pathway has the clear advantage of having condensed non-clinical and clinical programmes and clearly defined requirements of the quality programme, as defined by EMA biosimilar guidelines. Any submission made under this legal basis requires a European reference product with biologic origin, usually with a similar strength and same route of administration. In recent years, there have been several approvals in the EU that also included Pelmeg[®] and Ziextenzo[®] through 10(4) route. In general, biosimilar submissions are supported by at least one Phase III clinical efficacy and safety study; however in the case of Pelmeg[®], pharmacokinetics and pharmacodynamics data were the bases for approval without any Phase III

data. Tailor-made development plans in exceptional cases like that of Pelmeg[®] are encouraged and supported by EMA, if sponsors or applicants seek upfront discussions through scientific advice. Such unique development programmes also reduce the general development timelines proposed in Table 1. For cases like Pelmeg[®], the fastest development period could be 5 years.^{15,16} Extensive guidelines and support have been provided by EMA to biosimilar applicants as well as generic applicants on their website.¹⁷

However, there are certain products that fall under 10(4) which could still use more condensed clinical and non-clinical programmes compared even to classical biosimilar submissions mentioned above and may not even require a full-fledged efficacy and safety study. One example is enoxaparin (Crusia[®]), a low molecular weight heparin. The clear guidance issued by EMA for non-clinical and clinical development of low molecular weight heparins can be used by all applicants for submission of products in this category. As for the non-clinical programme of Crusia[®], a pharmacodynamics study in rabbits and certain in vivo studies showing activities of anti-factors Xa and IIa were performed. Similarly, for the clinical programme, as conventional

pharmacokinetics studies could not be performed, and as per the above quoted guidelines, similarity at clinical level could be shown using pharmacodynamics endpoints thereby having overall abridged and targeted quality, non-clinical, and clinical development. The above examples represent how better planning and understanding between applicant and regulatory authority, supported by appropriate guidance, can offload considerable development and submission activities and lead to a targeted submission.¹⁸

There are also other examples, in which a version of peptide depending on its source, could be either a generic (synthetic origin) or a biologic (biological origin). As the case study of teriparatide shows us, there is a generic version (synthetic origin, teriparatide), and also a biosimilar (rDNA origin, Terrosa[®] and Movymia[®]) version, whereas the European reference medicinal product (Forsteo[®]) is of biological

origin. Here, the generic version was approved using 10(3), whereas the biosimilar version was approved under 10(4).^{19,20} Overall, one can add that development and submission activities required with different regulatory pathways may need to vary accordingly.

Directive 2001/83/EC Article 10a application

As per legal basis 10a, “the applicant shall not be required to provide pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety profile”.¹ The applicant can use appropriate scientific literature to prove safety and efficacy. Reference to HA assessment reports from already approved products is, however, not acceptable for this purpose.

Directive 2001/83/EC Article 10b full application

Article 10b is the legal basis for the registration of combination products. However, the legal basis for registering combination products is open and can be decided on case-by-case basis. Moreover, applications can be submitted under alternative regulatory pathways to Article 10b. A specific guideline on clinical development of fixed-dose combinations (FDCs) is available.²¹ Non-clinical and clinical data for the FDC need to be provided. Referencing publicly available data including assessment reports and Summary Product Characteristics is also possible in case of expiration of relevant data exclusivity. In addition, the current guidance on clinical development for FDCs proposes to establish that there are no drug-drug interactions at the pharmacokinetic level. If this cannot be supported by literature, a clinical study will be required.

FDCs can also be approved under a legal basis

Table 2. Different regulatory pathways in the US ^{31,32,39}

Legal basis ^a	Application	Type of procedure	Needed clinical studies	Generally used for
FD&C 505(b)(1)	NDA	Full dossier, clinical safety and efficacy data required.	Yes, supported through several clinical pharmacology and efficacy/safety studies.	NME/NCE
FD&C 505(j)	ANDA	Abbreviated dossier, clinical mainly BE.	BE which may include clinical endpoint studies for some products	Generic application
FD&C 505(b)(2)	Hybrid between ANDA and full NDA	Full dossier, abbreviated clinical safety/efficacy studies may be needed to support the change.	Maybe – depending on the nature of the change	VAMs such as new dosage form, new combo, new indication
PHS 351(a)	BLA	Full dossier, clinical safety and efficacy data required.	Yes, supported through several clinical pharmacology and efficacy/safety studies.	BLA
PHS 351 (k)	Biosimilar/ interchangeable BLA	Full dossier, extensive CMC (analytical similarity) and at least one clinical efficacy and safety study.	Yes – at least one PK/PD study and in general one efficacy, safety and immunogenicity study. Interchangeable require one additional specific trial	Biosimilar or Interchangeable products

^a In general, 505(b)(1), 505(b)(2), and PHS 351(a) target 10 months for approval. Whereas, 505(j) and 351(k) aim for 12 months, review period varies depending on classification as standard or priority review, in which the latter aims for 6 months. There is no clock stop during review in the US-FDA unlike in the EU.

^b Other exclusivities from FDA include Generating Antibiotic Incentives Now (GAIN) and Qualified Infectious Diseases Product (QIDP), which would qualify product for additional 5 years of exclusivity from the time of approval.⁴²

NB. Development and submission timelines above were collected through available public information and projected accordingly.^{43, 44, 45} Please refer also to Appendix 1 for differences among applications submitted and approved under FD&C Act Section 505.

8(3) full or mixed application. In certain cases, legal basis 10(1) has also been used to obtain an approval for an FDC. This has been achieved by referring to an already approved FDC, for which any relevant data exclusivity period has already expired. Important bridges of efficacy and safety, drug-drug interaction, and bioequivalence data are needed irrespective of the legal basis and accordingly development and submission activities vary. The requirement of more than one bioequivalence study may arise, if at least one of the FDCs contains a modified release component, in which case the EMA's guidance on pharmacokinetic and clinical evaluation of modified release has to also be taken into consideration.²²

The approval of a new FDC of Glyxambi® (empagliflozin/linagliptin) is one of the examples under this category being filed under legal basis 10b. It required extensive non-clinical and clinical programmes, wherein several bridging studies

and Phase III studies were performed. Another example is the FDC of amlodipine and atorvastatin, where non-clinical and clinical scientific arguments were supported by bibliographic references and bioequivalence was also shown for the proposed FDC in comparison to the mono-products given simultaneously, e.g., Norvasc® and Lipitor®.^{23,24}

Directive 2001/83/EC Article 10c informed consent application

Article 10c can be used to introduce a duplicate of the originator product into the existing market without the need to perform any additional development activities. It is referred to as informed consent as all information provided comes from the Marketing Authorisation Holder of an already

authorised product in the EU region. An example of this type of submission is olmesartan plus hydrochlorothiazide, where the applicant of the reference medicinal product introduced a generic of its existing OlmetecPlus® product.²⁵

By remaining as the applicant of the subsequent application and referencing the pharmaceutical, pre-clinical, and clinical documentations contained in the previously approved product, no additional requirements have to be fulfilled.

The Federal Food, Drug and Cosmetic Act (FD&C Act) and its subsequent amendments form the centre of all possible legal bases in the US.

United States (US)

Situation in the US

The category of submissions generally possible in the US are in Table 2. These mainly include new

drug application (NDA); abbreviated new drug application (ANDA) for generics; hybrid applications for drugs falling in between an NDA and ANDA; and originator biologic license application (BLA) and biosimilar/interchangeable BLA. The table also provides other key information regarding other aspects of development and submission activities.

The Federal Food, Drug and Cosmetic Act (FD&C Act) and its subsequent amendments form the centre of all possible legal bases in the US. The entire FD&C and subsequent amending status are listed in Title 29 in Chapter 9 of the US Code (As Amended Through P.L. 115-271, Enacted October 24, 2018). Selected case studies are presented below with further explanation on how these different regulatory pathways are effectively used in practice. However, a detailed discussion as performed for the section on EU situation (see above) is not in the scope of this article.²⁶

FD&C 505(b)(1)

In general, a 505(b)(1) application requires a full dossier. As per the process used by the US FDA, any submission under FD&C 505(b)(1) is assigned an NDA classification code that is also reassessed at the time of approval by US FDA. All applications under 505 (b)(1) would not mean a new molecule entity, i.e., classified as Type 1 under NDA classification codes. The NDA classification codes include Type 1 to Type 10, e.g., a new indication or claim for the same application has an NDA of Type 6. The purpose

Reference to	Development and submission activities	Exclusivity and data protection ^b	Need for PSP
Active comparator/ placebo	8-15 years	5 years for NCE, 7 years for ODE	Yes
Yes, the US RLD or reference standard	2-5 years	180-day exclusivity possible for patent challenge, 180-day exclusivity for first to launch a competitive generic therapy	No
Active comparator, generally the US RLD	5-8 years	0-7 years, depending on designation and the need for new clinical studies	Yes per PREA
Active comparator/ placebo	8-15 years	5 years for NCE, 7 years for ODE	Yes Applications Covered by Section 505(b)(2)
Reference product	7-10 years	No	Yes per PREA but limited scope based on reference product PREA requirements

Abbreviations: ANDA, abbreviated new drug application; BLA, biological license application; CMC, chemical manufacturing and controls; D&C, food, drug and cosmetic act; PC, patent challenge; PD, pharmacodynamics study; PK, pharmacokinetic study; PREA, paediatric research equity act; NCE, new chemical entity; NDA, new drug application; NME, new molecule entity; ODE, orphan drug exclusivity; PSP, paediatric study plan; RLD, reference listed drug; VAM, value added medicine.



of these codes is to help the US FDA to coordinate an effective review process at Central Drug Evaluation Research and to promote consistency across review divisions.²⁷ All new applications as NDA are approved using this legal basis.

FD&C 505(j)

This regulatory pathway is meant for generics and as noted in Table 2, some bioequivalence data are requested with no additional studies requiring pre-clinical, clinical efficacy, and safety data, or paediatric data. It could be directly compared to legal basis 10(1) in the EU. The FDA has issued several guidance documents over recent years for generic applicants in regard to the requirements including bioequivalence study requirements, 180-day exclusivity, and so on. The FDA also provides recommended dissolution methods and product-specific guidance for generic drug development.^{28,29,30}

FD&C 505(b)(2)

The most relevant pathway for all applications aiming to obtain an approval for differential products, such as value added medicines, is the 505(b)(2) pathway, facilitated by the FD&C Act.

Legal basis 505(b)(2) permits the US FDA to rely on data not developed by the applicant alone and therefore, sometimes the term hybrid application is used. Some of the scenarios where 505(b)(2) pathway could be used include change in dosage form, strength, route of administration, and substitution of an active ingredient in a combination product. The FDA has also provided guidance regarding regulatory and scientific consideration for applications using 505(b)(2).^{31,32}

After an overview of different regulatory pathways with focus on generics and biosimilars, it is clear that there are different options available within the regulatory framework that could be used in both the EU and the US.

PHS 351(a) and PHS 351(k)

The Public Health Service (PHS) Act Section 351 is responsible for biological products. However, biological products are a subset of drugs and, as previously mentioned, all drugs in the US are regulated under provisions of the FD&C Act. In the case of biological products, these are licensed under section 351 of the PHS Act in view of specific requirements for manufacturing controls for such products regulated under this Act. In the case of biosimilars, an abbreviated

licensure pathway for biological products was created through the Biologics Price Competition and Innovation Act of 2009. To use this licensure pathway, a biological product should be

biosimilar to or interchangeable with an FDA-approved biological product. The original biologics used the approval pathway of 351(a), which is also referred to as the Original BLA pathway.^{33,34}

Before the 351(k) regulatory pathway was established for biosimilars, there had been approvals for “follow-on” proteins in the US, one of the case examples being somatropin (Omnitrope[®]), which was filed under the 505(b)(2) pathway. It was categorised under Type 5 – new formulation or new manufacturer submission classification for review – and was later approved in the US. In the absence of 351(k), choosing the 505(b)(2) regulatory pathway provided the applicant an opportunity to leverage existing data to reduce development requirements for these follow-on products. In addition, some follow-on protein approvals in the US were obtained using the regulatory pathway of the 351(a) of PHS Act, including insulin glargine (Lusduna[®] and Basaglar[®]). However, the introduction of the 351(k) pathway provided a dedicated pathway for the approval of biosimilars. Biosimilars in the US, following the implementation of this pathway, now have a well-defined legal pathway and clear guidance from US FDA with the possibility of targeted development and submission activities for applicant or sponsor. A review into recent approvals has shown that the requirements are clearly laid out and the review process by the FDA is well established.^{35,36,37} It has also been announced by the FDA that Congress will implement a direction that certain biologics including insulins will be regulated under PHS 351 starting March 2020.³⁸

Author's standpoint

After an overview of different regulatory pathways with focus on generics and biosimilars, it is clear that there are different options available within the regulatory framework that could be used in both the EU and the US. In certain cases, e.g., medicinal product or biologic or differential product (i.e., changes in dosage form or strength or combination of drugs or drug with device), there is more than one option that might be available to the applicant or sponsor. Any new development and submission strategy requires thorough planning and full understanding of the medicinal product itself, which could effectively be used to optimise effort for targeted development and submission activities. The case

examples presented also show that planning might have a direct impact on the financial budget and timelines of the projects. The impetus on planning lies completely on the applicant or sponsor as regulatory bodies encourage discussion on unprecedented cases. The development and submission activities irrespective of the kind of legal framework used either in the EU or the US are most essential activities for the applicant or sponsor. Therefore, it is in their best interest to plan these if possible, to perfection. The journey leading to a final submission-ready dossier is not an easy one. However, development and submission teams that have a good understanding of the legal framework, oversight of development activities, knowledge of the requirements of the CTD dossier, and submission writing expertise can bring results of cherished approvals. This also helps both pharma industry and regulators to achieve their aim, which is to have a safe and efficacious product complying all good practices for the patients.

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The opinions expressed in this article are the author's own and not necessarily shared by the author's employers or EMWA.

Conflicts of interest

The author declares no conflict of interest.

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Appendix

Appendix 1. Differences among applications submitted and approved under FD&C Act Section 505 ^{28,31,32,34,39,42}

	505 (b) (1) Application	505 (b) (2) Application	505 (j) Application
Patent and Exclusivity Information	Submit information on patents claiming the drug or a method of use; exclusivity request claiming exclusivity	Submit information on patents claiming the drug or a method of use (if any); generally, a patent certification (Paragraph I, II, III or IV) or “section viii” statement is required; exclusivity request claiming exclusivity and exclusivity statement the listed drug is subject to exclusivity (if any exists)	Patent certification (Paragraph I, II, III or IV) or a “section viii” statement is required; exclusivity statement the RLD is subject to exclusivity (if any exists)
Five-Year Exclusivity Subject to five-year exclusivity for 505(b)(1) or 505(b)(2) applicants.	Prevents the submission of an ANDA or 505(b)(2) application for 5 years after NDA approval, except an ANDA or 505(b)(2) application with a Paragraph IV certification to an Orange Book-listed patent may be submitted after 4 years	Only for applications for NCEs; prevents the submission of an ANDA or another 505(b)(2) application for five years after application approval, except an ANDA or other 505(b)(2) application with a Paragraph IV certification to an Orange Book-listed patent may be submitted after 4 years; also subject to NDA holder’s exclusivity	No Exclusivity
Three-Year Exclusivity Subject to three-year exclusivity for 505(b)(1) or 505(b)(2) applicants.	Only if one or more of the clinical studies, other than BA/BE studies, was essential to the product’s approval; prevents FDA from making effective an ANDA or 505(b)(2) application for the conditions of approval of the NDA	Only if one or more of the clinical studies, other than BA/BE studies, was essential to the product’s approval; prevents FDA from making an ANDA or other 505(b)(2) application effective for the conditions of approval of the 505(b)(2) application; also subject to NDA holder’s exclusivity	No Exclusivity
Orphan Drug Exclusivity Subject to 7-year exclusivity for 505(b)(1) or 505(b)(2) applicants.	Prevents FDA from approving an application for the same condition for 7 years	Prevents FDA from approving an application for the same drug for the same condition for 7 years; also subject to NDA holder’s exclusivity	No Exclusivity
Antibiotic Exclusivity Subject to 5-year exclusivity for 505(b)(1) applicants.	Provides an additional five-year exclusivity for qualified infectious disease products	Not Applicable	Not Applicable
Paediatric Exclusivity Subject to 6-month exclusivity for 505(b)(1) or 505(b)(2) applicants.	Extends by six months all other types of patent and non- patent market exclusivity an NDA holder may have under the FD&C Act for a particular active moiety	Extends by six months all other types of patent and non-patent market exclusivity an NDA holder may have under the FD&C Act for a particular active moiety; also subject to NDA holder’s exclusivity	No Exclusivity

Continued opposite

	505 (b) (1) Application	505 (b) (2) Application	505 (j) Application
180-Day Exclusivity Subject to 6-month exclusivity for 505(j) applicants.	Not Applicable	Not Applicable	Available to any “first applicant” that files an ANDA with a Paragraph IV certification; prevents FDA from approving other ANDAs submitted by applicants that are not “first applicants”
Orange Book Listing	Included in the Orange Book as a listed drug; may be identified as an RLD	Included in the Orange Book as a listed drug; can be identified as a therapeutic equivalent (e.g., “AB-rated”) to the listed drug if BE is demonstrated and also is a pharmaceutical equivalent	Included in the Orange Book as a listed drug; can be identified as a therapeutic equivalent (e.g., “AB- rated”) to RLD if BE study(ies) is/are demonstrated and also is a pharmaceutical equivalent; listed in the Orange Book as a “pharmaceutical alternative” without a therapeutic equivalence evaluation code if approved under an approved suitability petition

NB. Biologics (innovator) under 351(a) Act will get 12 years of market exclusivity. Under Biosimilar 351(k) Act, the period of exclusivity for biosimilar depends on a number of factors and can range between 12 months and 42 months.

Abbreviations: ANDA, abbreviated new drug application, BA/BE, bioavailability and bioequivalence; FD&C, food, drug and cosmetics act; NCE, new chemical entity; NDA, new drug application; RLD, reference listed drug.

Appendix 2. Registered trademarks referred to in this article with their respective owners

Trademark	Company
Basaglar	Eli Lilly & Co.
Buvidal	Camurus AB, Sweden
Crusia	Laboratorios Pharmaceuticos Rovi
Farmprojects	Farmprojects S.A.
Forsteo	Eli Lilly & Co.
Glyxambi	Boehringer Ingelheim International GmbH
Lusduna	Merck Sharp & Dohme
Movymia	Stada Arzneimittel AG
Novarsc and Lipitor	Pfizer, Inc. and Pfizer Ireland Pharmaceuticals

Trademark	Company
Olmotec Plus and Daiichi Sankyo	Daiichi Sankyo Co. Ltd.
Omnitrope and Ziextenzo	Novartis AG
Pelmeq	Comfa Biotech S.L.
Prostap	Takeda Pharmaceutical Co.
Ratiopharm	Ratiopharm GmbH
Subutex	Indivior UK Limited
Terrosa	Richter Gedeon Nyrt

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Biosimilar development – an overview

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Abstract

Biosimilars are biological drugs that are similar to, and cheaper than other biological drugs (called “reference originator biologics”) that are already in use. They share an identical amino-acid sequence but, given the inherent variability of biological molecules, not full “sameness”. Biosimilar registration follows a strictly regulated pathway based on a totality-of-evidence approach. This article critically discusses the particulars of biosimilar development, including the continuous development of regulatory guidelines, familiarises readers with biosimilar-specific terminology, addresses the typical challenges of writing biosimilar dossiers, and summarises future directions in biosimilar development in the context of a changing competitive landscape. After reading this article, medical writers with different backgrounds, including those previously unfamiliar with key aspects of biosimilar development, should be able to better understand and apply these guidelines in their daily biosimilar work.

What are biosimilars? What are they not?

Biologics or biological drugs are products created from living organisms or that contain components of living organisms. Biosimilars are biological drugs that are similar to, and cheaper than, other biological drugs (called “reference originator biologics”) that have already been approved for use on the market. Since biologics



Since biologics and biosimilars are created in living cells, they cannot be chemically synthesised like generic drugs.

and biosimilars are created in living cells, they cannot be chemically synthesised like conventional drugs and their generics.

While a biosimilar candidate and an originator biologic share the same amino-acid sequence, they can never be identical, due to the inherent variability of complex biological molecules. In other words, a biosimilar and its reference biologic share a similar (but never exactly the same) functional version of the active substance. Examples of biosimilars (and biologics) include monoclonal antibodies, hormones, small proteins, vaccines, and fusion proteins.¹ Biosimilars (and biologics) that are monoclonal antibodies or derivatives thereof target pro-inflammatory cytokines, most commonly tumour necrosis factor alpha.

In the EU, a biosimilar is defined as a biological medicine highly similar to another

biological medicine already approved in the EU, for which there are no clinically meaningful differences to the reference medicine in terms of safety, quality and efficacy.² In the US, a biosimilar product is defined as a biologic product approved based on demonstrating that it is highly similar to an US FDA-approved biologic product that has no clinically relevant differences in terms of safety and effectiveness compared with the reference product; only minor differences in clinically inactive components are allowed for a product to be deemed biosimilar.³ Other terms used to describe biosimilars are: follow-on biologic, follow-on protein, and subsequent entry biologic.⁴ An essential aspect to keep in mind is that the EU-approved and US-approved reference products are not considered equivalent by default.

Biological medicines (originator biologics



and biosimilars) offer treatment options for patients with chronic and often disabling conditions such as diabetes, autoimmune disease, and cancer.² Biologics have a 12-year exclusivity in the US⁵ and an 11-year exclusivity in the EU, comprising 10 years for new biologics (eight-year data exclusivity and two-year market exclusivity) and a one-year extension for a new indication.⁶

A biosimilar candidate can be manufactured and (once biosimilarity to an originator has been shown) sold at a lower cost than the originator biologic, as the clinical development programme for a biosimilar is lean and relies heavily on the efficacy and safety experience previously established with the originator. Thus, it can be beneficial for patients with chronic conditions to gain access to biosimilar medicines at prices more accessible than those of their originator biologics, and profitable for companies to specialise in

biosimilar development. Biosimilars have been on the market for 13 years in the EU (the first approval of a biosimilar product in the EU was in 2006)² and for 4 years in the US (the first approval by the US FDA was in 2015).⁷

Regulatory aspects of biosimilar development

Since variability (be it qualitative or quantitative) may result not only in a loss of biological function, but also in severe and potentially unknown adverse events, biosimilars need to follow a highly regulated regulatory pathway. This pathway differs between the EU and the US.

Historically, regulatory requirements in the EU and US have developed in parallel with the

development of biosimilars. The regulatory framework for biosimilars was established in the EU in 2003. The Committee for Medicinal Products for Human Use (CHMP) overarching guideline on biosimilars came into force in 2005 and a revised version came into effect in 2015.⁸ In recent years, both the overarching guideline and its sister guidelines (that focus on quality, non-clinical, and clinical issues) have been updated, reflecting the growing experience with biosimilars. In recent years, the US FDA has also been heavily engaged in developing guidelines for biosimilar development⁹ and providing advice to stakeholders. In 2010, the World Health Organization published a “similar biotherapeutic products” guideline.¹⁰ Efforts towards global guidelines are however still in a very early stage. See Table 1 for further details.

Additionally, different health authorities currently prefer and use slightly different terminology. It is thus up to pharmaceutical companies to develop internal best practices with input from their regulatory affairs departments regarding terms acceptable for use in the EU, US, and the rest of the world.

Interestingly, because of the inherent variability of biologics, an originator manufacturer of biological products also faces challenges when introducing changes in the manufacturing process, and needs to demonstrate equivalence, for example, for different formulations of the same medicinal product. Changes in the regulatory requirements intended primarily to support and facilitate changes to biologics’ manufacturing processes triggered the evolution of the concept of the biochemical bridge, whereby a comprehensive analytical (biochemical and biophysical) comparative testing programme could be used as part of the justification for demonstration of equivalence or similarity.⁴ The biochemical bridge easily lent itself to the analysis of candidate biosimilars and played an important role in starting to define

Biosimilars need to follow a highly regulated regulatory pathway. This pathway differs between the EU and the US.

The EU-approved and US-approved reference products are not considered equivalent by default.

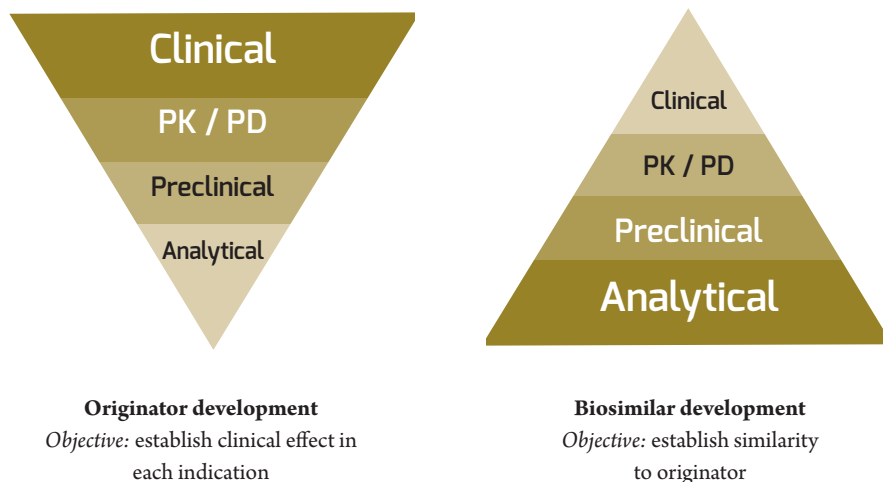


Figure 1. Biosimilar vs. originator development – the world upside down

PK = pharmacokinetics; PD = pharmacodynamics.

differences and their correlations to physiological and clinical effects (see section **The world upside down** below).

The EU-approved and US-approved reference products are not considered, by default, similar to each other and thus it is essential that studies aiming to establish similarity use the reference biologic matching the intended target region. In practice, in a lean

Paediatric development requirements for biosimilars differ between the EU and the US.

development programme, this often means that both reference products will be included in the same clinical study, and the equivalence of the biosimilar candidate will be tested against both.

Paediatric development

Regulatory requirements for paediatric biosimilar development differ between the EU

and the US. In the EU, Regulation (EC) No 1901/ 200 exempts manufacturers of candidate biosimilars from providing a paediatric investigational plan (PIP).¹¹ In contrast, according to the 2016 revised US FDA draft guidance on PSPs,¹² a paediatric study plan (PSP) is needed for candidate biosimilars in the US.¹³

The world upside down

Biosimilarity to a reference product (biologic originator) is established based on a so-called totality-of-evidence approach. The bulk of a biosimilar development programme is made of comprehensive analytical (biochemical and biophysical) comparative testing as part of the justification for demonstration of equivalence or similarity, while the clinical part is – especially when looking at it with an originator mindset – very lean (see Figure 1). Residual uncertainties need to be addressed.

Biosimilars follow a step-wise development, with the risk of failure decreasing at each step:

- **quality comparability** is essential and involves comprehensive characterisation and comparison of physicochemical and biological properties; the degree of similarity demonstrated at this level might determine the amount of additional evidence that needs to be generated at later stages; for further information on quality attributes requirements by region,^{14,15} see Table 1.
- **pre-clinical (functional) comparability**

Table 1. Biosimilars in the EU and in the US – a selection of key differences

Topic	EU	US
Definition ^{2,3}	A biological medicine highly similar to another biological medicine already approved in the EU, for which there are no clinically meaningful differences to the reference medicine in terms of safety, quality and efficacy	A biologic product approved based on demonstrating that it is highly similar to a US FDA-approved biologic product, and has no clinically relevant differences in terms of safety and effectiveness compared with the reference product; only minor differences in clinically inactive components are allowed
Quality attributes ^{14,15}	EMA Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development	US FDA Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
Animal studies	Focus on <i>in vitro</i> studies	Animal studies required
Paediatric development ^{11,12,13}	PIP not required	PSP required
Reference product	EU-approved originator biologic	US-approved originator biologic

EMA = European Medicines Agency; EU = European Union; US FDA = United States Food and Drug Administration; PIP = paediatric investigational plan; PSP = paediatric study plan; US = United States.

Biosimilarity to a reference product (biologic originator) is established based on a so-called totality-of-evidence approach. The bulk of a typical biosimilar development programme is made of comprehensive analytical (biochemical and biophysical) comparative testing as part of the justification for demonstration of equivalence or similarity, while the clinical part is (...) very lean. Residual uncertainties need to be addressed.



offers reassurance on similar effects and involves functional *in vitro* assays to define and compare the mode(s) of action:

- **in vitro studies** are always required and normally cover most functional aspects.
- it is essential to determine **the level of concern** depending on quantitative/qualitative differences in critical quality attributes.
- **in vivo PK (pharmacokinetics)/PD (pharmacodynamics) and/or safety studies** may be necessary in case of e.g., a new expression system; see Table 1 for details by region.
- **clinical comparability** involves testing in a sensitive population and dose at a sensitive time point using an appropriate statistical model and testing approach; usually the details for phase III conduct are agreed upfront with the health authority of the region intended for registration.

Clinical biosimilar development

Unlike in originator drug development, clinical programmes for biosimilar candidates are lean and rely on the clinical experience with the originator biologic. Most of these programmes only comprise:

- one phase I PK/PD bridging study in healthy volunteers.
- one phase III confirmatory efficacy and efficacy study in patients with the most sensitive indication; switching treatment groups is usually included in the study design.

The objective of both types of studies is to show equivalence between the proposed biosimilar and its corresponding originator product, for which a solid justification for the applied equivalence margins is required. For generics studies, a 90% confidence interval within 80%–125% equivalence margins is acceptable for demonstrating bioequivalence, on the assumption that the generic and originator medicines will have the same behaviour in the body once absorbed. For biosimilarity, however, a different confidence interval may be needed to demonstrate similarity in exposure; this needs to be discussed and justified. For generics, the focus is on comparing the absorption of the test and reference products, while for biosimilars it is of interest to determine a potential difference both in the absorption and the elimination phase.

As already mentioned, when running global development programmes and designing clinical

studies, it is to be kept in mind that the EU-approved product and the US-approved product are not by default equivalent, and that the equivalence margins and confidence interval requirements may differ between regions. In addition, what is considered the most sensitive indication (to show differences) and the most sensitive population within this indication is usually agreed upon upfront with the respective health authorities before running a comparative clinical efficacy and safety study.

Biosimilar studies do not test for superiority.

An equivalence design at the 90% or 95% confidence interval is used in phase III comparative trials (generally preferred to a non-inferiority design) and establishes that the biosimilar is neither superior nor inferior to the reference product.¹⁶ For detailed statistical considerations in biosimilar development, see Balfour and Schmitt in this issue.¹⁷

Dose-ranging studies are not conducted in biosimilar development, as a biosimilar candidate will be approved for the specific approved dose(s) of the originator once biosimilarity has been shown and extrapolation has been scientifically justified (see below for further details). Additionally, in the case of manufacturing

Clinical programmes for biosimilar candidates are lean.

Table 2. Interchangeability and substitution in the EU and in the US – key differences¹⁸

Topic	EU	US
Legal basis Interchangeability	European Commission Consensus Document “The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber”	2009 BPCI Act The medical practice according to which “the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product”
Substitution	An administrative measure defined as the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber	An interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product
Decisions on interchangeability and switching	Can only be reached at national level by individual states; the EMA does not have the authority to make such decisions. Thus, pharmacy-level substitution is not routinely practised in the EU.	Individual US states control pharmacy-level substitution; the US FDA may approve a product as interchangeable/switching; 35 US states have passed legislation addressing substitution.

BPCI = Biologics Price Competition and Innovation; EMA = European Medicines Agency; EU = European Union; US = United States; US FDA = United States Food and Drug Administration.

changes during the course of development of the biosimilar candidate, bridging studies between formulations are needed to establish their equivalence (just as they are needed for biological originator manufacturers in such situations) to ensure function preservation given the inherent biological variability of biologics.

Immunogenicity

Immunogenicity is a major safety concern (manifesting as hypersensitivity reactions) not only for biosimilars, but for the development of biologics in general. The development of antidrug-antibodies (in particular neutralising antibodies) could also impact efficacy (potentially resulting in a decrease or loss of efficacy), therefore clinical design and corresponding documents need to address such concerns. Antibody formation takes time, thus one-year immunogenicity data are required for most monoclonal antibody applications in the EU.

Previous knowledge about the immunogenicity of the originator biologic is valuable, nonetheless the immunogenic potential of small differences in quality attributes of the biosimilar candidate may not be easy to predict or understand. Methods for antibody detection are becoming increasingly

sensitive, thus it is often challenging to meaningfully compare data with the candidate biosimilar with historical data provided in the label of the originator biologic.

Overall, the biosimilar candidate should have the same safety profile as the originator biologic. Lower immunogenicity (and thus improved safety) could be accepted, whereas higher immunogenicity cannot. In cases of lower immunogenicity, however, efficacy could look artificially higher due to lower levels of neutralising antibodies and entail higher rates of other adverse events. This could nonetheless be accepted, provided that patients without anti-drug-antibodies show comparable efficacy.

Extrapolation

An essential concept for biosimilar development is the extrapolation to other indications. Once biosimilarity has been established based on the totality-of-evidence, extrapolation from the studied indication to all indications approved for the reference biologic is possible based on solid scientific justification.

In other words, extrapolation is the term used to describe the use of a biosimilar for an indication approved for the originator that was

not directly tested in the development programme of the biosimilar.⁴ Efficacy and safety do not need to be established *de novo* in each indication of the originator biologic, but a solid rationale is needed and extrapolation is granted on a case-by-case decision for each biosimilar. Key factors for the scientific rationale are usually a shared clinically relevant mode of action across indications, and the sensitivity of the studied indication and its relevance for other indications.

Once biosimilarity has been established based on the totality-of-evidence, extrapolation from the studied indication to all indications approved for reference biologic is possible based on solid scientific justification.

Interchangeability, substitution, and switching

Following the approval of a small molecule pharmaceutical product, being able to switch (or substitute) between pharmaceutical drug products (from originator to generic) is a well-



established and extensively used practice and is typically implemented at the pharmacy level. However, in addition to restrictions against biosimilar extrapolation, this type of switching (between originator and biosimilar) and interchangeability requires approval at the national level in the EU. The terms “interchangeability”, “substitution”, and “switching” all refer to the practice of treating patients with the originator biologic and then changing treatment to an approved biosimilar, or changing from one approved biosimilar to another approved biosimilar.^{4,18} There are a number of differences with which the EMA and the US FDA regard the interchangeability of biologics and biosimilars, as detailed in Table 2.

What writers working on biosimilar documents need to know

When working on biosimilar documents, writers should pay particular attention to the major key challenges described in Table 3.

For further relevant details and practical tips for the daily work of medical writers, see Brauburger and Heisel-Stöhr (focus: clinical study reports [CSRs] and common technical documents [CTDs]);¹⁹ Prechtel et al. (focus: pharmacovigilance documents),²⁰ and McMinn et al. (focus: lay summaries)²¹ in this issue of *Medical Writing*.

The terms interchangeability, substitution, and switching all refer to the practice of treating patients with the originator biologic and then changing treatment to an approved biosimilar, or changing from one approved biosimilar to another approved biosimilar.

Biosimilar development – what’s next?

“First wave” biosimilars (growth hormones and monoclonal antibodies) were vastly more complex than pharmaceutical preparations, yet relatively simple biological molecules. Biosimilars with more complex structures are currently under development, with multi-subunit, extensively post-translationally modified, and lipid-containing products; such products may raise new complications and concerns.⁴

In addition, the competitive biosimilar landscape is changing. A number of new companies have recently entered the biosimilar development scene and they are making fast progress. With speed-to-market being an essential factor for profitable biosimilar development, traditional key players/pharma giants that were once pioneers in the field may strategically opt out from pursuing certain biosimilar development

programmes,²² as their new competitors cut their way forward. With most monoclonal antibodies coming off patent by 2020 and given the introduction of biosimilars, existence of their originator biologics, and creation of biobetters (improved versions of the originator biologics), the oncology landscape and its key stakeholders (prescribers, pharmacists, nurses, patients, reimbursing bodies, and manufacturers) will be facing many challenges.¹ Several older challenges remain: the acceptance of biosimilars by the general public and their ample use in health care; a better understanding of the impact of differences in quality attributes on clinical efficacy and safety;^{14,15} a meaningful approach to collecting post-marketing safety data from biosimilars and their reference biologics; and efforts to globally converge regulatory requirements, including the potential use of a global reference product.

Conclusion

The world of biosimilars brings exciting opportunities for professional medical writers. As a new wave of biosimilars is currently under development, and regulations in the EU and the US are simultaneously becoming increasingly more complex, teams working on biosimilar development will need increasing guidance. Medical writers can play an important role in the efficient development of biosimilar documents

Table 3. Key challenges in writing biosimilar clinical documents and how to address them

Challenge	Situation	Way forward
The similarity mindset challenge (toughest)	We are creatures of habit who like to stick to familiar ways of doing (i.e., writing) things and usually it takes time for teams with an originator mindset to shift to the biosimilar mindset. In this context, clinical teams have a tendency to over-interpret minor treatment differences throughout the results sections, yet still tend to conclude “similar safety profiles”.	Writers should remind teams that the main goal of the biosimilarity exercise is to establish similarity to an already established product, not a treatment advantage compared with the standard of care. The efficacy and safety of a biosimilar candidate do not need to be demonstrated de novo, this has already been done for the originator biologic. Minor safety differences between treatments in rather small populations of patients in phase III trials should only be discussed extensively if confounders can be meaningfully attributed and the differences are clinically relevant and raise a true concern.
The multiple treatment periods and multiple database locks challenge (moderate and very time-consuming)	For comparative efficacy and safety phase III trials in patients, multiple treatment periods and interim database locks (DBLs) are the norm. After a certain treatment period, patients are switched to a different treatment (e.g., from originator biologic to biosimilar candidate). Data cleaning issues may arise after such an interim DBL and often, teams spend hours discussing how to best address it.	Ideally, companies have learnt their lesson and have developed best practice guidelines for dealing with such instances, which are not at all uncommon. If not, medical writers should encourage the development of best practices both in terms of dealing with data cleaning issues with impact on attributing patients to patient sets, and in terms of standardising the way new data will be added to the clinical package once available: in the form of a revised clinical study report (CSR) including all data and treatment periods; amendments, CSRs that only focus on data from specific treatment periods etc.
The consistency challenge (moderate)	If the similarity exercise is generally successful, the wording in the proposed biosimilar label will be the same as in the originator’s label. Teams often think of new key messages to include in documents as development progresses.	All documents within a clinical development programme should build into the extrapolation concept so that similarity can be concluded based on the totality of evidence. Messaging consistency across clinical and pre-clinical documents in the same programme is essential, and so is addressing any residual uncertainties. Medical writers should remind teams of this whenever discussions seem to drift off.
The redundancy challenge (moderate)	While complexity in terms of “writing volume” for Modules 2.7 and 2.5 may look low (often there are only 2 studies and no pooling), these documents are crucial for the submission. Teams often like to repeat the same level of detail across all clinical documents.	Only key data should be presented in Module 2 documents, with cross-references to the more detailed presentation in the individual CSRs. Medical writers should: <ol style="list-style-type: none"> remind their teams that the CSRs are just one click away establish biosimilar-dedicated document templates within an organisation, as documents will need to be structured differently than those for originators, in order to be fit-for-purpose.
The multiple therapeutic areas challenge (easiest)	Biosimilars are commonly developed for use in the therapeutic areas immunology (for treating chronic autoimmune diseases such as psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and juvenile idiopathic arthritis), oncology, and endocrinology (insulin analogues and growth hormone analogues).	Medical writers should be familiar not only with regulatory and preferred wording requirements for biosimilar development in the target registration region, but also with treatment guidelines specific to the indication selected for phase III development. The good news for medical writers in terms of volume of work: only data for one indication need to be presented, unlike for originator biologic applications. Extrapolation to other indications approved for the biologic originator is possible and within the scope of the similarity exercise, based on the totality of evidence and a solid scientific justification.

that are fit-for-purpose, both by proactively helping establish best practices for the writing of such documents and by generally driving the shift from an originator to a biosimilar mindset.

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Conflict of interest

The author declares no conflict of interest.

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Statistical principles in biosimilar development

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Abstract

Unlike new drug development where superiority over an active comparator or placebo often has to be proven, biosimilar development focuses on showing similarity of the proposed biosimilar to an already approved reference product. This affects the statistical aspects of clinical trials including choice of study design, endpoints, and analyses performed. In addition, there is a greater focus on margin justification and missing data imputation for efficacy. This article provides an overview of the statistical principles inherent to biosimilar development.

Lean clinical development programme

Biosimilar development is based on extensive physicochemical characterisation of the proposed biosimilar, followed by a lean clinical development programme to address any residual uncertainty about the similarity between the proposed biosimilar and the reference product. Typically, the clinical development programme is limited to two clinical studies: one pharmacokinetics/pharmacodynamics (PK/PD) similarity study and one confirmatory efficacy/safety/immunogenicity study. No dose finding study is usually conducted as the approved dose is known from the reference product.

Three arm active control PK/PD similarity study

The objective of the PK/PD similarity study is to demonstrate bioequivalence (show no clinically meaningful differences) in PK and/or PD between the proposed biosimilar and the authorised reference product. As different health authorities approve medicinal products in different regions, the authorised reference product may also vary by region, for example a US-licensed reference product versus an EU-licensed reference product. Due to this, the PK/PD similarity study usually includes three

treatment arms: the proposed biosimilar, the EU-licensed reference product, and the US-licensed reference product. This results in three treatment comparisons: biosimilar vs EU reference, biosimilar vs US reference, and EU reference vs US reference (Figure 1).

Interval hypothesis testing

Statistically, PK similarity is demonstrated if the 90% confidence interval (CI) for the ratio of geometric means of test product to reference product for the PK parameter(s) – typically area under the curve from time zero to infinity (AUC_{inf}), maximum measured concentration (C_{max}), and area under the curve from time zero until the last quantifiable concentration (AUC_{last}) – falls entirely within the pre-defined margin of 0.80 to 1.25. This method is equivalent to conducting two 1-sided tests at the 5% level. If μ_T and μ_R respectively denote the population means for test and reference product for a particular endpoint, then the following null (H_0) and alternative (H_1) hypotheses are being tested:

$$H_0: \mu_T/\mu_R \leq 0.80 \text{ or } \mu_T/\mu_R \geq 1.25$$

$$H_1: 0.80 < \mu_T/\mu_R < 1.25$$

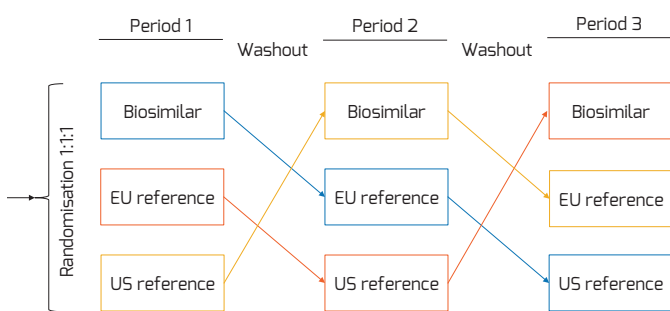


Figure 1. Typical PK/PD similarity crossover study design

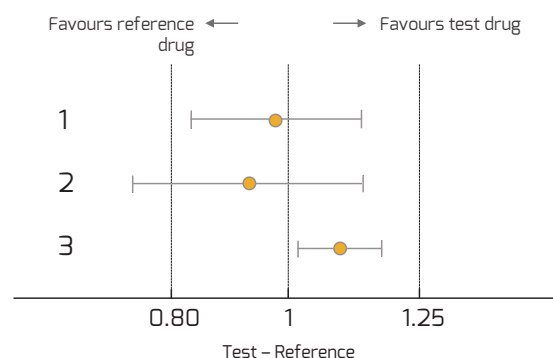


Figure 2. Examples of equivalence testing with confidence intervals.

1. Equivalence met: confidence interval contained entirely within margin of 0.80 to 1.25.
2. Equivalence not met: confidence interval partially outside the margin of 0.80 to 1.25.
3. Equivalence met, but additional explanation needed for why the confidence interval does not contain the equality point of 1.



variance (ANOVA) is performed on the log-transformed PK parameter and estimates for each treatment comparison are computed. For crossover studies the ANOVA model includes treatment sequence, treatment group, and period as fixed effects, and subject nested within treatment sequence as a random effect. For parallel group studies the ANOVA model should only include treatment group as a fixed effect. In addition, stratification factors used during randomisation and other important baseline characteristics may be used as covariates if clinically justified.

A standard margin of 0.80 to 1.25 for the ratio of geometric means for all PK parameters is suggested by regulatory guidelines^{1,2} and accounts for an acceptable difference in systemic drug exposure between treatments of up to 20% (Figure 2).

For most products and indications no PD marker exists. In addition, when a PD marker does exist, the margin for the PD marker is highly dependent on the PD marker chosen and therefore needs to be defined for each compound individually and agreed with health authorities,

following the same principles as for the efficacy margin in the confirmatory efficacy/safety study (see below). If a sensitive PD marker for the compound is available, efficacy can also be assessed in the PK/PD similarity study and may not have to be established in a confirmatory efficacy/safety study, which then would focus on safety and immunogenicity only. In any case, the EMA requires that at least 1 year of safety data be collected in the confirmatory efficacy/safety study.³

PK bridge and multiple comparisons

To demonstrate similar PK, three treatment comparisons are performed: biosimilar vs EU reference, biosimilar vs US reference, and the PK bridge of EU reference to US reference. The PK bridge, together with the analytical bridge (e.g., structural and functional data) comparing all three products (biosimilar, EU reference, and US reference), can then form the basis for justifying the relevance of data from in vivo non-clinical or clinical studies comparing the proposed biosimilar to a reference product authorised in a

different region (for example using EU reference data for an FDA submission). This potentially reduces costs and development time by including only one reference product in animal studies or the confirmatory efficacy/safety study.^{4,5}

Comparing all three products pairwise in the PK/PD similarity study leads to three treatment comparisons. In addition, multiple primary endpoints (AUC_{inf} , C_{max} and AUC_{last}) may be assessed, leading to up to nine possible comparisons. As a 5% false positive rate (one-sided directional hypothesis) is inherent in all comparisons, counter-measures need to be taken to avoid an inflated rate of false positive conclusions. A number of methods are available for controlling the rate of false positive conclusions.⁶ If multiple comparisons are made on multiple primary endpoints covering different aspects of the drug effect, all comparisons need to be successful for the study to be conclusive. As one option to control multiple comparisons, a hierarchical testing strategy can be applied, where all comparisons are first ranked in order and then each subsequent comparison is only tested if the previous higher-ranked comparison

is successful. In this case, no adaption of the significance level for each individual comparison is required (Figure 3).

Another consideration for multiple comparisons is the impact on the power of the study. Studies are often powered at an overall level of 80%. Therefore, each individual comparison should be powered at a higher power (for example 96%) to ensure that the overall power of 80% is maintained.

Single active control confirmatory efficacy/safety study

The objective of the confirmatory efficacy/safety study is to demonstrate that no clinically meaningful differences exist between the proposed biosimilar and the reference product (active control) in terms of efficacy, safety, and immunogenicity. The objective of this study is not to demonstrate patient benefit per se, which has already been established for the reference medicinal product, and therefore no placebo arm is required. Instead, an indirect comparison to placebo should be made through estimation of the equivalence margin. Justification of the equivalence margin is based on the past performance of the reference product, often in the pivotal studies used for the reference product approvals. A systematic review is conducted to identify studies relevant to the comparison of the reference treatment versus placebo in the indication being considered. These studies can be

used to estimate the effect size: difference between reference and placebo, with the corresponding CI. The planned confirmatory efficacy/safety study comparing the biosimilar product with the reference product will also provide an estimate of treatment effect with a CI. If these two CIs are combined, an indirect CI comparing the biosimilar test product and placebo can be obtained. Superiority of the biosimilar versus placebo is then demonstrated if the lower bound of the indirect CI is greater than zero (Figure 4).^{7,8}

Most sensitive setting with regards to indication and primary endpoint

The objective of the confirmatory efficacy/safety study is to demonstrate that no clinically meaningful differences exist between the test and reference products in terms of efficacy and safety. Therefore, the comparison between the products needs to be performed using the most sensitive model (indication plus endpoint) and study conditions in a homogeneous patient population to detect any product-related differences, should they exist. The approved indication chosen is not necessarily the indication for which the product is most frequently used. The same most sensitive principle applies when selecting the primary

endpoint for demonstrating similar efficacy. The chosen endpoint should be objective and exhibit a clear treatment effect. Often a continuous endpoint can be more sensitive to detect differences than a binary endpoint.

During biosimilar clinical development, similar efficacy and safety do not need to be demonstrated in every approved indication.

For example, in an oncology setting overall survival and progression free survival are important clinical endpoints with which to establish patient benefit for a new anticancer drug. However, these endpoints may not be feasible or sensitive enough for assessing similarity of a

proposed biosimilar and reference product since they may be influenced by various factors not attributable to differences between the biosimilar and the reference product, such as tumour burden, performance status, previous lines of treatment etc. Instead, overall response rate or percentage change in tumour mass from baseline may be used.⁹

During biosimilar clinical development, similar efficacy and safety do not need to be demonstrated in every approved indication. Instead, the confirmatory efficacy/safety study is conducted in the most sensitive indication only, and then biosimilarity is extrapolated to all other approved indications. A scientific argument including the mechanism of action of the product is provided to justify extrapolation to other indications and use of the full reference product label.

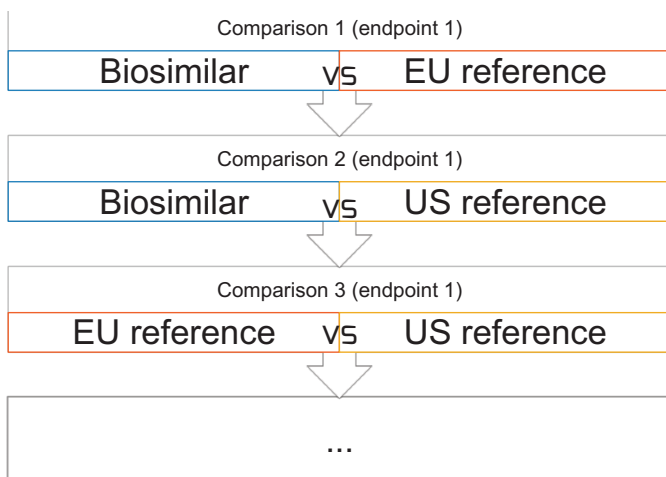


Figure 3. Hierarchical testing strategy. Three of the nine possible comparisons are shown.

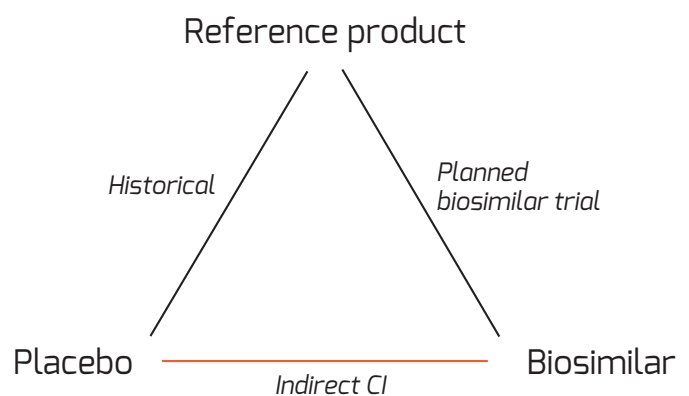


Figure 4. Indirect confidence interval (CI) showing superiority of biosimilar over placebo



Per-protocol analysis set as the most sensitive analysis set

Different to new study drug development where the objective is often to demonstrate superiority, for a biosimilar programme the objective is to demonstrate equivalence. Because of this, the primary statistical analysis of the primary endpoint should be performed on the per-protocol analysis set; the full analysis set is used for a secondary analysis. The per-protocol set is the cleanest analysis population to avoid biasing the comparison towards equivalence due to effect distortion by protocol deviations and imputation of missing data. Efficacy data for patients with major protocol deviations may not present an accurate picture of the product effect itself but are likely influenced by other factors. With such factors distorting the results for both the biosimilar and the reference drug it becomes

increasingly difficult to detect any potential differences between actual product effects. This biases the comparison towards equivalence.

Analysis of the primary endpoint

Statistically, the comparison between the biosimilar and the reference product in terms of efficacy is performed by demonstrating that the 90% (for the FDA) or 95% (EMA) CI for the difference between the products for the primary endpoint falls entirely within a pre-defined margin. Figure 5 illustrates an example where PASI75 response rate (percentage of patients achieving a 75% reduction in Psoriasis Area and Severity Index) is the primary endpoint, the difference between test (biosimilar) and reference (EU reference) products is estimated as a risk difference, and the pre-defined margin is -18.0% to +18.0%. In this scenario, equivalent

efficacy would be demonstrated by a risk difference of -2.5% with a 95% CI of -10.0% to 5.1% – or any other CI falling entirely inside the margin. agreed with health authorities. The margin is based on statistical as well as clinical considerations. Statistical significance pertains to whether or not the observed result could occur by chance alone, while clinical significance pertains to whether or not the observed result has “important” clinical, research, or public health relevance. The margin is derived based on past performance of the reference drug compared to placebo to ensure that the biosimilar drug maintains an agreed upon proportion (usually 50% or more) of the effect size of the reference drug. The effect size is estimated as the lower bound of the 95% CI for the difference between reference drug and placebo. A meta-analysis is performed where multiple data sources are available.^{7, 8}

Potential bias towards equivalence when imputing missing data

When comparing the biosimilar and the reference drug, special considerations have to be given to the occurrence and imputation of missing data so as to not bias the results to equivalence. To counter this potential effect, the main analysis is usually based on the per-protocol set, thereby excluding patients with missing data. The robustness of the conclusion from the per-protocol set should be assessed through sensitivity analyses to account for different missing data scenarios. For imputation of missing data for both the biosimilar and the reference product using the same imputation rule, equivalence may be falsely concluded due to the imputation rather than a similar therapeutic effect.¹⁰ For example, imputing all missing values as non-responders would reduce the treatment effect for both products and thereby reduce the

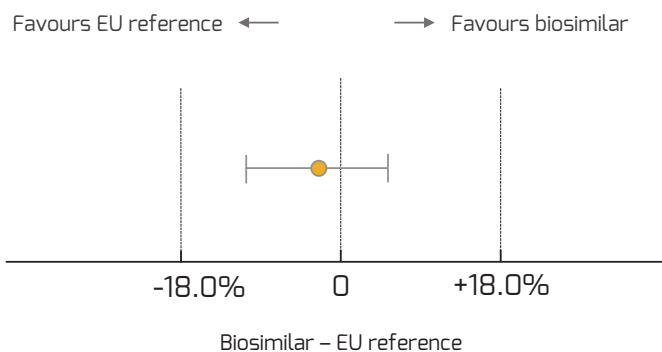


Figure 5. Plot for the risk difference between a biosimilar and an EU reference for PASI75 response rate. Equivalence met: 95% confidence interval for risk difference contained entirely within margin of -18.0% to +18.0%.

efficacy would be demonstrated by a risk difference of -2.5% with a 95% CI of -10.0% to 5.1% – or any other CI falling entirely inside the margin.

Importance of equivalence margin justification

As the equivalence margin defines the equivalence criteria and also drives the study sample size, it needs to be selected carefully and

treatment difference. One possibility is to impute the missing data for the reference product as responders and the missing data for the proposed biosimilar as non-responders and vice versa (extreme case scenarios). Alternatively, a tipping point analysis could be performed to understand the possible impact of missing data and which scenarios for the missing data would 'tip' the statistical analysis to no longer demonstrate equivalent efficacy.

Conclusion

With increased efforts to reduce health care costs, biosimilars have become more and more relevant. However, with biosimilars as a somewhat new concept in the world of medicinal product development, the regulatory environment and public understanding and acceptance are still evolving. As more guidelines on how to plan biosimilar trials become available, medical writers need to work closely with statisticians to determine which concepts from new drug development can be applied to biosimilar development and which aspects require different approaches. In addition, biosimilar-specific topics such as interchangeability [see Biosimilar development – an overview, p. 20] are still under discussion, making biosimilar development an interesting and highly relevant field to work in.

Conflicts of interest

The authors work for Sandoz, a Novartis division.

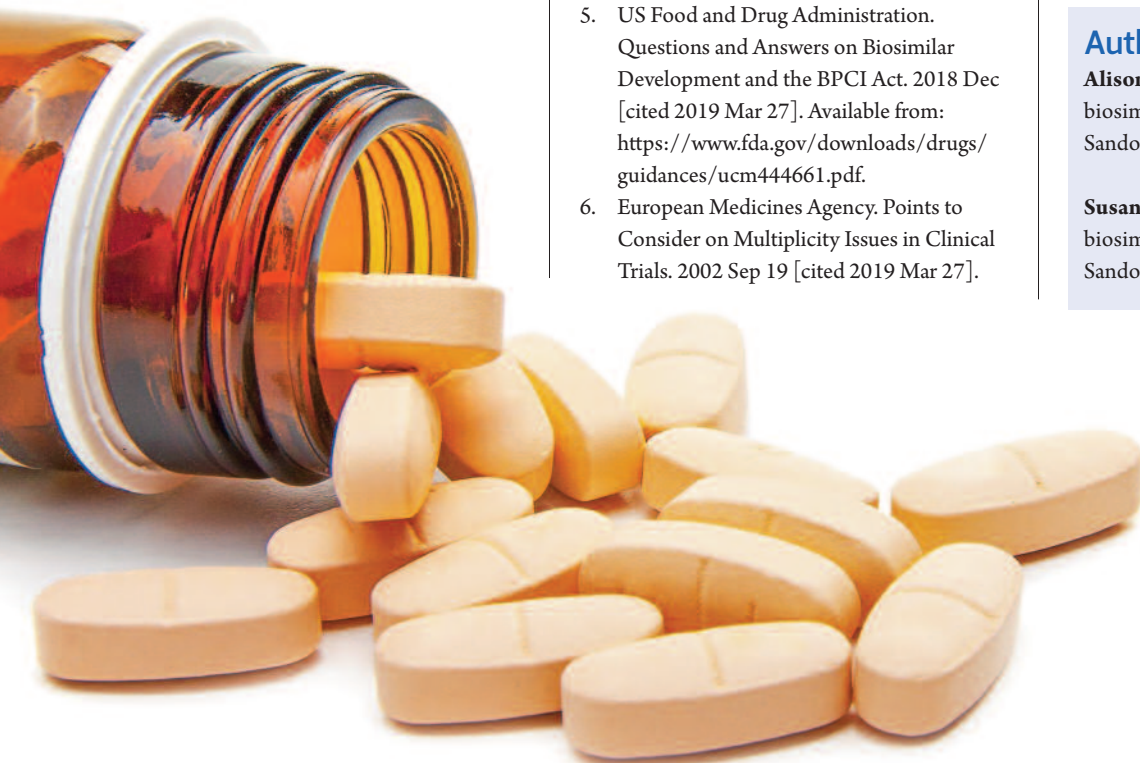
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Writing biosimilar clinical study reports and submission documents – what to expect and what to consider

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Abstract

With the emergence of biosimilars, the development process for these drugs is a topic of increasing interest to medical writers. Even though information and educational documents on the concept of biosimilarity are increasingly publicly available, it takes some practice for the medical writer to translate the specific requirements into fit-for-purpose documents. This feature article summarises the relevant regulatory requirements for the clinical development of biosimilars. It includes best-practice recommendations on how these requirements can be translated into the everyday work for medical writers.

Introduction

With the emergence of biosimilars, the development process for these drugs is a topic of increasing interest to medical writers. The common goal of a biosimilar development programme is to show that a biological medicine, the proposed biosimilar product, is “highly similar to another already approved biological medicine”.¹ The latter is referred to as the originator product in this feature article. This similarity to the originator product is to be established not only in terms of quality characteristics and biological activity, but also in

terms of safety and efficacy.² The main documents showing this similarity in clinical safety and efficacy are the clinical study reports (CSR) and the clinical summary documents included in the Common Technical Document (CTD). This article outlines the most currently available guidance and provides insight into typically occurring questions and problems faced when developing the clinical documents for a biosimilar development project.

Biosimilar CSR preparation

CSRs for studies included in clinical biosimilar development programmes should be authored the same way as any other CSR, following the common applicable guidance, such as ICH E3 and the ICH E3 Questions and Answers document.^{3,4} Additional resources used for the authoring of CSRs, e.g., the CORE reference or the TransCelerate Common CSR Template can be referred to as well.^{5,6} However, a number of biosimilar-specific topics exist that must be considered when writing a biosimilar CSR.

Study design and analysis

In biosimilar development, a minimum/standard clinical programme consists of a study investigating the pharmacokinetics (PK) and, if possible, pharmacodynamics (PD) of the proposed biosimilar (Phase I) and a confirmatory efficacy and safety study (Phase III).

The objective of both studies is to show equivalence between the proposed biosimilar and its corresponding originator product – equivalence either based on the PK/PD parameters, or based on efficacy, safety, and immunogenicity, depending on the type of the study. Consequently, each CSR needs to include a justification for the applied equivalence margins. This justification can be included as a reference to the respective protocol or statistical analysis plan, or as text directly in the CSR data-independent section (Section 9.7 as per ICH E3/CORE; Section 3.7 as per the TransCelerate Common CSR Template).

An important part within the concept of

biosimilarity is to conduct the study in a sensitive indication; therefore, the chosen indication needs to be justified.⁷ As the source for this justification is usually the protocol, the information can be added to the CSR either as a cross-reference to the protocol or as a brief summary (Section 9.3 as per ICH E3/CORE; Section 3.3 as per the TransCelerate Common CSR Template). In addition to describing the chosen sensitive indication, it is important to choose a sensitive population for the analysis. Whereas the intent-to-treat analysis set is the first choice for a superiority/non-inferiority study, biosimilar equivalence studies usually apply the per-protocol analysis set for the primary analysis (however, it is important to note that additional analyses on the intent-to-treat analysis set are always required).⁸

The primary objective of a biosimilar efficacy and safety study suggests a simple 2-group study design with the originator product as the comparator. However, the actual design of the study might be more complicated. The US concept of interchangeability requires studies to show that “the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch”.⁹ Therefore, biosimilar studies that are part of a global submission dossier often consist of several study periods with at least the originator product treatment group split into two groups, typically after the primary endpoint; a so-called switching study design (Figure 1). Note that this interchangeability concept is not applicable for other regions, such as the EU.

Even the design of a PK/PD equivalence study can become complicated if the study is planned to bridge two different regional originator products and, for example, if a three-way crossover design was applied.⁸ No matter which development strategy or which study design has been chosen, the medical writer needs to pay close attention to the structure of the CSR to present the study data adequately.


As a non-adequately planned analysis cannot be rescued at the level of the CSR, the medical writer should already be involved during the planning of the study and (at the latest) during the development of the statistical analysis plan. Furthermore, the reporting of the study results often must allow for several interim database locks that might be needed depending on the sponsor's submission plans. It needs to be discussed upfront how all analyses are planned to be executed and how this translates into the sequence of one or more interim CSRs – for

example, in terms of the sequence and numbering of the statistical outputs. If a long-term follow-up analysis for safety or immunogenicity is planned, an addendum to the final CSR might be needed. The number and sequence of CSRs also influences the resource planning, as blinded medical writers will have to be available after each unblinding event.

Interpreting and describing data

Development programmes for new biologic medicines usually comprise a number of clinical

studies with a large number of patients required to conclude superiority or non-inferiority. In contrast, biosimilar development programmes usually comprise only a relatively small number of subjects needed to address an equivalence objective. Thus, especially in the safety assessment, a numerical difference of only one patient per group can lead to a large percentage difference between treatment groups. Therefore, assessing biosimilarity requires a clear understanding of whether these differences are clinically relevant or not.



All documents need to be tailored to the needs of the product and a smart document strategy needs to be developed with the submission team.

When describing the data of the study, it is important to be aware that the overall safety and efficacy of the drug had already been established during the clinical development of the originator product. Therefore, the main goal of biosimilar clinical documents is to show that the proposed biosimilar is similar to the originator product in all aspects and *not* to establish the drug's efficacy or safety profile *de novo*. This is a fact the medical writer needs to keep in mind while writing, as inappropriate language easily obscures the scientifically appropriate message of the document (Table 1).

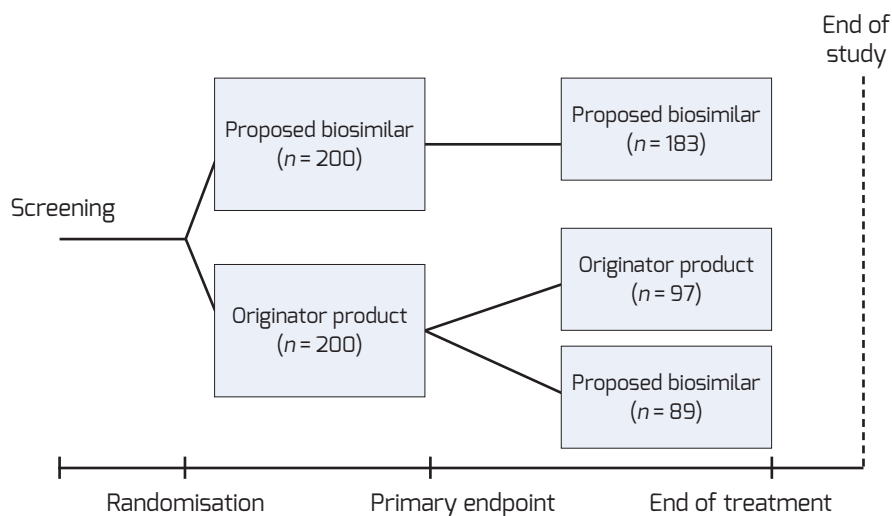


Figure 1. A typical study design of a biosimilar confirmatory efficacy and safety study
n = number of study participants per study group

Accordingly, the most important message in biosimilar documents is whether data in both study groups are similar.

No special focus on the overall results and no columns displaying total population results in in-text tables are required. If any general statement about the overall study population is needed, the text should typically refer to the end-of-text tables including the total column. Only when describing the subject disposition and referring to baseline characteristics, might some focus on the total characteristics remain; ultimately, the most important message is whether the biosimilar and the originator group performed similarly.

Immunogenicity

Immunogenicity is a topic not inherently linked to biosimilars alone, but in general to the development of biological medicines. In the CSR, immunogenicity is a separate topic that is often placed into the safety section (i.e., Section 12 as per ICH E3/CORE). However, it is important to note that anti-drug antibodies, especially neutralising antibodies, which inhibit the molecular function of the drug, also potentially influence the efficacy of the drug. Therefore, it is recommended to deal with immunogenicity either in both the efficacy and safety section, or in a separate new section dedicated to immunogenicity (for example Section 5.7 as per the TransCelerate Common CSR Template).

Biosimilar CTD documents

The fundamental premise underlying the development of a biosimilar is the establishment of similarity based on state-of-the-art analytics. This can take multiple iterations in early stage development and takes more time than would normally be required for an originator product. While the clinical development programme of an originator product is usually substantial, biosimilars require a tailored clinical programme. When illustrated graphically, this means the development programme of a biosimilar product resembles a pyramid, rather than the typically inverted pyramid usually shown for a standard development programme of an originator product (Figure 2).

These differences in drug development are reflected in the dossier structure, even though the submission dossiers for a marketing authorisation application of a biosimilar and an originator product use the same CTD structure and both development programmes include the same scientific topics.

Module 2

The overall goal in the overviews and summaries in Module 2 is to demonstrate similarity. However, we strongly recommend discussing the similarity of nonclinical and clinical properties in separate documents. The general CTD structure should be followed despite the need to establish the totality of the data/evidence. The individual



summaries and overviews should be focused and succinct and use smart cross-references rather than repetitions. With this document strategy, you will automatically follow the stepwise approach by showing:

- the analytical similarity, which justifies proceeding with the nonclinical programme, followed by
- the clinical programme that demonstrates PK/PD equivalence and similarity in efficacy and safety in a sensitive indication and population.

Modules 2.7.1 and 2.7.2

In biosimilar dossiers, Module 2.7.1 (Summary of Biopharmaceutics) and Module 2.7.2 (Summary of Clinical Pharmacology) are more important documents than in dossiers of new biologic medicines. PK/PD similarity is established and the biopharmaceutical testing strategy is discussed, both of which define the basis of the clinical development programme. Therefore, the medical writer should be involved at least in the review of these modules to ensure document consistency.

Modules 2.7.3 and 2.7.4

In the ideal clinical development of a biosimilar, one would expect one study per phase included in the dossier. Therefore, the Summaries of Clinical Efficacy and Safety are relatively short documents and can be co-developed with the CSRs. Close alignment of the content across the documents is key and having the same (lead) medical writers involved facilitates the document development.

The team should critically assess which analyses shall be reflected in the summaries and in which cases a cross-reference to the CSR would suffice. For example, not all study periods or analyses (subgroup/sensitivity) need to be copied from the CSR; only the most meaningful data should be summarised. Spending some time on mock tables, figures, listings (TFLs) and shell documents can accelerate the document development after database lock. Even mock text with an assumed similarity result can be drafted. Medical writers should use the time before database lock to establish rules on the use of terms such as similar/

comparable/ equivalent in a project-specific style guide.

Biosimilar dossiers usually do not include

... the medical writer needs to pay close attention to the structure of the CSR to present the study data adequately.

a formal Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS) as, with essentially one study each in Phase I/III, data cannot be pooled meaningfully. Instead, the CSRs are the main source for clinical summaries. Of course, if more than one Phase I study is needed in the clinical development, the pooling of these studies may be supportive.

When planning an FDA submission without ISS and/or ISE, this topic should be discussed with the FDA upfront and the medical writer should be involved in the writing of the briefing book. Even if safety data are pooled, the ISS can be limited to the TFLs and the text part can be covered in Module 2.7.4. Make use of the options listed in the relevant guidance documents.^{10,11}

Immunogenicity and extrapolation

Immunogenicity and extrapolation are both very important topics in the biosimilar dossier.

Immunogenicity can be described in dedicated sections of Modules 2.7.1 to 2.7.4 dealing with different aspects of immunogenicity. Alternatively, an Integrated Summary of Immunogenicity can be added to Module 5, so that all aspects of immunogenicity are summarised in a separate document to which Modules 2.7.1 to 2.7.4 provide meaningful cross-references. The team needs to decide on the strategy early on, taking into account the expected availability of the last immunogenicity data in relation to the planned finalisation timelines of all documents and the overall submission timelines.

A similar situation applies to the justification of extrapolation.⁷ This topic can be covered in Modules 2.7.1 to 2.7.4, which in this case deal with different aspects of the extrapolation exercise. Alternatively, the entire extrapolation topic can be covered in Module 2.7.3 only or in a separate extrapolation document. If the team plans to expand the nonclinical data section of the extrapolation exercise, a separate document may be the preferred choice as it allows the other clinical documents (including writing and review) to remain focused. This separate extrapolation document can be added either to Module 5 or as an appendix to the Clinical Overview.

As the extrapolation topic is not foreseen in the standard CTD structure, there is some degree of freedom and creativity to help develop the best

document strategy for the dossier and the submission plan. Extrapolation is a relatively new topic and we advise medical writers to check EMA and FDA homepages for already published dossiers, assessment reports, or briefing books before planning their own document strategy.

Module 3 – as far as relevant for clinical documents

As outlined in the EMA Quality guideline, the biosimilar dossier should provide a demonstration of similarity.¹² This similarity exercise for a biosimilar product versus the originator product is an *additional* element to the usual requirements of the quality dossier. It should be discussed separately in Section 3.2.R of Module 3, in the Similarity Assessment Report.

If reference products of a different origin are used in the nonclinical or PK/PD studies as compared with the clinical efficacy and safety study, a justification for the bridging of the reference product in the latter study is required.^{7,8} This justification should also be provided in Module 3.

When writing Modules 2.7.1, 2.7.2, or 2.5, cross-references to Module 3 will be needed. Hence, the medical writer should stay closely aligned with the Chemistry, Manufacturing, and Controls writer for consistency of the document contents.

Module 5

The bulk of documents in Module 5 are the CSRs and the bioanalytical reports. As discussed above, some additional documents may be added in Module 5.3.5.3, e.g. an Extrapolation Assessment Report, Integrated Summary of Immunogenicity, or a Statistical Overview to expand on statistical topics (such as the definition of the equivalence margin).

Biosimilar special documents/topics

Several topics in a biosimilar dossier need the medical writer's special attention:

- Justification for the equivalence margins: can be included in Module 2.7.2/2.7.3, in a separate document in Module 5, or as appendix to the Clinical Overview. The document strategy depends on the extent of the statistical modelling, which may be too extensive for inclusion in the CSRs or the summary documents.

Table 1. Differences in the description of endpoints between new biologic medicines and biosimilars

Topic	New biologic medicine	Biosimilar
Safety	Overall, out of 347 subjects, 110 subjects (31.7%) experienced at least one AE. The incidence of AEs in the test group was lower (50 subjects, 28.7%) than in the placebo group (60 subjects, 34.7%). The most common AEs were nasopharyngitis (test group: 25 subjects, 14.4%; placebo group: 27 subjects, 15.6%). More patients with back pain were reported in the test group (7 subjects, 4.0%) than in the placebo group (1 subject, 0.6%).	The proportions of patients with AEs were similar in each treatment group (biosimilar group: 50 subjects, 28.7%; originator group: 60 subjects, 34.7%). The proportion of patients with back pain appeared to be higher in the biosimilar group (7 subjects, 4.0%) than in the originator group (1 subject, 0.6%), but this difference was not considered clinically relevant.
Efficacy	At Week 16, the mean percent improvement in PASI from baseline was 80.9 for the test group and 8.1 for the placebo group. The PASI percent improvement from baseline to Week 16 between the test group and the placebo group (-72.8) was statistically significant with a p-value of <0.001.	At Week 16, the mean percent improvement in PASI from baseline was 80.9 for the biosimilar group and 83.1 for the originator group. The PASI percent improvement from baseline to Week 16 between the biosimilar and the originator group was -2.2 with a 2-sided 95% CI of (-7.4, 3.0). The 95% CI was within the equivalence margin of (-15, 15), indicating similarity / therapeutic equivalence between the biosimilar and the originator group.

Abbreviations: AE, adverse event; CI, confidence interval; PASI, Psoriasis Area and Severity Index

- Justification for the chosen sensitive population: needs to be included in the CSR in Module 5, in the clinical development section of the Clinical Overview, and in Module 2.7.3.
- Extrapolation across indications: can be rather extensive, depending on the list of approved indications of the corresponding originator product. It can be covered in Modules 2.7.1 to 2.7.4, in a separate document in Module 5, or as an appendix to the Clinical Overview.
- Comparison to literature: is usually requested by authorities. The team needs to align on the originator studies and/or other biosimilar studies that should be included in the comparison and on the cut-off date for this comparison. The comparison can be part of the Clinical Overview only or split across the Clinical Overview (brief summary) and the clinical summaries (a tabular presentation may be useful).
- Critical assessment on biosimilarity: should be provided in the Clinical Overview, but may also be added to Modules 2.7.2 to 2.7.4.

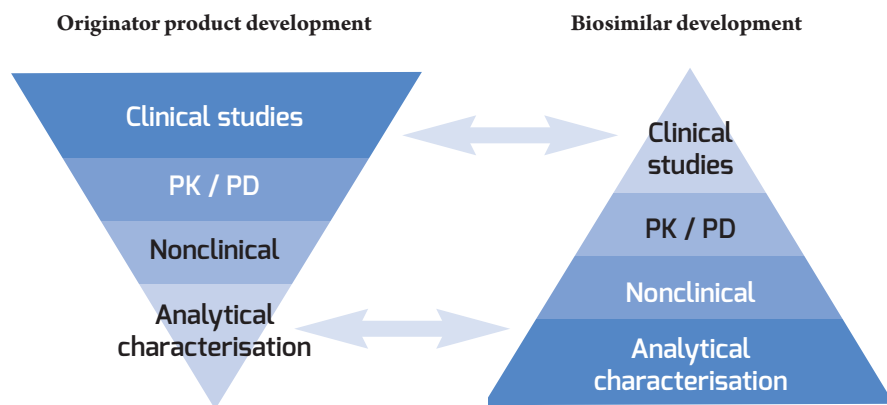


Figure 2. Inverted development pyramid showing the different foci during the development of a biosimilar compared with the development of a new biologic medicine.

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics. Source: adapted from ¹³

Whether all of the topics listed above are relevant for the submission depends upon the nature of the proposed biosimilar product and on the originator product label. All documents need to be tailored to the needs of the product and a smart document strategy needs to be developed with the clinical submission team.

Summary and conclusion

Although information and educational documents on the concept of biosimilarity are increasingly publicly available, it takes some

practice to translate the specific requirements into fit-for-purpose documents, even for medical writers experienced in the drug development of new biologic medicines. It may be beneficial to develop separate templates for CSRs and clinical summaries in the CTD, or to request a waiver from the usual templates used for new biologic medicines to allow more flexibility with the document structures.

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Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

Conflicts of interest

The authors declare no conflict of interest.

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Medical writing for generics throughout the life cycle

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Abstract

Medical writing plays an integral part in the pharmaceutical industry, be it for originator or generic drug companies. Most writers are working for medium to large research-based companies. However, even for generic drug firms many documents need to be composed, preferably by or with the help of a medical writer. This article aims to familiarise the reader with the usual terminology and relevant guidelines. Key documents throughout the entire life cycle of generic medicinal products are described, starting with the clinical documents during the development process, continuing with required support for the authorisation process, and concluding with post-marketing material.

In the pharmaceutical environment there are two types of companies: originator and generic companies. To put it in a nutshell: the former typically heavily invest in research and development to produce new drug products while the latter reproduce the originator companies' ideas. Generic medicines may only be marketed after the original patent has expired. This is usually 10 years from the date of first authorisation.

Because the manufacturers of generic drugs have not had the expenses of developing a new drug, their products

are cheaper. Unlike their larger originator counterparts, generic companies are typically smaller and usually don't have their own clinical and in-house writing capabilities. Therefore, they often need to outsource these activities.

It's probably fair to say that most medical writing is done for originator medicinal products. If you have only been involved with new chemical entities, you may ask yourself what medical writing for generics has in store. The legal basis of marketing authorisation applications is associated with specific data requirements and will heavily influence the types of documents written, as well as the content of the submission dossier. In this introduction section I will give you a very short guide to "all you need to know about generic medicinal products" before we dive headfirst into the practical part of medical writing for generics.

A generic medicine is developed to be the same as the reference medicine, which has already been authorised on the basis of a complete dossier. If the marketing authorisation application for a generic medicinal product can demonstrate bioequivalence, no additional preclinical tests or clinical trials are needed. Instead, the application refers to the preclinical and clinical data for the reference product.

According to the definition given by the EMA, "a generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). However, a generic medicine's inactive ingredients, name, appearance and packaging can be different."¹ As the inactive ingredients do not have to be identical, the generic medicinal product may have different side effects or contraindications based on the pharmaceutical excipients used.² Broadly speaking, differences in the excipient content can result in variations in safety profiles. Lactose for example is widely used as a diluent and filler-binder in oral capsule and tablet formulations.³ Medicinal products containing

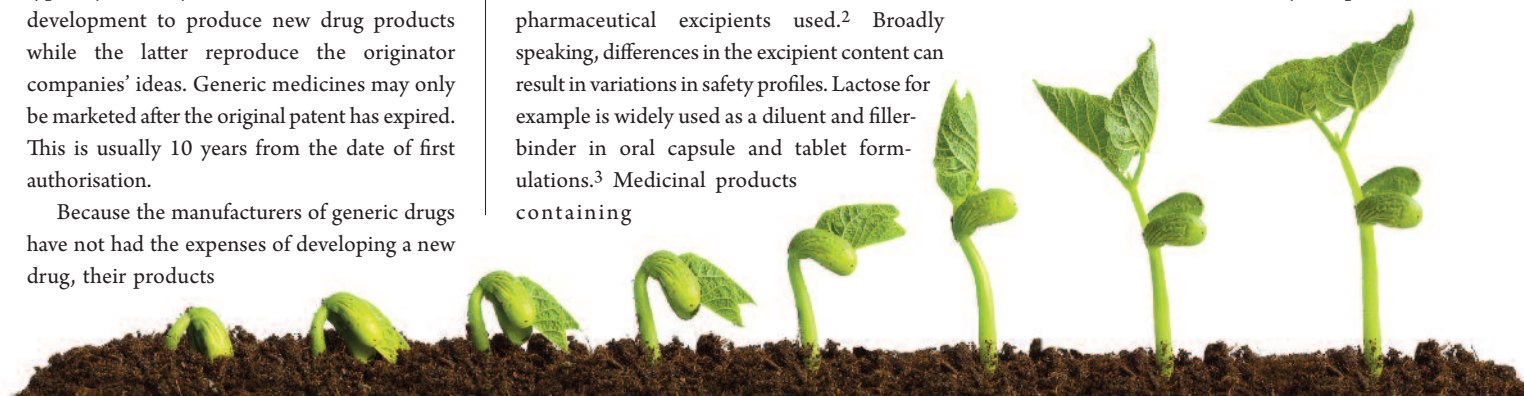
lactose must carry a labelling warning according to the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal products for human use".⁴ Therefore, any medical writer preparing the submission documentation for a generic medicinal product should be aware of differences in composition in relation to the originator product. Any differences regarding the excipients, including possible safety-related issues, should be discussed in the dossier.

According to Article 10(1) of Directive 2001/83/EC,⁵ bioequivalence to the reference medicine must be demonstrated. In some cases, bioequivalence studies are not mandatory, e.g., for simple oral solutions or aqueous solutions for intravenous or intramuscular injection, provided they contain the same active substance in the same concentration as the currently authorised product.⁶

The following sections aim to guide you through the whole life cycle of a generic medicinal product, starting with the clinical documents during the development process, continuing with the preparation of the submission dossier, and concluding with post-marketing material (see Table 1 for an overview).

Medical writing during the drug development process

Generating bioavailability (rate and extent of absorption) and bioequivalence study data is a critical step in the development process for a generic drug. Since the EMA (and the FDA for that matter) do not ask for clinical outcome data for the registration of generics, the demonstration of bioequivalence based on pharmacokinetic (PK) criteria is the key component of



therapeutic equivalence. The most important reference source in the EU for the investigation of bioequivalence is EMA guideline CPMP/EWP/QWP/1401/98 Rev. 1.⁶ It is, however, always worth checking which guideline(s) apply to the particular characteristics of the medicinal product (e.g., dosage form). Specific recommendations for modified release products, transdermal products, and orally inhaled products are given in various guidelines. Making use of regulatory or scientific advice prior to submission may save the generic company a lot of money and prevent the wrong studies being performed or rejected later during the authorisation process.

Medical writers who already work in the area of clinical trials will be familiar with the documents that are typically needed for bio-

equivalence studies, such as protocols, informed consent forms, study reports, and manuscripts. Publishing the outcomes of bioequivalence studies is not common practice, although increased transparency is highly desirable considering the number of people treated with generic drugs.⁷ Another typical document in clinical research, the Development Safety Update Report, is not required for bioequivalence studies.

Bioequivalence studies are usually randomised, two-period, two-sequence, single-dose crossover trials including a small sample of healthy volunteers. Their aim is to demonstrate that two molecules are chemically bioequivalent based on the following PK criteria: rate of absorption, as determined by the peak plasma concentration (C_{max}), and area under the plasma concentration–time curve from time 0 to end of

study (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$). Limits used to conclude bioequivalence are fixed by regulatory agencies (see below).⁷

The report of the bioequivalence study should be written according to ICH E3. It should include evidence that the choice of reference medicinal product is in accordance with Article 10(1) and Article 10(2) of Directive 2001/83/EC.^{5,6}

In the bioequivalence assessment of two brands, the 90% confidence interval for the geometric mean ratios of AUC and C_{max} should be contained within the acceptance interval of 80.00-125.00%. For drugs with a narrow therapeutic index (a small window between their effective dose and the dose which has a toxic effect), a tightened acceptance interval of 90.00-111.11% applies. There are further different assessment requirements for highly variable drug

Table 1. Overview of typical documents written for generic medicinal products

Lifecycle stage	Type of document	Type of medical writing required	Nature & content	Applicable guideline
Development	Protocol	Regulatory	Same as for any CT	ICH E6
	Informed consent form	Regulatory	Same as for any CT	ICH E6
	IMPDP	Regulatory	Special requirements	EMA/CHMP/QWP/54552/5/2017
	IB	Regulatory	The approved SmPC may be used	ICH E6
	Study report	Regulatory	Full	ICH E3 CPMP/EWP/QWP/1401/98 Rev. 1/ Corr
	Manuscript	MedComms	Same as for any publication	Journal's author guidelines, CONSORT Statement, etc.
Authorisation	Module 1.5.2 Information for Generic, "Hybrid" or Bio-similar Applications	Regulatory	Concise summary document	NTA
	Module 2.4 Non-clinical overview	Regulatory	Bibliographic / Refer to data for reference product	NTA ICH M4
	Module 2.5 Clinical overview	Regulatory	Bibliographic / Refer to data for reference product + information on BE study	NTA ICH M4
	Module 2.7.1	Regulatory	Key document to present BA and BE data	NTA ICH M4
	RMP	PV	Abbreviated	GVP Module V
Post-marketing	ACO	PV	Full, if required (check national requirements)	CMDh Best Practice Guide on the processing of renewals in the MRP / DCP
	PSUR	PV	Full, if required	GVP Module VII ICH E2C(R2)

Abbreviations: ACO, Addendum to the Clinical Overview; BA, bioavailability; BE, bioequivalence; CMDh, Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human; CONSORT, Consolidated Standards of Reporting Trials; CT, clinical trial; DCP, decentralised procedure; GVP, good pharmacovigilance practices; IB, Investigator's brochure; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMPDP, Investigational Medicinal Product Dossier; MedComms, medical communications; MRP, mutual recognition procedure; NTA, Notice to Applicants; PSUR, Periodic Safety Update Report; PV, pharmacovigilance; RMP, Risk Management Plan; SmPC, Summary of Product Characteristics

products.⁶ The assessors will *always* check whether AUC and C_{max} are within the 90% confidence interval, unless the acceptance intervals have been defined otherwise and justified before the conduct of the study. The regulatory authorities adhere very strictly to the bioequivalence guideline on this point and will generally leave no room for discussion.

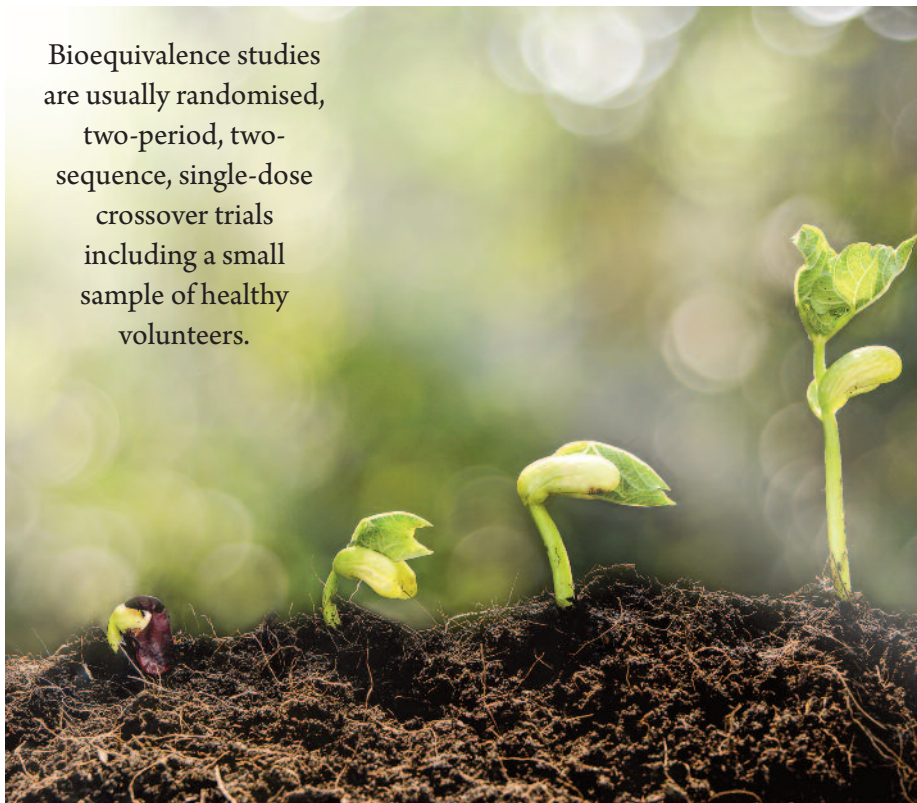
One other thing of high importance is the *in vitro* dissolution of the biobatches. Dissolution testing measures the amount of a given substance that goes into solution per unit time under standardised conditions. It is one of the most important tools to predict the *in vivo* bio-availability of oral solid dosage forms.⁸ Dissolution studies have to be performed using three different buffers (normally pH 1.2, 4.5, and 6.8). However, if the *in vitro* dissolution studies fail but bioequivalence was demonstrated *in vivo*, the latter prevails.⁶

As a surrogate for *in vivo* bioequivalence, the Biopharmaceutics Classification System (BCS)-based biowaiver approach may be used under certain circumstances.⁶ According to the BCS, drugs are usually divided into four classes depending on their solubility and their permeation capacity. BCS-based biowaivers can only be applied for highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The EMA accepts BCS-based biowaivers for both BCS class 1 and class 3 immediate-release drug products, which have high solubility and either complete (class 1) or limited (class 3) absorption.⁹ The ICH M9 draft guideline on BCS-based biowaivers describes the recommended format and content of documentation to support waivers for bioequivalence studies.¹⁰

Preparation of the submission dossier

The EU legislation allows for abbreviated applications for generic medicines. The dossier nevertheless needs to follow the requirements set out in the Notice to Applicants (NTA), regulatory guidelines, and the Common Technical Document (CTD) format.¹¹ Submissions should contain the complete administrative and quality data (Modules 1 and 3) and relevant preclinical and clinical data (Modules 2, 4, and 5). Reference is made to data in the originator product's authorisation application that demonstrate the safety and efficacy of the active molecule. Applicants have to show that the medicinal

Bioequivalence studies are usually randomised, two-period, two-sequence, single-dose crossover trials including a small sample of healthy volunteers.



product is a generic version of the reference product by summarising the relevant bio-availability and bioequivalence data, as well as by providing information on the qualitative and quantitative composition, the pharmaceutical form, and the safety/efficacy profile.¹² The non-clinical and clinical overviews should focus on particular issues concerning the basis for the application (see below for further information).¹³

Module 1

- Module 1.3.1 (Product information): the EMA has published Quality Review of Documents (QRD) general principles regarding the Summary of Product Characteristics (SmPC) for a generic. The content of the generic's SmPC should be consistent with that of the reference medicinal product *except* for indications or dosage forms still covered by patent law. Any differences in the proposed SmPC or claims not inferred from the composition or other properties of the generic need to be discussed and justified.¹⁴ This should be done in the non-clinical and/or clinical overviews and be substantiated by published literature and/or additional studies.¹³

- Module 1.5.2 (Information for Generic, "Hybrid" or Bio-similar Applications): In a concise document, the grounds and evidence used for demonstrating that the medicinal product is a generic version of the reference medicinal product need to be summarised. The summary should include details on the generic medicinal product, notably its composition and pharmaceutical form and the safety/efficacy profile of the active substance(s) in comparison to the reference medicinal product. Where necessary, details related to bioavailability and bioequivalence of the generic medicinal product should also be included.¹³
- Module 1.8.2 (Risk Management Plan [RMP]): It is expected that the safety specification is the same as that of the reference product. Any deviations need to be properly justified, since regulatory agencies are generally very reluctant to allow discrepancies with approved RMPs. According to the Guideline on good pharmacovigilance practices (GVP) Module V, new marketing authorisation applications for generic medicinal products have abbreviated content requirements (see Table 2).¹⁵ Generic RMPs

will not require RMP Modules SI (Epidemiology of the indication(s) and target population(s)), SII (Non-clinical part of the safety specification), SIII (Clinical trial exposure), SIV (Populations not studied in clinical trials), SV (Post-authorisation experience), and SVI (Additional EU requirements for the safety specification). Furthermore, Module SVII (Identified and potential risks) is only relevant if the originator product does not have an RMP and its safety profile is not published on the CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human) website. If more than one list of safety concerns published on the CMDh website applies for the same active substance, the applicant needs to justify the choice of proposed safety concerns in Module SVIII. RMP Part IV (Plans for post-authorisation efficacy studies [PAES]) is only relevant when a PAES was imposed for the originator product. In RMP Part V (Risk minimisation measures) a statement of alignment of safety information in the product information is sufficient.¹⁵

It is important to point out here that with revision 2 of GVP Module V, the definitions of safety concerns have changed. This poses challenges both for the applicant and the regulatory authorities if the originator RMP was compiled according to revision 1. Different EU member states have taken different approaches to dealing with this situation until all originator RMPs have been updated according to the current definitions. This has led to a situation where different generic products have identified safety concerns that deviate from the reference product. The following principles have been proposed by the Austrian competent authority: for active

substances for which there is no innovator or the innovator has no RMP, only safety concerns that have 1. ongoing additional pharmacovigilance activities, 2. ongoing additional risk minimisation measures, or 3. essential targeted questionnaires in place should be listed. For active substances for which there is a centrally authorised generic, the safety profiles of RMPs for subsequent generics should be aligned with the RMP for the centrally authorised generic. This applies to all national (including decentralised or mutual recognition procedure) and centralised marketing authorisation applications.

Module 2

Essential documents for Module 2 are the quality overall summary (Module 2.3), non-clinical overview (Module 2.4), clinical overview (Module 2.5), and Module 2.7.1 of the clinical summaries. The non-clinical summaries and the other modules of the clinical summaries (Modules 2.6.1 to 2.6.7 and 2.7.2 to 2.7.6, respectively) are only mandatory if additional studies have been performed.

As the applicant is not required to provide the results of pre-clinical tests and clinical trials, Modules 2.4 and 2.5 are mainly based on published literature. It is common practice to provide a description and justification of the literature search strategy. All documentation, whether favourable or unfavourable, should be included. A statement on GLP/GCP compliance is usually included in the overviews. In addition, a summary of impurities and relevant decomposition products should be provided.¹²

When different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that the safety and/or efficacy

profile is not different from that of the originator should be submitted.¹²

The results of the bioequivalence studies or a justification (biowaiver) for why studies were not performed should be presented in Module 2.5 and 2.7.1. The objective of Module 2.7.1 is to summarise all relevant information about biopharmaceutical studies and associated analytical methods. Appendix IV¹⁶ of the Guideline on the Investigation of Bioequivalence⁶ contains a set of template tables to assist applicants in the preparation of Module 2.7.1 and provides guidance regarding data to be presented. If a BCS-based biowaiver is submitted, Module 2.7.1 should contain a summary of the in vitro dissolution data with a justification for not performing a bioequivalence study and a list of relevant references.

Module 3

The CMC part of the dossier is very similar for generic and originator medicinal products, as quality always needs to be demonstrated. Therefore, a complete Module 3 of the CTD needs to be submitted in accordance with the requirements set out in the NTA. For solid dosage form generic medicinal products, comparative dissolution studies will be provided in this part of the dossier.

Modules 4 and 5

Modules 4 and 5 for generic medicinal products mainly contain bibliographic data, as it is not necessary to provide the results of toxicological and pharmacological tests or of clinical trials. Module 5.3.1 (Comparative Bioavailability and Bioequivalence Study Reports) should contain the results of the bioequivalence studies performed or relevant data justifying the BCS-based biowaiver, if applicable.

Table 2. Summary of minimum RMP requirements for generic medicinal products

Part I	Part II								Part III	Part IV	Part V	Part VI
	SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
✓	N/A	N/A	N/A	N/A	N/A	N/A	‡	✓	✓	*	†	✓

European Medicines Agency and Heads of Medicines Agencies, 2017¹⁵

✓ Applicable

N/A Not applicable

‡ Relevant only if the originator product does not have an RMP and its safety profile is not published on the CMDh website

* Relevant only when a post-authorisation efficacy study was imposed for the originator product

† Statement of alignment of safety information in the product information is sufficient

Post-marketing medical writing

Periodic Safety Update Report

According to Directive 2010/84/EU,¹⁷ generic medicinal products are usually exempt from Periodic Safety Update Report (PSUR) submission. However, for some products, the submission of PSURs is a condition of marketing authorisation. In addition, competent authorities are empowered to request the submission of a PSUR at any stage. This could be based on safety concerns relating to the emergence of new data or due to the lack of PSURs when the reference medicinal product is no longer marketed. Evaluation of the literature plays an integral part in the preparation of PSURs. Please note that literature should not only be presented in the PSUR; assessors also want to see a comment or conclusion on the risk-benefit balance. Even if no new literature is found for an active substance, the search terms and databases used should be mentioned in the PSUR.

The list of European Union reference dates specifies the substances for which PSURs for generic medicinal products are required.

Do not send PSURs which are not required! However, even where PSURs do not need to be submitted routinely, marketing authorisation holders still need to regularly evaluate the safety of their products and report any new safety information that affects the risk-benefit balance or the product information.¹⁸

Medical writers may also be asked to write a PSUR for a marketing authorisation for a generic drug outside of the EU, e.g., in Eastern Europe. If a PSUR is required for a generic drug, the requirements as to the content are the same as for the originator medicinal product.

Addendum to the Clinical Overview

An Addendum to the Clinical Overview (ACO) is submitted during a marketing authorisation renewal and basically follows the same format as a PSUR. The aim is to present all relevant safety and efficacy information since the granting of the marketing authorisation or the last renewal, along with a critical discussion of the risk-benefit balance. For renewals of products authorised under Article 10(1), a shortened procedure can be applied, in which case no ACO needs to be submitted.¹⁹ There are, however, exceptions to

this rule. In Austria, for example, an ACO always needs to be submitted for national authorisations or, in the case of a decentralised procedure, if Austria is the Reference Member State. This requirement applies irrespective of the recommendations published in the CMDh Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedures.²⁰ It is always worth checking the national requirements! In addition, ACOs are also requested by many national authorities outside the EU. The ACO should cover the period from the date of approval to the date of submission of the renewal. Use GVP Module VII¹⁸ on PSURs as guidance for preparation of the ACO and use the structure given in the CMDh Best Practice Guide.¹⁹

Other post-marketing documents

Other post-marketing medical writing for generics often involves pharmacovigilance activities, such as updates of RMPs or the preparation of educational materials. The frequency of RMP updates should be proportionate to the risks of the product. RMPs are continually updated throughout the product life cycle, as new information becomes available. Companies need to submit an updated RMP at the request of a competent authority or whenever new information may significantly affect the risk-benefit profile or as a result of an important pharmacovigilance or risk-minimisation milestone being reached.

When updating an existing RMP prepared according to revision 1 of GVP Module V, it may be necessary to adapt the safety concerns according to the current definitions (see above).

Conclusion

Medical writing for generics poses its own challenges and requires some specialist knowledge. The skills of a professional medical writer might be repeatedly required throughout the life cycle of a generic medicinal product. Getting familiar with the relevant guidelines, including national requirements, is essential to prepare for this task.

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Medical writing for generics poses its own challenges and requires some specialist knowledge.

Conflicts of interest

The author declares no conflicts of interest.

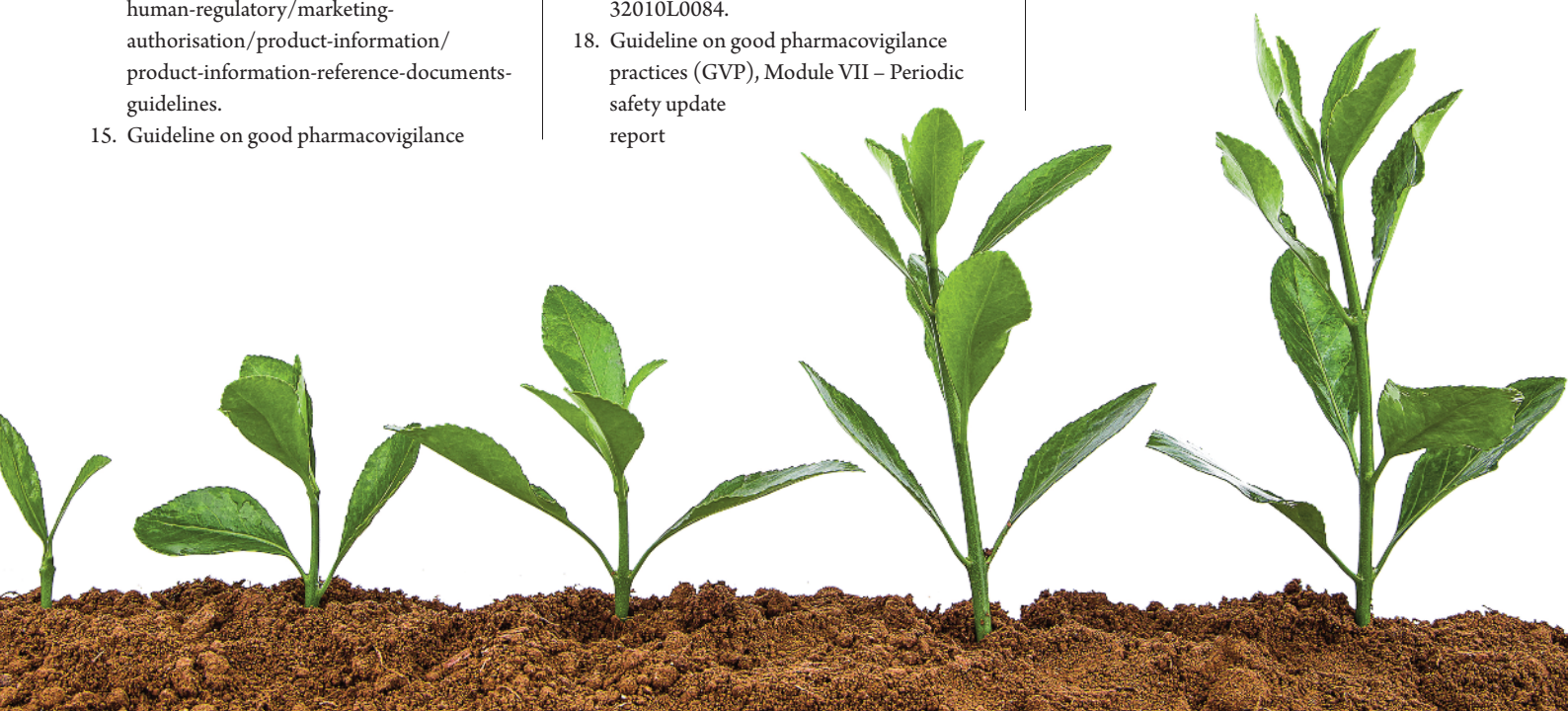
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Same but different: Basic tools for biosimilar and generic pharmacovigilance writing

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Abstract

Biosimilars are medicinal products, which are highly similar to an already authorised biological product; generics are identical copies of an already authorised chemical entity. As for any other medicinal product, biosimilars and generics require the writing of pharmacovigilance documents, such as DSURs, RMPs, and PSURs, for submission to health agencies. Due to the nature of biosimilars and generics, the medical writer needs to take into account some specifics while preparing pharmacovigilance documents.

Introduction

At a first glance, generics and biosimilars seem very much alike: both contain the same active substance (or a version of it) of already existing, authorised medicines (the reference medicinal product, or originator). However, a second look reveals some relevant differences between these two types of medicinal products.

A biosimilar is a biological medicinal product that is very similar to an already authorised biological drug.¹ Biologicals are produced using cells; these can be yeast, bacteria, animal, or plant cells. The characteristics of biologicals are determined by the used organisms and by the manufacturing process. Even minor

changes to this process can have a major impact on efficacy, safety, and tolerability of the product. Due to the inherent complexity of biological molecules (e.g., regarding molecular weight, spatial structure, etc., see Figure 1 opposite), a biosimilar is therefore never identical to its originator and can always only be similar. Biosimilars have come on the stage only a few years ago, and their manufacturing requires highly specialised expertise, staff and equipment, and substantial financial effort (see Figure 1).

All of this is contrary to a generic product, which is a copy of an already authorised chemical entity, the originator. Generics have been available on the market for decades and contain the same qualitative and quantitative composition in active substances and pharmaceutical form as the originator. Apart from proving bioequivalence to the originator, there is usually no requirement for generics to prove efficacy and safety in clinical studies; instead, reference to the originator's data is sufficient.

In summary, the main differences between biosimilars and generics are:

- **Complexity of the molecule:** biological

molecules are much more complex than chemical entities.

- **Manufacturing:** biological molecules are produced in pro- or eukaryotic cells, which is a much more complex and challenging process than a chemical synthesis.
- **Authorisation:** for biosimilars, not only bioequivalence studies need to be performed, but additional comprehensive comparability testing is required (see Figure 2).

All of the above mentioned has an impact on the scope of pharmacovigilance documents, as outlined in the following sections. The most relevant terms used in the context of pharmacovigilance writing for biosimilars and generics are summarised in Table 1 overleaf.

Pharmacovigilance documents required during a product's life-cycle

Depending upon the developmental stage of a product, various types of pharmacovigilance documents are required by legislation. A product's life-cycle is divided into pre-authorisation, submission and post-authorisation phases (see Figure 3), and each of these phases has its own requirements regarding the pharmacovigilance documents that need to be written and submitted.

Development phase: development safety update reports (DSURs)

The DSUR is usually the first safety document to be written for a new substance under development, and thus the first occasion where the important identified and potential risks of the compound are defined.⁶ In general, this first list of important risks needs to be set up carefully, as at this early stage



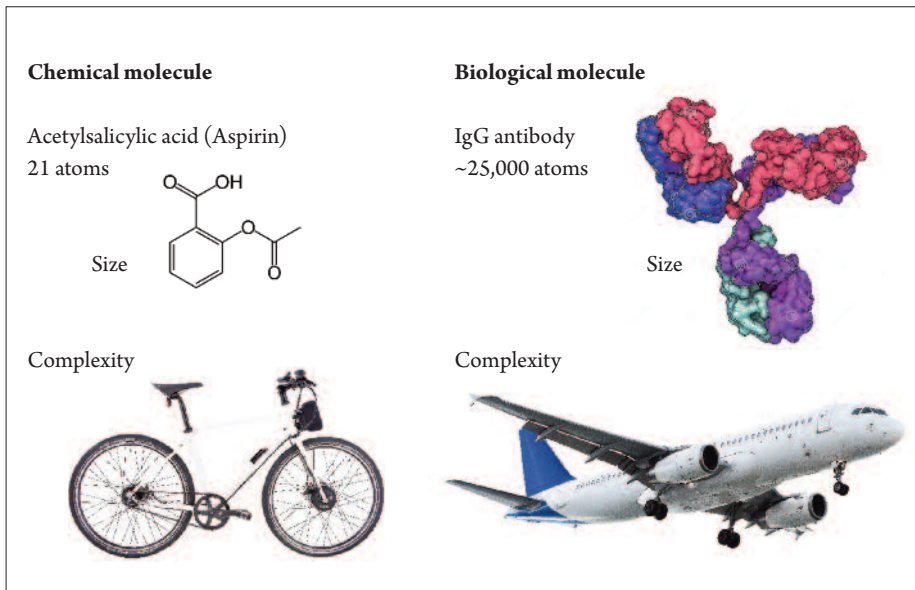


Figure 1. Comparison of biosimilar versus generic. Adopted from Sydow S.²

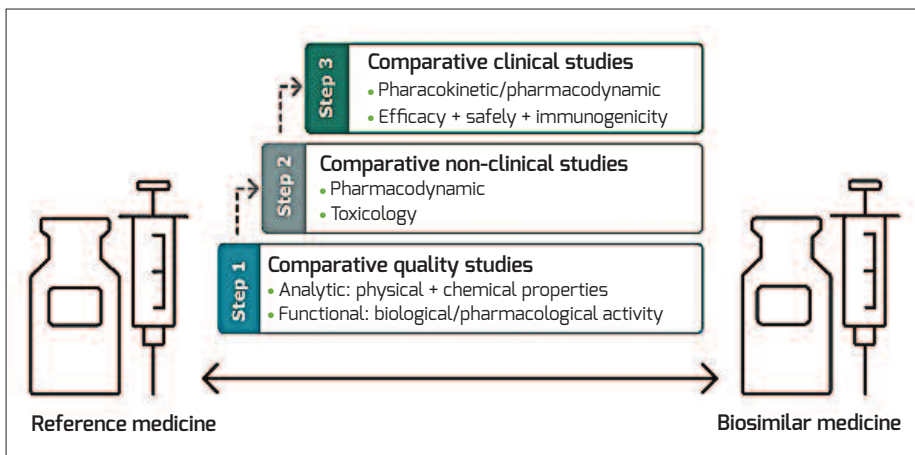


Figure 2. Development programme of biosimilars.

Source: <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation> (accessed 15 Feb 2019)

only limited information on a drug's risk profile is available, so that it is difficult to judge whether the inclusion of a risk is justified. In addition, the decisions made for the DSUR impact documents that are required later in the product life-cycle, like the risk management plan (RMP) and the periodic safety update report (PSUR). A careful evaluation is even more important since the

DSUR risk-section is cumulative, i.e., also resolved risks remain in the DSUR's list of safety concerns (albeit an explanation is added in the case of a resolved risk).

For biosimilars and generics, the situation is different. The set of safety concerns is based on that of the originator (lean approach) and, therefore, this first definition of important risks



Figure 3. Overview of pharmacovigilance documents required during a product's life-cycle.

is not necessary. However, some safety concerns of the originator may not apply to the biosimilar or generic product, because they are associated with, for example, a certain component, formulation, route of administration, or specific use of the originator. The lean approach facilitates DSUR writing in terms of this early decision-making on the important risks, and the originator's DSUR or RMP can even be requested and used as a basis for the generic or biosimilar product's DSUR. The downside is that a biosimilar/generic marketing authorisation holder (MAH) may have to deal with important risks in their DSUR (and potentially later on in other safety documents) that they might never find confirmed by their own data due to the limited clinical trial programme.

One aspect of the DSUR remains independent of the originator: the document periodicity. The DSUR development international birthdate (DIBD), which determines the document periodicity, is not harmonised with the DIBD of the originator. This is due to the fact that the DIBD is always determined by the authorisation date of the first clinical trial that is conducted worldwide for a substance, and this also applies to generics or biosimilars. This is true even if only small bioequivalence trials are conducted, which are standard for generic products.

For biosimilars, additionally, extensive comparability testing is required, so that DSURs include more data (from the biosimilar MAH's own clinical trials) than those for generics. Nevertheless, fewer trials and less data are required for a biosimilar than for the originator, which includes data from non-clinical studies and from the clinical development. Biosimilar development programmes require, in general, only phase I and phase III trials. Differences exist not only in the phases and number of trials that need to be conducted to obtain marketing authorisation, but also in the number of trial subjects that need to be included; for biosimilars, trials can usually be smaller than for an originator. Overall, DSURs for generics and biosimilars contain substantially less data than DSURs for the originator.

Submission phase: risk management plans (RMPs)

For initial marketing authorisation applications, an RMP is required for all medicinal products.⁷

As mentioned above, as a general rule, generic

Table 1. Pharmacovigilance writing for biosimilars and generics: basic definitions

Bioequivalence	Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.
Biological medicinal product	A medicinal product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.
Biosimilar medicinal product	A biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal) in the European Economic Area, and which has shown similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.
Development safety update report	Format and content for periodic reporting on drugs under development.
Generic medicinal product	A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.
Important identified and important potential risk	An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.
Periodic safety update report/Periodic benefit-risk evaluation report	Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.
Pharmacovigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.
Reference medicinal product (also originator medicinal product, innovator medicinal product)	The product that has been authorised first worldwide for marketing. The reference medicinal product is a medicinal product which has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e., with the submission of quality, pre-clinical and clinical data and to which the application for marketing authorisation for a similar biological medicinal product refers.
Risk management plan	A detailed description of the risk management system.
Risk management system	A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.
Risk-benefit balance	An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e., any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health.
Safety concern	An important identified risk, important potential risk or missing information.

Sources: GVP Annex I Rev 4,³ EMA homepage,⁴ GaBI online⁵



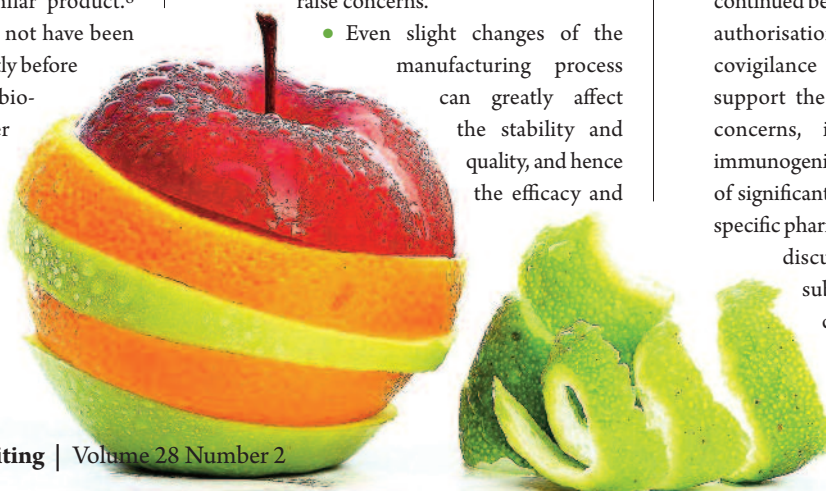
Medical writers need to be aware of specific considerations for biosimilars and generics, while at the same time ensuring pharmacovigilance documents are compliant with the regulatory requirements.

and biosimilar products follow the originators with regard to the list of safety concerns. For originator-specific risks that do not apply to the biosimilar/generic product, it is advisable to consult the health authority (HA) in advance. The RMP of the originator should be requested from the competent HA to align the safety concerns and the related pharmacovigilance and risk minimisation measures. For biosimilars, the comparability exercise could reveal differences in the seriousness and frequency of the risks as compared to the originator: the RMP should discuss these differences and assess the need for additional pharmacovigilance and risk minimisation measures for the biosimilar product.⁸ Since the originator's RMP may not have been updated for a longer period, shortly before submission the MAH for biosimilars/generics may consider asking for the most recent originator's RMP or checking the most recent public summaries on the EMA webpage. Although both generic and biosimilar RMPs follow the originators, the

RMP content requirements are different, thus reflecting the different characteristics of these products.

For biosimilars, an almost full RMP is required, with the exception of part II module SI ("Epidemiology of the target population").⁷ Due to the nature of biological active substances, some safety concerns are intrinsically related to manufacturing and immunogenicity. These aspects are reflected in the content requirements for the RMP:⁸

- Immunogenicity is not a safety concern *per se* and should not be included as an important potential risk if the data evaluation does not raise concerns.
- Even slight changes of the manufacturing process can greatly affect the stability and quality, and hence the efficacy and



safety, of the active substance. In some cases, the outcome of the comparability test for biosimilars may point towards a deviation from the safety profile of the originator. Significant changes to the manufacturing process trigger an RMP update to provide a specific risk analysis and discuss potential immunogenicity and clinical consequences of significant manufacturing changes.

- A risk might not be associated with the product itself (i.e., with the active substance), but with a component/factor/manufacturing process of the originator, so that the risk's seriousness and frequency for the biosimilar could be unclear as compared to the originator. If there are safety concerns or uncertainties related to the comparability test, the biosimilar RMP should include these and discuss the need for additional pharmacovigilance or risk minimisation measures.
- A specific aspect of pharmacovigilance monitoring for biologicals and biosimilars is the batch traceability. Traceability allows to clearly identify (by name and batch number) a biological product associated with adverse reactions. In case of safety concerns or immunogenicity, it is important to promptly identify the exact product, batch, and supply step. Therefore, the RMP part III ("Pharmacovigilance plan") will describe the clinical settings of use, product's name, batch recording and reporting, and related follow-up and signal detection activities.
- The RMP should include in part III any specific safety monitoring imposed on the originator and discuss its relevance for the biosimilar product.
- Since the pre-authorisation clinical evidence is usually insufficient to identify rare adverse effects, the pharmacovigilance plan of biosimilars must ensure close monitoring of the clinical safety on an ongoing basis and a continued benefit-risk assessment in the post-authorisation phase. Additional pharmacovigilance activities may be needed to support the characterisation of the safety concerns, including the potential for immunogenicity, or batch traceability. In case of significant manufacturing changes, batch-specific pharmacovigilance measures must be discussed in detail at the time of submission of the manufacturing change variation.

- The risk minimisation measures of the originator should be included in the RMP part V (“Risk minimisation measures”) and any deviations should be justified. The RMP part V should describe, in addition, measures planned to improve the biosimilar product’s traceability: for example, the summary of product characteristics (SmPC) and, as applicable, educational material and direct healthcare professional communication, should include a statement recommending that the name and batch number of the product must be recorded in the patient file. Further measures addressing traceability (e.g., sticky or tear-off labels in the product packaging, bar code scanning) are considered risk minimisation measures as well. The RMP for generic products can follow modified requirements, depending on the life-cycle stage and the regulatory settings (see Figure 2).⁷

In general, the safety specification/list of safety concerns is expected to be aligned with that of the originator or other generic products. In case of discrepancies between the approved RMPs of such products, the generic MAH should justify the choice of the safety specification. Exceptionally, if the MAH has more up-to-date data or a certain risk is not associated with the active substance, it is acceptable to propose changes in the list of safety concerns compared with the originator.

The guidance⁷ acknowledges three situations in the life-cycle of a generic product that may determine the need for a different format for the RMP part II (“Safety specifications”):

- The originator product has an RMP: as shown in Figure 4, only part II module SVIII (including the list of safety concerns) is required. The generic RMP is aligned with

that of the originator and there is no need to provide new data to determine the list of safety concerns. If the data collected for the generic product point towards removal or new identification of safety concerns compared to the originator, they should be included in part II module SVII.

- The originator product does not have an RMP, but the safety concerns of the substance are published on the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) website: the same approach as in the situation above can be followed.
- The originator product does not have an RMP and the safety concerns of the substance are not published on the CMDh website: the MAH should propose a list of safety concerns based on its own pre-clinical and clinical data, scientific literature, and the originator product’s information. The generic product’s safety concerns have to be characterised and summarised in part II modules SVII and SVIII, respectively.

The RMP parts III and V follow the originator. In case of specific pharmacovigilance or risk minimisation measures being planned or imposed for the generic product, these are included with the appropriate level of detail. If the originator product does not have additional risk minimisation activities, the information provided in the generic RMP part V can be limited to a statement that the safety information in the product information of the generic product is aligned with the originator. If the generic RMP includes additional safety concerns compared to the originator, the risk minimisation activities for these safety concerns should be presented in part V.

The guidance acknowledges the possibility to

adapt the contents of the RMP part VI (“Summary of the RMP”) to the extent indicated by data provided in the other parts of the document.

There can be further scenarios that are not covered by the guidance. In such cases, it is recommended to clarify individual solutions with the responsible HA.

Post-authorisation phase: periodic safety update reports (PSURs)

At the time of marketing authorisation, experience with and knowledge about the benefits and risks of a medicinal product are limited. This is even more the case for biosimilar and generic products, as these have a reduced development programme compared to regular medicinal products. In the post-authorisation phase, the PSUR periodically evaluates the benefits and risks of a medicinal product in everyday practice and with regard to long-term use. In the EU, the periodicity and data lock points (DLPs) for PSURs are defined in the European Union Reference Date (EURD) list, which is legally binding. The alignment of periodicity ensures parallel PSUR assessment of all products containing the same active substance.

The objectives and format of this type of periodic report are laid out in Good Pharmacovigilance Practices (GVP) Module VII-Periodic safety update report.⁹ The required format and content of PSURs in the EU guidance are based on those described for periodic benefit-risk evaluation reports (PBRERs) in International Council on Harmonisation (ICH)-E2C.¹⁰ To keep the terminology consistent with the one used in the EU, the new PBRER format is still referred to as PSUR.

Post-marketing data normally represent the main data source for a sound evaluation of a product’s benefit-risk balance/profile. However,

Figure 4. Minimum RMP requirements for initial marketing authorisation applications of generic products. Adapted from the GVP Module V (Rev 2), Table V.5⁷

Part I	Part II								Part III	Part IV	Part V	Part VI
	SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
✓	N/A	N/A	N/A	N/A	N/A	N/A	‡	✓	✓	*	†	✓

- ✓ applicable/relevant
- ‡ Relevant only if originator product does not have an RMP and its safety profile is not published on the CMDh website
- * Relevant only when a post-authorisation efficacy study was imposed for the originator product
- † Statement of alignment of safety information in product information is sufficient

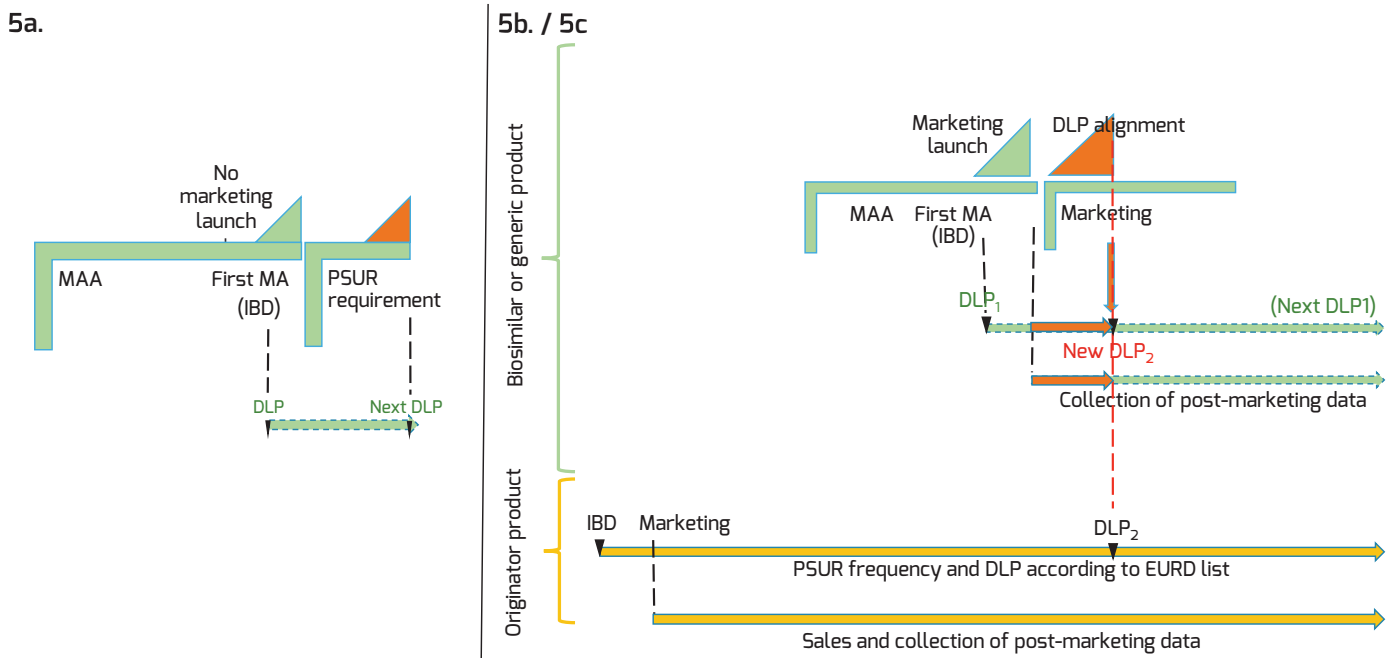


Figure 5. Post-marketing scenarios for generics and biosimilars.

5a. No post-marketing data available:

No launch, but PSUR requirement (launch is only possible when the marketing exclusivity rights of the originator product have expired).

5b. Little post-marketing data available:

Short marketing phase between launch and PSUR requirement due to the alignment of DLP between generic/biosimilar and originator.

5c. Post-marketing data available despite short post-marketing time:

A company holds MA for originator and generic product. One PSUR for all products with the same active substance.

Abbreviations: DLP = data lock point. EURD = European Union Reference Date. IBD = international birth date. MA = marketing authorisation. MAA = marketing authorisation application.

post-marketing data can be available to a different extent, depending on the regulatory circumstances and life-cycle stage of each product. A few examples are given in Figure 5.

There can be several biosimilars for one single originator on the market, owned by different MAHs. It is important that all safety data collected for these biosimilar products can be evaluated in parallel with data from other biosimilars and originators (PSUR EU single assessment procedure for biologicals for centralised procedure).⁸ Consequently, the periodicity of a biosimilar PSUR does not start with the biosimilar’s own international birthdate (IBD), as this is usually the case for newly authorised products, but instead the DLPs of the biosimilar PSURs are aligned with the one from the respective originator. The periodicity of the PSUR depends therefore on the originator’s DLP, which is not the case for the DSUR, as outlined in the section above.

With regard to PSUR format and content, a biosimilar follows the same rules as the originator, i.e., there is no separate biosimilars template in place. Nevertheless, there are some specific topics to be considered when writing a biosimilar PSUR, e.g.:

- The extent of biosimilar (non-) clinical data is limited compared to the amount of data that is usually available from a non-biosimilar development programme; this might sometimes require explanation.
- When relevant to signal assessment and interpretation of data, the MAH should include in the PSUR the method of calculation of batch exposure and a summary of the reporting interval batch information. The latter includes batch numbers and size, EU countries and regions of delivery, and, if possible, the number of batches delivered per country/region.
- The available safety information and any relevant differences from the originator should be evaluated in the context of the product’s life-cycle and the batch-specific exposure. Signal evaluation should assess whether the risk (particularly immunogenicity) is specific to a product name/batch or whether the signal applies to the product in general, and/or to all products containing the same active substance.
- If manufacturing changes trigger an RMP update, the evaluation of any associated

- clinical consequences/safety concerns should be supported by batch-specific data and exposure patterns. Depending on the impact of the manufacturing changes, the PSUR cycle of submission may be amended following the updated RMP, meaning that the PSUR submission will no longer be harmonised across biosimilars and related products.⁸
- Given a comparable safety profile between the biosimilar product and its originator, the safety concerns and their related pharmacovigilance activities and risk minimisation measures (e.g., participation in registries, SmPC wording, educational material, etc.) should be aligned with those from the originator and are not derived from the biosimilar’s data and observations (as described in the section on RMPs above). This might need to be explained and consistency with the originator needs to be ensured.
- Any changes to safety concerns, related measures, monitoring topics, SmPC, etc. are usually triggered by activities from the originator. It therefore needs to be ensured that these activities are aligned with the originator.

- Any deviations from the originator’s safety profile based on the biosimilar’s data and signal evaluation should be justified and adequately discussed.

Generic products can be exempted from submitting PSURs under certain circumstances (details are provided in GVP Module VII).² If a PSUR is required for a generic (e.g., if this is a condition of the marketing authorisation), the same rules as outlined in GVP Module VII apply;^{9,11} there is no separate template for generics. With regard to the content, similar considerations as mentioned above for biosimilars apply for generics, e.g., scope of (non-) clinical data, definition of safety concerns and related measures, alignment with the originator, etc.

Post-authorisation and beyond

The writing of the above-mentioned documents continues in the post-authorisation phase. Although the DSUR focusses on the development of a new medicinal product, the requirement for DSUR submission does not cease with the granting of the marketing authorisation. DSURs must be prepared and submitted on an annual basis as long as clinical trials are being conducted for the product. Once the clinical development programme has ended, DSUR writing can be discontinued.

The RMP is part of the submission dossier; however, the RMP is not prepared just once for the purpose of a marketing authorisation application (MAA) but is a living document that will be updated multiple times during the course of the evaluation of the MAA and thereafter. Triggers for RMP updates are plenty, e.g., *ad hoc* due to an agency request, changes in the safety concerns or benefit-risk evaluation, completion of milestones in the pharmacovigilance plan, etc. The RMP needs to be maintained as long as the product is on the market. Post-authorisation RMP updates prompted by safety concerns identified for the originator will be applied to its generic/biosimilar products (and vice versa), unless the trigger of the update is unrelated to the active substance or other common excipients.⁸ Since HAs do not inform a biosimilar/generic MAH about RMP updates of the originator, it is advisable to monitor the HA webpage to check for recent updates of public summaries.

PSURs must be written periodically after grating of the MAA according to the schedule

outlined in GVP Module VII,⁹ which usually is every six months during the first two years after initial placement on the market, then annually for the following two years, and thereafter every three years (unless required otherwise by the HA). The preparation of PSURs for generics and biosimilars is not a purely regulatory exercise but can lead to a more up-to-date understanding of the product’s safety profile, e.g., if the originator product has a low PSUR frequency requirement. The EMA guidance acknowledges the possibility for MAHs of biosimilar/generic products, as an exception, to propose changes in the list of safety concerns compared to the originator product,⁷ where justified by the MAH’s data and evaluations.

Conclusions

Biosimilars and generics show some specific characteristics compared to other types of medicinal products. As for any other product, pharmacovigilance documents are required for biosimilars and generics, based on the current legislation, the life-cycle stage of the product, and taking into account the individual characteristics as outlined above. The medical writer needs to be aware of these specific considerations for biosimilars and generics, while at the same time ensuring pharmacovigilance documents to be compliant with the regulatory requirements.

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Disclaimers

The opinions expressed in this article are the authors’ own and not necessarily shared by their employer or EMWA.

Conflicts of interest

The authors declare no conflicts of interest.

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Layperson materials in the sphere of biosimilars and generic medicines

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Abstract

Generics and biosimilars offer effective treatment alternatives to branded reference drugs at a lower cost. Despite their widespread use, patients have misconceptions regarding their efficacy and safety. Layperson materials offer an important means by which patients can be educated in this regard. Here, we provide an overview of generics and biosimilars, describe how layperson materials fit into this landscape from a patient-centricity and regulatory perspective, and provide example language that can be used when developing layperson-orientated materials for generics and biosimilars.

In recent years, the pharmaceutical industry has seen an increased recognition of the importance of patient- and layperson-orientated materials.^{1,2} This has likely stemmed from an acknowledgement of the key role that patients play as active contributors to the drug development process as study participants, as well as being the end-users of medicines. Additionally, patients and patient-advocacy groups are becoming increasingly mobilised and vocal in relation to taking control of their health decisions, and have a growing appetite for tailored information about the drug development process and available treatments.³ This increased appreciation for the central role of patients within health systems has manifested itself in two tangible ways:

1. an increase in patient-centred initiatives on the part of pharmaceutical companies and
2. new patient-focussed requirements set out by pharmaceutical regulators.

Patient centricity has been defined as “Putting the patient first in an open and sustained engagement of the patient

to respectfully and compassionately achieve the best experience and outcome for that person and their family”. In practice, this involves ensuring that people who need medicines have access to them; providing transparent and unbiased information on diseases, treatment options, and other available resources; equipping patients to make informed healthcare decisions; companies listening and responding to patient feedback with respect and humility; and providing easy-to-understand and convenient information in plain language.⁴

With regards to regulatory initiatives that have the patient in mind, European Union regulation 536/2014 stipulates that, in addition to providing a technical trial report, sponsors of clinical trials with at least one site in the European Union will be required to provide a trial summary “that is understandable to laypersons”. This requirement will become live following the launch of the online EU Clinical Trial Portal and Database, which is expected to happen during 2019. Having this online repository of plain language trial summaries will provide



patients with a valuable resource, empowering them to make informed healthcare decisions. Currently, these plain language trial summaries are only required for trials with a site in the European Union, though it is expected that other regulatory bodies will implement similar requirements in the future.

Given the outlined growing necessity for patient-orientated materials, combined with an increasing patient appetite for such materials, it is important to understand how best to communicate often complex scientific content to a “non-scientific” audience.

Key principles in the preparation of lay summaries

There are some key guiding principles that can be used when developing layperson materials, most of which can be grouped under three headings:

- **Format:** Documents should be as short as possible to improve accessibility and increase the likelihood that readers will read the whole document. Content should not be squeezed onto pages; rather there should be sufficient white space. Graphics can be used to break up text and to improve the aesthetic appeal of the document.
- **Word choice:** The choice of words used in these documents should facilitate readability and be understandable to people from the age of 12 years. Tools like the Flesch-Kincaid test can be used to assess readability. Short sentences can also aid comprehension.
- **Numeracy principles:** For example, presenting percentages rather than risk ratios or odds ratios, using whole numbers rather than decimals, and stating the numerator and denominator when reporting percentages.

Although following these guidelines will help develop quality layperson materials, there are still challenges.⁵ Perhaps the biggest challenge is the tension between the need to develop short

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documents with the fact that a large number of words is often required to explain a single medical term in lay language. For example, to someone with a basic knowledge of oncology, the single word ‘metastatic’ will be well-recognised. To someone with no medical knowledge, however, it may take several words to explain what this means: e.g., “a cancer tumour that has spread to other parts of the body”. It’s therefore easy to see how the length of a document can increase substantially. Other challenges include avoiding generalisations that may be perceived as promotional, communicating necessarily complex terms such as lists of adverse events, and selecting appropriate graph or chart types that can be understood by non-specialists.⁶

Recommendations have been provided by the European Commission on the development of layperson summaries in the EU regulatory context.⁷ However, these recommendations appear to be open to a degree of interpretation that may lead to variability between documents in terms of content and appearance. Furthermore, those who have traditionally been responsible for developing technical study reports may not be best suited to developing clinical trial lay summaries, given that their frame of reference has almost exclusively been related to high-level scientific language. Writing for a lay audience requires not only an understanding of the science, but also the skillset to communicate this information to a non-scientific audience.

Background to generics and biosimilars

Before it can be approved for its use in humans,

a new drug undergoes a protracted and complex stage of development and testing. This involves the systematic completion of laboratory-based studies, studies in animals, safety testing in humans, and large-scale clinical trials. Once complete, data from these studies are assessed by regulatory bodies such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), who decide whether or not the drug may be made available for use. This process is both lengthy and costly, and once approved, the drug makers may have limited time to make and sell the drug exclusively before the patent expires. Once this exclusivity period comes to an end other companies may seek to develop and market the same (or very similar) drug under a different name. Such drugs are known as generics and biosimilars; the key characteristics of generics and biosimilars are outlined in Table 1.

One of the key differences between a newly developed drug (i.e., a reference or originator drug) and a generic or biosimilar is the regulatory approval process applied. The reference drug will have gone through a lengthy rigorous development process, as described above. However, the manufacturer of a generic must simply provide evidence that the generic drug is equivalent to the reference. Equivalence must be shown with respect to identity, strength, purity, and quality, and it must be demonstrated that the generic medicine produces the same levels of the active substance in the human body as the reference medicine. This is usually achieved by conducting “bioequivalence” studies, demonstrating that the generic drug reaches the bloodstream in the same time and at the same concentration as the reference drug. Once the generic drug has been shown to have an identical structure *in vitro* and identical pharmacokinetics *in vivo* to the reference, it can be approved.⁸

In the case of biosimilars, the regulatory bodies compare molecules from the biosimilar to

Table 1. Key characteristics of generics and biosimilars

	Generics	Biosimilars
Composition	Simple molecules	Complex molecules
Storage	Stable and easy to store	Sensitive to storage and handling conditions
Mechanism of action	Do not induce an immune response	Induce an immune response
Manufacture	Straightforward to manufacture	Require intensive complex processes

Table 2. Example lay language for commonly used technical terminology in the sphere of generics and biosimilars

Technical term/concept	Lay language explanation
Generic medicine	<ul style="list-style-type: none"> • A generic medicine is a medicine that contains the same ingredients and has been made in the same way as another medicine already available for use by patients. • The medicine that is already available for use by patients is known as the reference medicine. • Generic medicines have a simple chemical design (or structure) and the manufacturing process for generic medicines is quite straightforward. • It is therefore possible to make generic medicines that are almost identical to the reference medicine.
Generic medicine approval process	<ul style="list-style-type: none"> • Reference medicines go through a very long and complex development process before they can be used by patients, to make sure they are effective and safe to use in humans. • This involves doing tests in laboratories and running several studies in humans known as clinical trials. • Generic medicines do not need to go through as much testing before they can be used by patients. • Instead, the makers of a generic medicine only need to show that their medicine works in the body in the same way as the reference medicine.
Biosimilar	<ul style="list-style-type: none"> • A biosimilar is a very complex type of medicine that has been designed to work in the body the same way as a medicine already available for use by patients. • The medicine already available for use by patients is known as the reference (or bio-originator). • Bio-originators have very complex chemical designs and require precise manufacturing processes. • This makes it very difficult to make a biosimilar that is exactly the same as the bio-originator.
Biosimilar approval process	<ul style="list-style-type: none"> • Bio-originators go through a very long and complex development process before they can be used by patients, to make sure they are effective and safe to use in humans. • This involves doing tests in laboratories and running several studies in humans known as clinical trials. • Biosimilars do not need to go through as much testing before they can be used by patients. • Instead, the makers of a biosimilar need to show that there are no major differences between their medicine and the bio-originator. This involves doing tests in laboratories and doing one clinical trial in patients to show that the biosimilar has a similar level of effectiveness and safety compared with the bio-originator.
Regulatory body/agency	<ul style="list-style-type: none"> • A committee of experts that reviews laboratory and clinical trial data for a medicine and decides whether the medicine can be used safely in patients.
Bioequivalence	<ul style="list-style-type: none"> • Two drugs are said to be bioequivalent if, when taken at the same dose, they reach the same concentration levels in the body and reach these concentrations after a similar period of time.
Immunogenicity	<ul style="list-style-type: none"> • Immunogenicity is the term used to describe the process of the body's immune system being activated against a perceived external threat. This can sometimes happen when patients take biosimilars.
Pharmacokinetics	<ul style="list-style-type: none"> • Pharmacokinetics describes the study of how a drug moves in the body. This relates to the maximum concentration a drug will reach in the body, how long it will take for a drug to reach the maximum concentration, and how long it will take for a drug to leave the body.
Pharmacodynamics	<ul style="list-style-type: none"> • Pharmacodynamics describes the study of how a drug affects the body. For example, establishing whether a drug speeds up or slows down certain normal biological processes in the way it was designed to do.
<i>In vitro</i>	<ul style="list-style-type: none"> • <i>In vitro</i> relates to study techniques that are done on cells or molecules outside of their normal living environment. For example, studies done using test tubes in the laboratory.
<i>In vivo</i>	<ul style="list-style-type: none"> • <i>In vivo</i> relates to study techniques carried out using whole living things such as animals or humans.

those of the reference drug to make sure that there are no meaningful differences that would affect how the drug works in the body. In practice, this involves establishing that the new medicine is similar to the reference in its physicochemical characteristics, composition, and *in vitro* biological function (based on a wide range of relevant assays). Additionally, a single pharmacokinetic study must be conducted to establish equivalence, and a single suitably-sized randomised trial conducted to demonstrate clinical and safety equivalence (including immunogenicity).⁸ Biosimilars may be approved

via “extrapolation”, a process that allows approval of a biosimilar in a non-studied indication, based on studies in other indications. Extrapolation is permitted by regulatory authorities providing biosimilarity has been established and there is a scientific justification.

Lay summaries in the sphere of generics and biosimilars

What then is the role of lay summaries in the sphere of generics and biosimilars? Generics and biosimilars are often copies of well-established well-known drugs for common diseases. Add to

this the fact that they are far less expensive than reference drugs; therefore, generics and biosimilars are widely used by the general population. Despite their widespread availability and use, patients still have misconceptions about these types of medicines, including that generic drugs are less effective and take longer to work, are not safe, and are manufactured in substandard facilities.^{9,10} Here then lies one of the key reasons why lay person materials are important in this context: to ensure that patients understand that generics and biosimilars are of the same standard as the original ‘branded’ reference drug, and are

not in any way “substandard” because of their lower price.

While clinical trials are not necessary for the approval of generics, and therefore not subject to the requirement of EU regulation 536/2014 to have an associated lay person summary, sometimes the manufacturers of a generic drug will run a trial comparing the generic to its reference. In such cases, the trial sponsor will be required to develop a lay person summary in addition to the technical trial report. With regards to biosimilars, because a single clinical trial is required to establish clinical and safety equivalence, then a corresponding lay person summary will be required. As such, from a regulatory perspective, lay summaries of clinical trials may be more prevalent for biosimilars than generics.

Aside from the regulatory imperative for clinical trial lay summaries, given the increasing move towards patient centricity, it may be prudent for the makers of generics and biosimilars to develop layperson materials as standard practice. In so doing, they will help to educate patients, empowering them in their treatment decisions.

Describing the clinical trial process in layperson language can be challenging at the best of times, and this arguably becomes more complex by adding generics and biosimilars into the equation, because of the need to explain complex processes and procedures like pharmacokinetics, pharmacodynamics, and bioequivalence. As such, we have provided some suggested wording that writers may find helpful to use when developing layperson materials related to generics or biosimilars (Table 2).

Conclusions

Generic medicines and biosimilars are widely used, yet there is large scale misconception among patients regarding their safety and effectiveness. Layperson materials therefore represent an important way to educate patients in this regard, helping them to make better-informed treatment decisions. Fewer clinical trials are required in the development of generics and biosimilars compared with reference or originator drugs. However, there are still circumstances where trials are carried out in this setting, and where there will therefore be the requirement for a trial lay summary, in line with EU regulation. Outside of the regulatory sphere,

while not mandatory, it may be prudent for the manufacturers of generics and biosimilars to develop layperson materials as standard practice, given the increasing appetite for, and importance of, patient-orientated materials.

Conflicts of interest

The authors have ownership interest in Lay Summaries Ltd.

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Insulin biosimilars



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Abstract

Insulin was first purified in 1921 by Frederick Grant Banting and Charles Herbert Best at the University of Toronto. Soon after, the benefits of using insulin to treat diabetes was discovered, the patent was sold to the University of Toronto for \$1, and Eli Lilly received the contract to manufacture insulin. Banting believed that insulin must be widely available for treating diabetes. A century later, insulin is so expensive that 50% of the estimated 100 million patients that need it lack reliable access. With many of the patents for insulin expiring and forthcoming changes

to the US biosimilar regulations, things should be about to get better for people with diabetes. Biosimilar insulin products are expected to reach the US markets, and it will be interesting to see who achieves success.

Insulin was first purified from an animal pancreas in 1921 at the University of Toronto by Frederick Banting and Charles Best. Professor John MacLeod and biochemist J.B. Collip helped with this endeavour. Then in a paramount development in 1922, it was first used to treat a person with diabetes; the scientists went on to receive a Nobel Prize in 1923.¹ They soon recognised the significance of their finding to help people with diabetes mellitus and so sold their patent for \$1 to the University of Toronto. Banting wanted insulin to be mass-produced and widely available. He said "Insulin does not belong to me; it belongs to the world." Let's fast forward to 2019. An estimated 100 million people live with diabetes worldwide, yet more than half do not

have access to reliable and affordable insulin. High prices of insulin are a significant cause.²

What is insulin and why is it important?

The cells in our body need sugar for energy to drive cellular metabolism and function. When we eat, carbohydrates are broken down into glucose (sugar), which is the primary source of energy. But the sugar cannot enter the cells directly. After a meal, glucose levels in the blood increase and beta cells in the pancreas secrete insulin, an important anabolic hormone. Insulin then attaches to the cells around the body, helping them to take up the circulating glucose from the bloodstream. When there is an excess of glucose in the blood, insulin helps store the excess glucose in the liver as glycogen. Between meals or while exercising, when the cells need more energy and blood glucose level is low, this stored glucose in the liver is made available and gets used up by the cells that need it.

Blood glucose concentration needs to be maintained in a narrow range to prevent long-term health issues, including weight gain, and for

overall wellbeing. Thus, insulin plays an important role in regulating the blood sugar levels and maintaining it within a narrow range.

Diabetes is a chronic condition; there are two types. Type 1 usually occurs in young people and type 2 develops in older people. Approximately 1.25 million children and adults in the US have type 1 diabetes.⁴ People living with type 1 diabetes cannot maintain their blood sugar level in the normal range because the beta cells are damaged and the pancreas makes little or no insulin. It is an autoimmune disease initiated by cytokine rich natural killer cells. The regulatory T cells activity is compromised and cell mediated β -cell destruction via apoptosis dominates. Cellular and humoral components of the immune system involved in type 1 diabetes can be detected for months or sometimes years before the onset of clinical diabetes. It is believed to be caused by a combination of genetic and environmental factors.⁵ β -cell death means type 1 diabetics need daily insulin therapy. In people with type 2 diabetes, either the pancreas does not produce enough insulin or the body does not use the insulin properly. Type 2 diabetics can initially control their blood glucose with diet and exercise and may need addition help with oral glucose-lowering medication. But as the condition progresses insulin therapy might become necessary to maintain blood glucose levels. Therefore, people with type 1 diabetes need insulin for survival and many with type 2 diabetes need insulin therapy as well.³ Poor long-term blood sugar control has been shown to lead to complications such as cardiovascular disease, kidney failure, nerve damage, and eye problems.

Three large manufacturers (Eli Lilly & Company, Novo Nordisk, and Sanofi) hold 96% of the global insulin market share. These drug companies have successfully kept insulin under patent from 1923 to 2014 by making incremental improvements to their products, which has kept the current price of insulin high. The number of people living with diabetes in the US is 30.3 million as of 2015. In 2017, the US healthcare expenditure on people with diabetes was 15 billion dollars. However, as these patents have expired, the insulin market will open worldwide. Therefore, biosimilar insulins have been a subject of great interest for patients, healthcare community and governments.

What are the differences between generics and biosimilars?

Generic drugs contain the same active ingredient as the originator product and are made from simple small, well-defined molecules that do not require complex modifications. However, the inactive excipient ingredients can be different. Generic drugs are administered in the same dose as the originator product and approved to treat the same disease. The manufacturing process is simple and must follow the same standard FDA good manufacturing practice regulations as the originator product. No preclinical or clinical studies are required and the approval process is straightforward. The investment required is around \$2 million to \$3 million.

On the other hand, biosimilars are complex molecules with post-translational modifications. They require a more complex manufacturing process. Unlike generics, they are not copies; they are similar to the originator product. The required investment is around \$3 billion and they take longer to reach the market. Biosimilars also have to go through a phase III clinical trial before reaching the market.

Biologics include products such as vaccines, antibodies, and blood components. They are complex molecules derived from micro-organisms, animals or through biotechnology techniques and contain sugars, proteins and nucleic acids. A biologic is different from chemically synthesised drugs where the structure is known. Insulin is a typical example of a biologic.

The manufacturing protocol for biologics is proprietary information known only to the originator pharmaceutical company. This is to prevent other manufacturers from producing copies that are identical to the originator biologic product. Therefore, biosimilars, which are very similar to the FDA approved originator biologic product, are manufactured differently. The clinical studies for biosimilars must show no difference in comparison to the reference product in terms of safety, purity and potency.^{6,7}

Biosimilar Insulin and the FDA

In total, there are 11 biosimilars currently approved in the US. Basalgar is the only approved insulin biosimilar; however, it has been classified as a follow-on to the basal insulin Lantus. What

is a follow-on? Follow-on is a copy of an originator biologic product and is approved under the Food, Drug & Cosmetic Act (FD&C) 505 (b)(2) pathway. Basalgar was introduced by Eli Lilly & Company in 2015. To be approved, a product has to be shown to be bioequivalent to the reference biologic. The applicant relies on the safety and efficacy data from the published studies for the reference biologic to support the application. Additional clinical trials may be required for the FDA to approve follow-on biologics.

Manufacturing of biologics is challenging and well regulated. The Biologics Price Competition and Innovation (BPCI) Act of 2009 was signed into law via the Patient Protection and Affordable Care Act on March 23, 2010. The approval of biosimilars under these new regulations is challenging and requires a series of studies. For example, analytical studies demonstrating that the product is highly similar to the reference product, animal studies, toxicity studies and a range of clinical studies that include pharmacokinetic, pharmacodynamic and immunogenicity studies. Immunogenicity studies are significant, as even a small difference in the structure of the biosimilar could elicit an immune response. Immunogenicity study is important

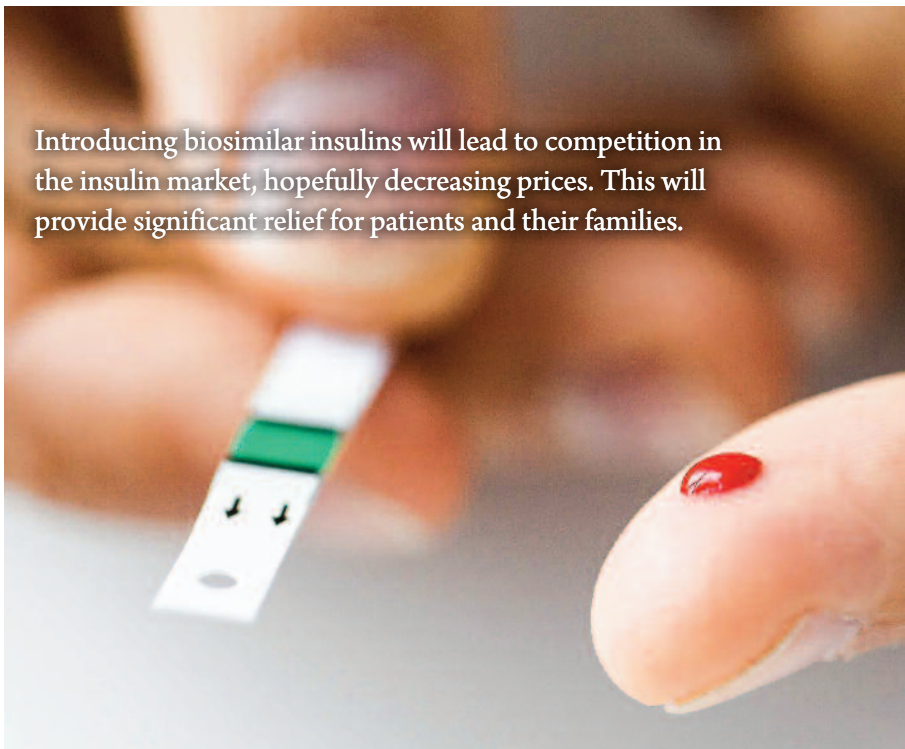
for a product like insulin which would be taken by the patient on a regular basis.

Any uncertainty must be addressed with additional studies.

Currently, there are separate approval pathways in the US, one for biosimilars and one for follow-on biologics. However, the less stringent

FD&C (follow-on) act will soon give way to the more stringent BPCI Act (biosimilar). When the BPCI Act was initiated, it came with a 10-year transition period. During the transition period, a biosimilar product application must include a reference product approved under section 351 of the Public Health Service (PHS) Act. However, no insulin has yet been approved under the PHS Act as an exception was made during this transition period, where applications for drugs such as insulin could be submitted as follow-on biologics until March 23, 2020. For the follow-on biologics application, there is no need to present a reference product approved under section 351 of the PHS Act. This is how Eli Lilly was able to get the approval for Basalgar as a follow-on insulin. The safety and efficacy of

In total, there are 11 biosimilars currently approved in the US.



Introducing biosimilar insulins will lead to competition in the insulin market, hopefully decreasing prices. This will provide significant relief for patients and their families.

Lantus was used to support the application. With March 23, 2020, approaching, the pharmaceutical companies are waiting. They do not want to submit a follow-on biologic application as we are nearing the cut-off date. The applications for biosimilar insulins have to wait as well.

Many clinical trials with biosimilar insulins are being carried out in the US. For example, Basalgar has been subjected to various clinical trials and has undergone pharmacokinetic, pharmacodynamic and immunogenicity studies. Three other potential biosimilar insulins have completed their phase 3 clinical trials.⁶

Biosimilar Insulin and EMA:

LY2963016 insulin glargine was the first biosimilar introduced in Europe. Following this, many biosimilar insulins have been introduced to the European market. EMA developed the guidelines for biosimilars 10 years ago. It involves both preclinical and clinical evaluation. Pre-clinical evaluation includes physical characteristics, structural characteristics, and analysis of the purity and impurities. The evaluation process also includes phase I and phase III clinical trials. This would include pharmacokinetic, pharmacodynamic and immunogenicity studies. Any uncertainties had to be supported by additional studies in the application.⁷

Interchangeability:

Interchangeability will be a major concern with

insulin biosimilars. It will address questions such as, can a prescriber switch between the reference product and a biosimilar? What will happen if the patient substitutes the reference product without a prescriber's consent? The current European regulations do not require studies showing evidence of interchangeability. With the new FDA guidelines, applicants for biosimilar products can submit studies that would classify them interchangeable.^{6,7}

Conclusion

When all the regulatory hurdles are overcome by biosimilar insulins, a huge market is awaiting them. Introducing biosimilar insulins will lead to competition in the insulin market, hopefully decreasing prices. This will be significant relief for patients and their families. Once biosimilars reach the market, the transition is not expected to be smooth. To help overcome the hurdles of substitution and interchangeability, all necessary support and education must be given to physicians, nurses, and the patient community. They must understand that biosimilars are similar to the originator products but not the same. Patients should be made clearly aware about the product they are prescribed and how it might differ from the product they were using before. If there is an adverse event, the patient should know which product they took. Comfort and familiarity of the delivery devices used with biosimilar insulins will also play a role in their

success. We do not know what the initial cost differences would be when the biosimilar insulin enters the US market or how prices will change over the years. The costs of insulin in most of Europe is one-sixth of what it is in US. Insulin prices have tripled in US in the last decade. This has led to people cutting back and skipping insulin doses, putting their health at risk. Now we just have to wait and watch and hope for relief for the patient community.

Conflicts of interest

The author declares no conflict of interest related to this article.

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Biosimilars: Change, challenge, and accomplishments

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Abstract

Since the first biosimilar product was approved in Europe in 2006, there have been many developments in the global regulatory environment, and the healthcare community's understanding and acceptance of biosimilars. However, there are still a number of challenges in developing, registering, and marketing biosimilar medicines, with the ultimate objective always being to increase competition, drive down costs, and increase access to biological medicines. This article examines progress to date in the establishment of the biosimilar market, challenges in bringing biosimilars to patients, the impact biosimilars have had, and potential future trends.

Establishment of the biosimilar market

Various terms have been used to describe biosimilar medicinal products: "similar biotechnological product" (WHO), "follow-on protein" (US), "subsequent entry biologic" (Canada), and "Similar Biological Medicinal Product (Biosimilar)" (EU). However, this latter term, abbreviated to "biosimilar" captures the essence of both the opportunity and the challenge represented by this type of medicine.¹

In this context, "Bio" indicates a biological medicinal product. These products are typically complex protein-based molecules, which may

also incorporate carbohydrate and lipid moieties as well as other post-translation modifications. They are usually generated by exploiting living organisms as production systems. Biological medicines differ from small molecule medicines in a key respect as they are not produced by a defined chemical synthesis process. This results in any biological medicine having a degree of intrinsic variability. Biologic products will also have a certain amount of batch-to-batch variation, arising from variations in manufacturing process steps e.g., fermentation, cell separation/disruption, purification, filtration.

However, their complex nature also means that biological medicines can be used to treat serious and chronic conditions that are themselves complex, such as cancers and autoimmune diseases. They have the potential to address a range of unmet medical needs and are key

enablers of the trend towards increasingly personalised medicine.

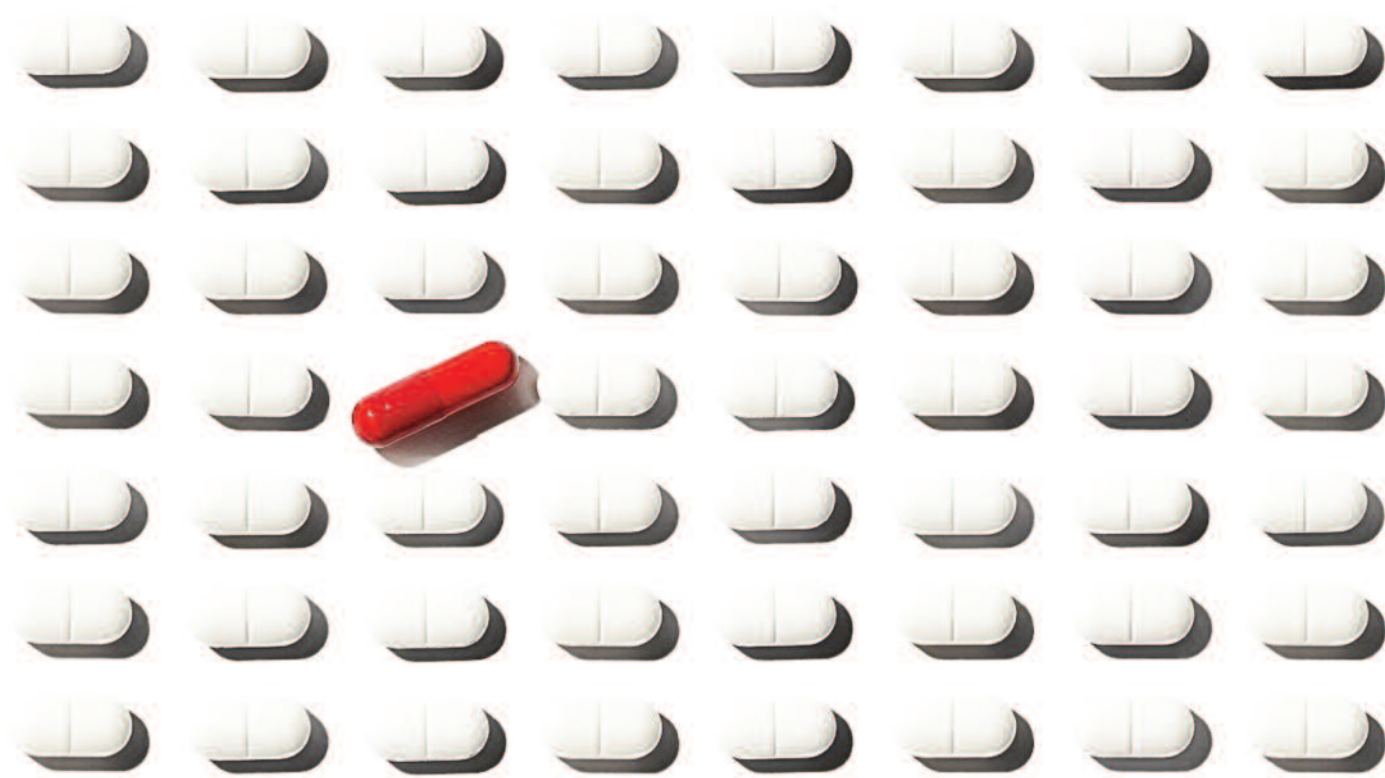
At the same time, the cost to develop, register, and manufacture biological medicines, along with the premium that goes with novelty and innovation, means that treatments can come with a high price tag. This is why the highest-selling biological medicines are currently generating worldwide revenues in the multi-billion euro range.

Thus, cost can be a barrier to treatment, and there is a need for enhanced competition in the market for biological medicines, as this traditionally drives down costs and increases accessibility. For small molecule medicines this competition arises from generic products, manufactured using chemically identical Active Pharmaceutical Ingredients as originator products.

As the intellectual property protection of the

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earliest biological products ran out in the early years of this century, biological manufacturers took the opportunity to develop, register, and launch their own versions of these medicines. The regulatory environment around biological medicines was also changing around this time, beginning to provide routes for establishing similarity between these new products and their original counterparts.

In 2005, the European Medicines Agency published guidance on biosimilar products, establishing:

“A biosimilar is a

A biosimilar product cannot be viewed as a “generic biologic” medicine, which has significant implications for their development, regulation and marketing.

biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA.”²

The term “similar”, interpreted in line with the WHO definition, thus leads to a requirement to demonstrate “an absence of relevant difference in parameters”.

Since biological products have an inherent variation in their properties, the biologic Active Pharmaceutical Ingredient in a biosimilar cannot be identical to the

reference product. This leads to the inevitable position that a biosimilar product cannot be viewed as a “generic biologic” medicine, which has significant implications for their development, regulation, and marketing.

Challenges in bringing biosimilars to patients

The ultimate objective in developing any new medicine is to provide a safe and effective treatment option for patients. However, a number of other stakeholders are involved with different needs and perspectives, which are critical to the successful development, authorisation, and marketing of a biosimilar.

Table 1. Key terminology

Term	Definition
Biological medicine	A complex, protein-based medicinal molecule generated in a biological system
Small molecule medicine	A chemically manufactured medicinal molecule, typically <900 Daltons in size
Active Pharmaceutical Ingredient	The ingredient in a pharmaceutical product that is biologically active
Originator or reference product	An authorised biological medicine used as a reference for developing a biosimilar
Biosimilar	A biological medicine that is highly similar to the originator product in terms of biologic activity, immunogenicity, efficacy, and safety
Non-originator/non-comparable biologic	A biological medicine intended to mimic a reference product that has not been through a rigorous comparability exercise with the reference product

Analytical characterisation



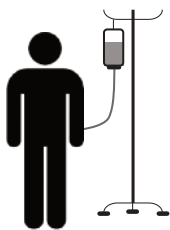
- State-of-the-art validated analytical methods and appropriately qualified characterisation methods must be applied to demonstrate the similarity of the quality attributes of the biosimilar and reference products.
- Addressing the biophysical and biochemical properties of the Active Pharmaceutical Ingredient, the biological activity, assessment of product and process impurities, and (where applicable) immunochemistry.
- Together, these data provide the justification for allowing reduced clinical and non-clinical submissions, so are expected to comprise over and above the amount of data usually submitted for a biological medicine.

Non-clinical evaluation



- The minimum requirement is a head-to-head repeat-dose toxicity study carried out with the final formulated biosimilar product.
- The precise requirements and balance of in vitro to in vivo studies will be driven by the category and complexity of the biosimilar product. However, overall, they must add to the comparability exercise and be designed to show any differences between the reference and biosimilar product.
- Informed by the characterisation data and knowledge of the manufacturing process, more limited studies may be justified compared to a novel biological medicine.

Clinical evaluation



- Clinical data required encompass pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity, generated using the final formulated biosimilar product. Studies must be designed to be sensitive enough to detect any relevant differences between the reference and biosimilar product.
- The volume of clinical information required is usually significantly less than for a novel biological medicine, but similar efficacy to the reference product must be demonstrated in an adequately powered, randomised, controlled trial, with appropriate blinding, and the safety profile data must be characterised in a sufficient number of patients.
- Equivalence study designs (with upper and lower comparability margins) are preferred, but non-inferiority designs (with only one margin) may be considered if appropriately justified. The comparability margins must be justified on the basis of clinical relevance, such that the margin represents the largest difference in efficacy that would not matter in clinical practice.
- Safety data can be expected mainly to detect frequent and short-term adverse events, but further close monitoring of clinical safety is usually necessary in the post-marketing phase.

Who are the stakeholders for (biological) medicines and what do they want?

- **Patient:** to receive the most effective treatment with minimal side effects
- **Healthcare professional:** to provide the best clinical outcomes for their patients
- **Payer:** to manage their budgets by selecting the most cost effective, appropriately efficacious treatment
- **Manufacturer:** to provide efficacious treatments for patients at a price level that sustains their business model

Since no two biologic products can be truly identical, a comprehensive comparability exercise is required to demonstrate that the biosimilar has no relevant differences from the originator or reference product in terms of quality, safety, and efficacy, with respect to the same indication. The reference product itself for this exercise must be selected carefully. Some considerations include:¹

- The dosage of the reference must be identical to the proposed biosimilar.
- The same reference must be used throughout the development of the biosimilar product, therefore a source and supply strategy for the reference is critical.
- The reference and proposed biosimilar product must have a demonstrably similar Active Pharmaceutical Ingredient. Given that the reference will almost certainly only be obtained as the finished drug product, likely with additional excipient materials, this must be factored into the characterisation strategy for the comparison.
- Usually, the reference must be registered in the same territory to which the biosimilar product application will be made, although this requirement does vary across markets.
- The reference product must be established over a sufficient period of time, in a sufficiently high patient population, and have been registered with a full dossier (i.e., it cannot be a biosimilar itself).

A company intending to develop a biosimilar product must therefore be able to make the considerable investment in expertise, facilities, and technology to create a biological medicine manufacturing process, analytical strategy, and clinical study approach. The process design and development must be carried out with the objective of yielding an output that corresponds

Figure 1. Key steps in demonstrating comparability of a biosimilar to the reference product



to the perceived target product profile of another manufacturer's product – but in the absence of any proprietary information.

This comparability exercise must demonstrate that the biosimilar product and the reference product are highly similar.¹ The key parts of this demonstration are summarised in Figure 1.

Bringing a biosimilar to market

Beyond the technical challenges involved in developing a biosimilar product and generating all the data required for approval, manufacturers must overcome regulatory (and potentially legal) barriers before attempting to gain sufficient market access and uptake to justify their initial investment. Regulatory and legal challenges have been particularly acute in the US market, where the abbreviated application pathway for biosimilar products did not come into force until 2010 and it was 2015 before the first biosimilar was approved. Furthermore, some approved biosimilar products in the US are not yet on the market, due either to ongoing patent litigation, or 'pay for delay' deals, whereby manufacturers agree to delay the launch of their products in the US in return for some benefit, such as earlier access to European markets.³

In terms of market access, a number of different factors influence a biosimilar product's progress and there is wide variation in policies and guidelines across markets. For example, in some countries biologic medicines have to go through a Health Technology Assessment, while in others this is not a requirement. Similarly, there are differences in tendering

A comprehensive comparability exercise is required to demonstrate that the biosimilar has no relevant differences from the originator.

processes, the approach to International Non-proprietary Name prescribing, and substitution.⁴

Ultimately, uptake is dependent on not only the availability of a biosimilar product to prescribers, but also the level of trust and understanding healthcare professionals and patients have in the product. Thus, education and appropriate marketing also play a critical role in ensuring a biosimilar medicine, once authorised, actually reaches patients who can benefit from it, and has the desired impact of driving competitive pricing in a market.

Impact of biosimilars on global markets

Since the ultimate objective of introducing biosimilar medicines is to increase competition, drive down cost, and increase accessibility, the key question is: how successful have biologics been in achieving this objective? In addition, it is important to understand what the future trends may be in biosimilar development. The earliest biosimilar products will soon reach the age that their respective originator products were when used as reference; is there any indication that this coincides with reduced momentum in the introduction of new biosimilar products?

The current biosimilar market

Currently, biosimilars are growing worldwide, with product approvals increasing ten-fold in the last ten years. In 2018, the EMA authorised 17 products,⁵ the FDA approved seven,⁶ taking the total numbers to 59 and 17 respectively. These represent the highest number of approvals in a year, to date.

Biosimilar products are available to treat a growing range of conditions, with corresponding increasing breadth in types of molecules and modes of action (Table 2).

The regulatory authorities of the larger pharmaceutical markets in the world are broadly aligned with the approaches to biosimilars described by the European Medicines Agency in 2005. Other regulatory authorities have been slower to provide formal guidance, notably in Japan (2009), Canada (2010), Brazil (2010) and the US (2010).⁷ China has recently adopted guidance (2015), and although applications are under review, no biosimilar products have yet been approved in this territory. As these regulatory approaches are clarified and harmonised, barriers to biosimilar development and authorisation are reduced, increasing the attractiveness and scale of opportunity to potential manufacturers.

There are also some emerging markets with less mature regulatory environments and more flexible approaches to international intellectual property considerations. Consequently, some countries have seen the development of "non-originator" or "non-comparable" biologic medicines, which have not undergone a rigorous comparability exercise with the reference product. For example, Reditux was approved in India in 2007 as a "similar biologic" without ever having been studied head-to-head versus the anti-CD20 monoclonal antibody reference product (rituximab). The approval was instead based on a single phase II study conducted in 17 patients.⁸ This raises obvious concerns regarding the insufficient evidence available on the efficacy and safety; however, products such as these will undoubtedly be impacting on the market in these territories.

As the most mature biosimilars market, Europe provides a good indicator of the impact they may be able to achieve around the world. A recent report identified the following key findings:⁹

- There has been a demonstrable decrease in price when biosimilar products enter the market place.
- The biosimilar product does not need a large market share for a reduction in price in the treatment area to occur.
- There do not need to be multiple biosimilar products available within a class to see price reduction in the total market.
- In some classes, reduction in the price of the originator reference product can reduce the impact of the biosimilar product in terms of market penetration.
- Where multiple biosimilar products are available in the same class, the first to market typically secures the highest market share.

Influencing factors and potential future trends

A number of different factors currently influence, or have the potential to influence, the scale of the continued opportunity for biosimilars and their continued attractiveness to manufacturers and investors. In turn, these trends will influence the future direction of the market and the further impact biosimilars can have on competitiveness, pricing, and accessibility. For example, the potential for combination therapies and personalised medicine, particularly in oncology, encourages manufacturers to develop a portfolio approach in their chosen disease areas. The addition of biosimilars to such portfolios potentially allows for easier development of treatment regimens involving multiple biological medicines, without the need for complex cross-manufacturer collaborations.

Manufacturers of originator biological medicines are adopting a range of tactics to maximise the return on their investments, many of which drive innovation or reduce prices e.g.,:

- Developing a next-generation medicine or ‘biobetter’ to supersede the reference medicine, such as Amgen’s Neulasta, a pegylated version of filgrastim, which is longer-lasting due to decreased renal clearance¹⁰
- Modifying the reference medicine to differentiate it from the biosimilar, as Roche have done in developing a subcutaneous (SC) formulation of MabThera, which can be

administered over five minutes vs. two and a half hours for the IV formulation¹¹

- Making market access less favourable for competing biosimilars by methods such as price cuts, negotiating supply deals, and initiating patent litigation.

The concepts of extrapolating new indications, switching patients between reference product and biosimilar, and interchangeability of reference product and biosimilar, are important factors that influence uptake of biosimilars that are not yet fully established in all markets.

Extrapolation is when a biosimilar is approved for use in an indication held by the originator biologic that has not been directly studied in a comparative clinical trial. Regulatory approval of biosimilars for new indications is made on a case-by-case basis after evaluating the totality of evidence. However, this allows substantial scope for interpretation, meaning different regulatory agencies can reach different decisions.¹² It is also worth bearing in mind that once a biosimilar is approved, it embarks upon its own post-approval regulatory life-cycle, distinct from its reference product. So, if the safety profile or Summary of Product Characteristics of either product should subsequently change, does the established biosimilarity remain? It is not currently clear how this would be managed and regulated.

When, how, and why to switch patients from a reference product to a biosimilar is another area where understanding, opinion, and clinical practice are still in flux. A key factor influencing whether a patient switches products is who makes the ultimate decision as to which product the patient receives. The drivers of the decision will vary depending on whether it is in the hands of clinicians or payers and what incentives are in place to encourage a change, which may range from financial benefits to manufacturers providing specific data on the switching process.

Going beyond decisions about switching is the concept of treating a biologic and its reference product as truly interchangeable (much as generic medicines can be) allowing, for example, pharmacy-level substitutions. Interchangeability is a matter of ongoing debate and not yet widely established. However, in 2017, the FDA issued draft guidance¹³ outlining the requirements for a biosimilar product to be authorised as interchangeable, such that “the

biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product”.

The conditions that must be met in the application are that the biological product:

- “is biosimilar to the reference product”
- “can be expected to produce the same clinical result as the reference product in any given patient”
- “[if] administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”

Whilst the FDA “Purple Book” lists 17 approved biosimilar products, currently none of these products has achieved the interchangeable designation,¹⁴ thus, it remains to be seen how the future availability of interchangeable products will influence the US market.

The FDA has also recently issued a statement stressing the importance of biosimilar products in providing patients with “lower-cost, high-quality products”.¹⁵ This statement indicated a change in the FDA’s guidance on separating the nomenclature of biological and originator medicines, in response to stakeholder feedback. The updated policy “will provide consistency among biologics and will help ensure health care providers and patients have confidence in the safety and effectiveness of any biological product on the market”, and is intended to make it easier to monitor the ongoing safety of products. Overall, the statement reflects a positive forward-looking position on the role of biosimilars in providing cost-effective, efficacious, and safe medicines for patients.

Conclusions

The introduction of biosimilars to markets across the globe has had some success in increasing competition and reducing healthcare costs, as evidenced by review of the European market. However, the regulatory environment is still evolving, at different paces in different markets, and achieving a balance between the different needs of the various stakeholders is still a work in progress. Nonetheless, it is clear that there remains significant opportunity for manufactur-

ers, further gains to be made in terms of competition and cost reductions within health-care systems, and scope for better treatment options to become available for patients.

Conflicts of interest

Martin Mewies is an employee of Woodley BioReg Ltd, which provides services to pharmaceutical industry clients, some of whom manufacture biologic medicines.

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Table 2. Biosimilar categories and examples

Category	Example indications	Example biosimilars
Anti-inflammatory and immune modulators	Rheumatoid arthritis	Amgevita
	Inflammatory bowel disease	Flixabi
	Psoriasis	Solymbic
	Ulcerative colitis	Zessly
Oncology targeted therapies	Wide variety of cancers e.g.,	
	• Breast cancer	Ogivri
	• Leukaemia	Truxima
	• Stomach cancer	Herzuma
	• Lung cancer	Mvasi
Hormones and cytokines	Diabetes	Abasaglar
	HGH deficiency	Omnitrope
	Anaemia	Binocrit

Abbreviation: HGH, Human Growth Hormone



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International Committee of Medical Journal Editors' requirements for sharing individual participant data from interventional clinical trials



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Abstract

Sharing of deidentified/anonymised individual participant data is rapidly becoming the norm. The International Committee of Medical Journal Editors recently implemented requirements for data sharing as a condition for considering publication of clinical trial reports in member journals. These requirements are: 1. manuscripts that are based on results of a clinical trial submitted on or after July 1, 2018, must contain a Data Sharing Statement at the manuscript submission stage; and 2. interventional

clinical trials that began enrolling participants on or after January 1, 2019, must include a Data Sharing Plan in the trial's public registration record. The full effect of these data sharing requirements and the resolution with other legal provisions still need to be resolved, especially regarding protection of personal information of clinical trial participants and commercially confidential information for clinical trial sponsors. Nevertheless, sharing of deidentified individual participant data from clinical trials will continue to expand.

Introduction

Most sponsors of clinical trials around the world are aware of the legal requirements to disclose information about their clinical trials in a publicly accessible database or databases on the Internet. Disclosure of information is based on the trial protocol for *new* clinical trials (*trial registration*) and on the clinical trial report for *summary results* of completed trials (*trial results posting*).

Complex legal mechanisms emerge when it comes to sharing deidentified/anonymised individual participant data (IPD) generated during a clinical trial. The recently introduced EU General Data Protection Regulation (GDPR) is a case in point: EU member states may have different interpretations of the GDPR when it comes to sharing data from clinical trials for purposes other than just the initially intended analyses (primary use) or evaluation of trials for further research activities (secondary use).

This article discusses the requirements of the International Committee of Medical Journal Editors (ICMJE) on Data Sharing Statements and plans for the sharing of deidentified/anonymised IPD from clinical trials. The topic is relevant to medical writers working on regulatory and medical communication documents as well as to data managers and statisticians who participate in collating and processing IPD. Of course, other stakeholders involved in planning, implementation, and reporting of clinical trials should understand the implications of IPD sharing and the commitments on data sharing that are expected to be made by the trial sponsors upfront *before* the trial has actually started. Upper management of the clinical trial sponsor also needs to be aware about these decisions and processes because, as described below, the data sharing commitments have wide and long-term implications for drug development and life cycle.

Legal requirements for public disclosure of information on clinical trials

The legal requirements for public disclosure of information from clinical trials are based on Regulation EU 536/2014 in the EU/European Economic Area (EEA)¹ and in the US on FDAAA Section 801² and its Final Rule 42

CFR Part 11.³ Failure to comply with Regulation EU 536/2014 (Articles 94 and 95 of the Regulation EU 536/2014¹) or the FDAAA/Final rule could result in civil monetary penalties or withholding of research funding.^{4–7}

Clinical trials may need to be registered and results posted at multiple sites. Some parts of the world have regional or country-specific requirements and expect the sponsor to register the clinical trial at a regional or national level. Moreover, in some cases, in addition to registration, summary results must be reported at study completion or after reaching a particular milestone in the trial conduct (e.g., after completing the primary endpoint; FDAAA 801/Final Rule).³ Keeping up with the various disclosure and transparency requirements can be a challenge – especially for sponsors of multinational trials.⁵

ICMJE requirements

In addition to the legal requirements for public disclosure, some organisations, such as the ICMJE, previously known as the Vancouver Group, also have recommendations and requirements for public disclosure. The ICMJE is a group of currently 16 full members (journal editors and representatives of related organisations), working together to improve the quality of medical science and its reporting.⁸

Over the past several decades, the ICMJE has implemented requirements for publishing in professional scientific and clinical journals, which is entitled “*Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals*”. The ICMJE also endorses the dissemination of information based upon the World Health Organization (WHO) definition of clinical trials as “*any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes*”.^{9,10} The ICMJE recommendations and requirements have been adopted by many other journals¹⁰ and although the recommendations and requirements are not legally binding, they will influence the likelihood of publishing results in peer-reviewed journals.

The
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and the Data Sharing
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journal.

Prospective registration of clinical trials in a public registry

One of the ICMJE’s earlier requirements (in 2004) was that clinical trials be registered in a publicly accessible database *before enrolment of the first patient*. Since then, such “prospective registration” is a condition for publication of trial results in all journals that have adopted the ICMJE principles, as evident in their instructions for authors.^{9–12} This applies to *all* interventional clinical trials (*including* Phase I trials) that began on or after July 1, 2005.¹⁰ The ICMJE accepts trial registration in ClinicalTrials.gov¹³ as well as in any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.¹⁴

Registering new clinical trials in an ICMJE-accepted register is now an established procedure for most clinical trial sponsors. Since this ICMJE initiative was introduced, registrations of clinical trials skyrocketed¹⁵ and opportunities for subsequent selective or biased reporting of trials plummeted.^{16,17} Timely registration (*before the first subject enrolment in the clinical trial*) can be easily established because all trial registries include the dates when the trial was first registered as well as when the first study subject was enrolled or randomised. These dates are routinely cross-checked by the journal’s editorial staff when a manuscript is submitted for publication.

Some journals may reject manuscripts that do not fulfil the ICMJE public registration criteria, while others may be more lenient. Nevertheless, in our experience, all journals insist on trial registration in an ICMJE-accepted public registry as a condition for manuscripts review, even if the trial is registered retrospectively.

Data sharing

Sharing of deidentified/anonymised IPD from clinical trials is not new. An obligation to share IPD has been encouraged for some time by many stakeholders, including academic institutions, the pharmaceutical industry, health regulatory authorities, medicinal product pricing agencies, patient lobby groups, investigative journalists, and public media representatives.^{18–22}

Sharing data from clinical trials benefits patients by pointing to new research questions that can lead to new discoveries. It also allows clinical trial results to be included in meta-



Sharing data from clinical trials benefits patients by pointing to new research questions that can lead to new discoveries. It also allows clinical trial results to be included in meta-analyses, which increases standards of evidence, and it allows published results to be confirmed, reducing bias.

analyses, which increases standards of evidence and it allows published results to be confirmed, reducing bias. Furthermore, data sharing provides a noble way to honour the generosity of clinical trial participants by increasing the utility of their data and thus the value of their contribution.^{21,23–25}

On January 1, 2014, EFPIA and PhRMA released a joint “Principles for Responsible Clinical Trial Data Sharing”.²⁶ These principles allow researchers to submit proposals to receive access to patient level data, protocols, and clinical study reports for new medicines approved in the US and EU after January 1, 2014. Similar commitments were adopted on January 15, 2018, by the IFPMA, in their “Principles for Responsible Clinical Trial Data Sharing”.²⁷

After an active and turbulent public discussion on the IPD sharing proposal by the ICMJE in January 2016, the ICMJE announced in June 2017 two requirements on sharing IPD, generated during interventional clinical trials:^{16,28}

1. Authors of manuscripts based on results of a clinical trial submitted on or after July 1, 2018, are asked to submit a Data Sharing Statement at the manuscript submission stage.
2. Interventional clinical trials that began enrolling participants on or after January 1, 2019, must include a Data Sharing Plan in the

trial’s public registration record.

In line with these ICMJE requirements (November 2017), the WHO International Clinical Trials Registry Platform expanded the Trial Registration Data Set to incorporate four new data elements that include a new field for the IPD sharing statement.¹⁴

The US-based ClinicalTrials.gov registry has added the IPD Data Sharing field in their “Protocol Registration Data Element Definitions” for new trial registrations.¹³ For interventional studies, a “Yes” or “No” answer is expected for Plan to Share IPD. Although the response to Plan to Share IPD is optional in the Protocol Registration and Results System, it is required by the ICMJE as part of the registration information for interventional studies.

It should be noted that EudraCT, the EU/EEA-based clinical trials register, does *not* have a dedicated field for the Data Sharing Statement. The EudraCT database is currently used for registering clinical trials and for posting results of trials that are under the EU/EEA jurisdiction.

The EudraCT database will be replaced by a new Clinical Trials Information System (CTIS) for all EU/EEA-relevant clinical trials, as specified in Regulation EU 536/2014. However, implementation of the CTIS has been delayed due to technical issues that should be resolved by late 2020. In the meantime, it is not

clear how the sponsors of trials performed in the EU/EEA will comply with the ICMJE data sharing requirements, given the lack of a data sharing field in EudraCT database.

The ICMJE expects that the Data Sharing Statement and the Data Sharing Plan will include the items listed below. Examples of possible responses are available in the editorial by ICMJE and on the ICMJE website.⁹

1. Whether individual de-identified IPD (including data dictionaries) will be shared
2. What data will be shared
3. Whether additional, related documents will be available
4. When the data will become available and for how long
5. What access criteria will be used to decide if data will be shared (e.g., with whom, for what types of analyses, and by what mechanism).

As stated by the ICMJE, data sharing requirements are not mandatory:

These initial requirements do not yet mandate data sharing, but investigators should be aware that editors may take into consideration data sharing statements when making editorial decisions.

Thus, if the authors of a manuscript are not prepared to share their data, a short statement, such as, “Data will not be shared”, should satisfy the new requirements. Nevertheless, as noted above, the authors’ response to Data Sharing

Data-sharing platforms are an alternative option for clinical trial sponsors to share IPD.

Statement may affect the editorial decision.

Similarly, describing the Data Sharing Plan is not required to register a trial in the ClinicalTrials.gov database, although a clear “Yes” or “No” is expected and the responses will be visible to the public as part of the trial registration record and history of changes. Furthermore, the Data Sharing Plan – including all changes to it – will be reflected in the subsequent Data Sharing Statement when the results of the trial are submitted to a journal for publication.

The final decision on how to deal with a submitted manuscript and the Data Sharing Statement rests with the editor of each journal. So far, it appears that many journal editors that follow the ICMJE requirements will grant manuscript authors a grace period and do not insist on a clear “Yes” to data sharing as a condition for publishing a manuscript. Nevertheless, some ICMJE member journals already maintain, or may choose to adopt as a condition of publication, stringent requirements not only for a positive Data Sharing Statement but also submission of the trial protocol and data analysis plan and their amendments at the time of manuscript submission. The latter is meant to avoid selective reporting, endpoint switching, or distorted interpretation of statistically non-significant results (“spin”), which continue to persist despite editorial advice and the existence of clinical trial registries.^{29–31}

Recently, several companies reported that editors of *JAMA* have asked for an *unredacted* trial protocol and statistical analysis plan as part of their review of submitted manuscripts. Redacted documents, however, will probably be made available to the public when a manuscript is published. Another company reported that, after submitting a manuscript to the *New England Journal of Medicine* together with proposed redactions to the trial protocol and statistical analysis plan, the company was asked for all commercial confidential information to be unredacted; the journal allowed for the personal protected data to remain redacted. The editors also asked for justification for all redactions.

Complex legal mechanisms emerge when it comes to sharing deidentified/anonymised individual participant data (IPD) generated during a clinical trial. The recently introduced EU General Data Protection Regulation (GDPR) is a case in point.

Highlights from a recent session on ICMJE requirements on Data sharing

At a Drug Information Association Medical Affairs (DIA) and Scientific Communications Forum held in Orlando, Florida, on March 18–20, 2019, it was noted that some ICMJE journals such as *PLoS* and *British Medical Journal* already require data sharing as a condition for publication. Other ICMJE journals have not yet taken a position on this; the expectation is, however, that further ICMJE

journals will do so in the future, as illustrated above by the recent experiences with manuscript submissions to *JAMA* and the *New England Journal of Medicine*.

The ICMJE requirements do not provide a set or prescribed time from when and for how long the IPD will be available. Rather, the decision is up to the individual trial sponsors when they register the trial. If a clinical trial sponsor indicates at the original registration stage that they are *not* willing to share data, this could have ramifications if the compound or product used in a clinical trial is out-licensed or partnered in a co-development agreement. For example, this could affect a decision to in-license the compound, the publication strategy for the compound, who is responsible for changing the “No” to “Yes” for sharing data in the registry, or who will provide the rationale of the change when the manuscript is submitted. Initial decisions regarding data sharing will very likely lead to further discussions between the sponsor and the in-licensing company or the co-development partner.

It was also clear from the speakers’ messages at the DIA meeting that clinical trial sponsors need to have well-defined, established internal processes with clear responsibilities for 1. the Data Sharing Plan and 2. evaluating data sharing proposals submitted by external researchers. The internal stakeholders responsible for these two items could include teams from Clinical Trial Disclosure, Therapeutics, Regulatory, Legal, Intellectual Property and Patents, and

Publication Planning. Finally, the time scale affecting these processes should be kept in mind; it can take more than 4 years to proceed from the initial trial registration and the Data Sharing Statement (e.g., on ClinicalTrials.gov) to submission of the manuscript to a journal for publication.

Responsibilities and expectations from users performing secondary use research analyses from shared data

The ICMJE acknowledges that some issues of IPD sharing remain unresolved. These include questions such as:

- What constitutes appropriate evaluation of the data (for secondary use)?
- How should scholarly credit be given to those who share data?
- What resources are needed for data access?
- How should data requests be transparently processed?
- How should data be archived?

The ICMJE welcomes creative solutions to such questions.²⁸ Many publications elaborating the underlying principles on the advantages and disadvantages of data sharing are already available. They highlight the perspectives and concerns of both researchers generating data (trialists) and the data users (external requestors wishing to repurpose the initial data for secondary use and analyses).^{24,32–34}

IPD sharing and its consequences are relevant not only to medical writers who collate and describe the trial data but also to data managers and statisticians who are an integral part of collecting, collating, and processing IPD. Statisticians should move from their classical role as data gate-keepers to be data facilitators. The technical and statistical challenges of accessing research data for reanalyses and other secondary uses are not trivial. Specific skills and techniques are required to convert the initially collected data into sets that can be used for analysis by external researchers.^{32,35}

GDPR and sharing of IPD from clinical trials

The main goal of IPD sharing is to enable other researchers to repurpose the data for secondary uses and applications. Access to the data can allow for the study to be independently replicated, prevent duplicative studies, provide the basis of



generating or testing new hypotheses, and generally advance medicine and biology.³⁶

In the US, the Office for Human Research Protections has indicated that sharing of *deidentified* IPD from clinical trials does not require separate consent from trial participants, provided that the appropriate conditions are met by those receiving the IPD.²⁸ In contrast to the situation in the US, some concerns have recently arisen in the EU on how to consolidate the data sharing principles for information from clinical trials with Regulation (EU) 2016/679, better known also as the EU GDPR, which has been in force only since May 2018.

It appears that some EU member states have taken different positions on the GDPR when it comes to deciding whether the Patient Consent Form should be the *only* legal grounds for processing and sharing deidentified/anonymised IPD from clinical trials for secondary use. There is legal uncertainty about whether the consent to participate in a clinical trial is equivalent to the consent for secondary processing of the data. International legal experts and members of the European Data Protection Board are currently evaluating ways to harmonise interpretation across the EU for GDPR and sharing of IPD from clinical trials for secondary use.^{37–39} In April 2019, the European Commission Directorate-General for Health and Food Safety released a Question and Answer document on the interplay between the Regulation EU 536/2014 and the GDPR, clarifying that informed consent obtained under these legislative instruments serves different purposes.⁴⁰

Describing requirements in the various countries regarding clinical data sharing is out of scope for this article. Nevertheless, it should be recognised that globally, the EU GDPR is not the only recently updated or introduced legislation dealing with citizens' data protection. Personal information protection laws similar to the EU GDPR also exist elsewhere, for example, the Japan Personal Information Protection Act and the Canada Personal Information Protection and Electronic Documents Act. Interestingly, the US does not have an equivalent to the EU GDPR; the topics are governed by a mixture of different state and federal rules rather than by a central authority or rule.

Sponsors of clinical trials and their policies on data sharing

Many sponsors of clinical trials (pharmaceutical industry and academic institutions), including those in the industry that are not members of pharmaceutical associations, have updated their general policies on disclosure and transparency to include consideration of data sharing with qualified external parties. For most pharmaceutical industry sponsors, sharing of clinical data is specified in their company policies, for example, data may only be shared for products that are approved (in US *and* in EU) or for trials that have been completed (whereby some trials may have many years of follow-up before they are considered as completed).

Data-sharing platforms

Data-sharing platforms are an alternative option

for clinical trial sponsors to share IPD. This can be done through different repositories recently developed by several joint initiatives. Sponsors subscribing to such a platform(s) provide the platform administrator with the relevant documents and datasets from selected clinical trials. For external requestors interested in performing secondary or meta-analyses, each platform has conditions as to what a data sharing request should contain, in which format the data sets will be provided, and which working site can be used for secondary data analysis.^{5,25,32,33}

Clinical trial sponsors pay a fee for participating in some of these platforms, which provide most of the services relevant to assessing and processing the data sharing requests for IPD. These platforms help clinical trial sponsors meet the ethical obligations for sharing of deidentified/ anonymised IPD. Some current data-sharing platforms include the ClinicalStudyDataRequest consortium,⁴¹ the YODA Project,⁴² Vivli,⁴³ Project Data Sphere (does not charge any fees),⁴⁴ and DataCelerate.⁴⁵ Furthermore, several other clinical data-sharing platforms concentrate their efforts at a national or institutional level (e.g., US National Institutes of Health), or at a disease-specific level (e.g., Alzheimer's Disease Neuroimaging Initiative).⁴⁶

Although the efforts to set up and maintain the clinical trial sharing platforms are highly commendable, it is still too early to make definitive conclusions about their effectiveness to fulfil the high aims of clinical IPD sharing. This is because membership in these data-sharing platforms is relatively low, membership costs are high, platforms are not interoperable, and availability of the

In June 2017, the ICMJE announced two additional requirements on sharing IPD generated during interventional clinical trials:

1. Authors of manuscripts based on results of a clinical trial submitted on or after July 1, 2018, are asked to submit a Data Sharing Statement at the manuscript submission stage.
2. Interventional clinical trials that began enrolling participants on or after January 1, 2019, must include a Data Sharing Plan in the trial's registration record.

IPD from sponsor-selected clinical trials is fragmented. As such, identifying, obtaining, and evaluating all relevant documents remains challenging for external requesters.

Conclusions

Clinical data sharing can be justified on scientific, economic, and ethical grounds. Large IPD repositories and improved technologies that can cope and analyse large datasets are becoming available. Current legal questions regarding national interpretations of the laws surrounding IPD sharing will be resolved and harmonised. Clearly, sharing of deidentified/anonymised IPD from clinical research is here to stay and will continue to develop and expand.

Finally, while appreciating "*The Importance – and the Complexities – of Data Sharing*",⁴⁷ it is essential to keep in mind the benefits to patients offered by clinical data sharing, while respecting and ensuring privacy of the clinical trial participants who contribute their data.^{5,32,34,36,48}

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The opinions expressed in this article are the authors' own and not necessarily shared by EMWA.

Conflicts of interest

The authors declare no conflicts of interest related to this article.

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Medicinal products and medical devices in clinical trials conduct and disclosure – and ~~never~~ the twain shall meet!



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Abstract

“Medicinal products and medical devices are different species...they live in parallel universes” according to a medical device expert. But is it really so? This article challenges that notion by comparing the Clinical Trial Regulation EU No. 536/2014 (CTR) and the EU Medical Device Regulation 2017/745 (MDR) in the context of clinical studies and public disclosure.

Despite some fundamental differences, similarities and overlaps in the requirements and details between the CTR and MDR are evident. There is also a clear aim for the electronic databases, as described in the two regulations, to be interoperable. This high-level comparison of the CTR and MDR shows that while the *requirements* of the two regulations have been aligned and are very similar, their *impact* on the respective industries is quite different.

Two parallel universes

“**WARNING:** Medicinal products and medical devices are different species. They live in parallel universes. They may appear similar (“medicinal products”), but they are not. **Carelessly switching between universes may be deadly.**” These words are taken from a presentation by Ronald Boumans, a Senior Regulatory Consultant at Emergo Group.¹ Jokes aside, after evaluating the two regulations, we are compelled to challenge this statement. As professional regulatory medical writers who have been developing regulatory documents for both pharmaceutical drug products and medical devices for many

years, we already switch between these universes and firmly believe that linking these two is not only feasible but also profitable, as other colleagues can also attest.² Nevertheless, the school of thought that “a drug is a drug, a device is a device, and never the twain shall meet” is relatively widespread.³

Two universes, two regulations

In 2014, the Clinical Trial Regulation European Union (EU) No. 536/2014⁴ (henceforth referred to as CTR) was released. The detailed requirements and documentations of this legislation were really nothing new for the

pharmaceutical industry. The major changes were the centralised clinical trial application, the increased disclosure requirements, and the setting up of a new EU portal and database (to replace the existing ones).

In 2017, the EU Medical Device Regulation 2017/745⁵ (henceforth referred to as MDR) was released. Literally “left to its own devices till now”,³ the medical technology industry struggles with the drastically increased and unfamiliar regulatory requirements of this legislation.^{6,7} Following the thread of Bouman’s analogy, it felt like aliens had invaded the medical device universe.



As professionals working for the two industries, we were obliged to familiarise ourselves with these two new legislations. This article makes a high-level comparison between the CTR and the MDR (Table 1) based on the original texts of the legislations and the authors' interpretation of those texts built on their experiences of working in the pharma and medical device industry. The comparison is focused on the conduct and disclosure of clinical studies, often referred to as clinical *trials* for medicinal products and as clinical *investigations* for medical devices.

Obvious differences

The most obvious difference is the scope of the two regulations. The CTR, as its name implies, covers interventional clinical trials for medicinal products and supersedes Directive 2001/20/EC and Paediatric Regulation (EC) No. 1901/2006. The purpose of the CTR is to add clarity to the previous laws as well as simplify and harmonise the administrative processes for clinical trials performed in the EU/European Economic Area (EEA). Other regulatory aspects of CTR, such as market authorisation and pharmacovigilance, are covered by the Directive 2001/83/EC and Regulation 726/2004.

The MDR, on the other hand, has a much broader scope than the CTR and goes beyond clinical investigations by including manufacturing, market access, and post-market vigilance. MDR supersedes two Directives, 90/385/EEC (active implantable devices, 2007) and 93/42/EEC (other devices, 2007). The main objectives of the MDR are "to establish a robust,

transparent, predictable, and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation [and] to ensure the smooth functioning of the internal market as regards medical devices . . ."⁵

The other important difference is that under the CTR, the EMA ("the Agency") has the major responsibility of implementation, with support from the European Commission (EC) and the member states. For the MDR, the major responsibility of the implementation lies with the EC, working together with the competent authorities of the EU member states.

Similarities and overlaps

The MDR and CTR were written three years apart and our initial reaction when we first read the MDR was that the two universes are coming together, especially when it comes to clinical study conduct, reporting, and disclosure, as summarised below and also in Table 1 (that compares the CTR and MDR).

Clinical study conduct

Clinical evidence is needed for new health products to be granted market access. Clinical studies (trials or investigations) are performed to collect data on efficacy and safety of the tested products. The CTR and MDR are relatively aligned in their definitions of clinical trials and investigations, respectively, as well as in respect of the key involved stakeholders (Table 1). In some cases, the terminologies used differ slightly while the definitions are almost identical. In general, it seems that fewer clinical studies are

needed for approval of a new device than for a new medicinal product.³

Clinical study registration

Both CTR and MDR require registration of clinical studies in a publicly accessible registry. Each study must be identified with a unique ID number. This requirement was already covered in the previous legislation for medicinal products but not in the predecessors of the MDR.

In the USA, the database ClinicalTrials.gov provides a clear breakdown of clinical trials by drugs, biologics, surgical procedures, and devices. To date, this kind of breakdown of clinical studies is not readily available for studies performed in the EU or the states of the EEA in the current database, the EU Clinical Trials (CT) Register. Currently, the EU CT Register requires only registration of medicinal products tested in interventional clinical trials with at least one trial site in the EU/EEA and "does not provide information on clinical trials for surgical procedures, medical devices, or psychotherapeutic procedures". The MDR may resolve this information gap, as discussed in the following sections.

The electronic systems and databases

To support the CTR harmonised approach to submission, assessment, and reporting of clinical trials, the EC has mandated the EMA to establish a new EU portal and database according to the specifications in the CTR. Data submitted through the new portal will be stored in an EU database that is open to the public. Duplications with the existing databases (Eudravigilance and

Table 1. Comparison of the requirements for clinical trials/investigations conduct and disclosure under the CTR 536/2014 and MDR 2017/745

	EU CTR 536/2014	EU MDR 2017/745
Full name	Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
Scope	Clinical studies in medicinal products: submission, assessment, notification, disclosure	Clinical studies in medical devices: submission, assessment, notification, disclosure (Article 62, Annex XV) Manufacturing, CE-marking (market authorisation), post-market surveillance of medical devices
Definitions of terms related to clinical studies (per CTR or MDR)	Clinical study ^a : any investigation in relation to humans [intended to study clinical, pharmacological, pharmacodynamic effects, identify any adverse reactions, study absorption, distribution, metabolism and excretion] ... with the objective of ascertaining the safety and/or efficacy of those medicinal products	Clinical investigation : any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device
	Investigational medicinal product : a pharmaceutical form of a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial	Investigational device : a device that is assessed in a clinical investigation
	Protocol : a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial	Clinical investigation plan : a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation
	Sponsor : an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial	Sponsor : any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation
	Subject : an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control	Subject : an individual who participates in a clinical investigation
	Investigator : an individual responsible for the conduct of a clinical trial at a clinical trial site	Investigator : an individual responsible for the conduct of a clinical investigation at a clinical investigation site
	Informed consent : a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate, or in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial	Informed consent : a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical investigation
Clinical trial / investigation conduct	<ul style="list-style-type: none"> Required for all investigational medicinal products 	<ul style="list-style-type: none"> Required for certain device classes (Class II to III) that do not have a CE mark
Clinical trial / investigation registration	<ul style="list-style-type: none"> Obligatory for all studies with at least 1 EU site, submitted via EU portal, stored in the EU database Unique EU trial number (Article 81) 	<ul style="list-style-type: none"> Obligatory for all investigations with at least 1 EU site, submitted on the electronic system for clinical investigations within the Eudamed (Article 73) Unique ID number for each investigation (Article 62) If the application is submitted in parallel with an application for a clinical trial in accordance with Regulation (EU) No 536/2014, reference to the official registration number of the clinical trial (Annex XV, Chapter II)

Continued opposite

	EU CTR 536/2014	EU MDR 2017/745
Databases	<ul style="list-style-type: none"> • EU portal as a single entry point for the submission of data and information relating to clinical trials (Article 80) • Data and information submitted through the EU portal shall be stored in the EU database (Article 81) • Unnecessary duplication between database and EudraCT and EudraVigilance databases to be avoided • Partial public access • European Medicines Agency as controller 	<ul style="list-style-type: none"> • Eudamed that integrates several electronic systems (Article 33) • The electronic system for clinical investigation is the entry point for the submission of all applications or notifications for clinical investigations (Articles 70, 74, 75, 78); for all other submission of data, or processing of data • Partial public access, all public parts should be user-friendly and in an easily searchable format • European Commission is the controller • To ensure synergies with the area of clinical trials on medicinal products, the electronic system on clinical investigations should be interoperable with the EU database to be set up for clinical trials on medicinal products for human use (Preamble 67)
Public disclosure: Clinical study application	<ul style="list-style-type: none"> • Protocol, IB, IMPD (S and E), SmPC (Annex I) • Protocol to describe publication policy (Annex I, D 17-ai) Potentially all publicly accessible 	<ul style="list-style-type: none"> • Clinical investigation application dossier (Article 62; Article XV) • Clinical Investigation Plan (CIP), IB (Annex XV) • CIP to contain policy on the CIR and publication of results (Annex XV, Chapter II, 3.17) • Potentially all publicly accessible
Public disclosure: Study results reporting	<ul style="list-style-type: none"> • Public access via the EU database • A summary of the results of the clinical trial irrespective of the outcome, to be submitted within 1 year (Article 37; Annex IV) • Layperson's summary (Article 37; Annex V) • CSR within 30 days post-MAA decision (Article 37) 	<ul style="list-style-type: none"> • Public access via the Eudamed • CIR within one year of the end of the clinical investigation or within 3 months of the early termination or temporary halt, irrespective of the outcome (Article 77) • Summary easily understandable by a user (Article 77) • Publication of results according to legal requirements and ethical principles (Annex XV, Chapter II; see next row)
Other ethical guidances that can impact disclosure	<ul style="list-style-type: none"> • Declaration of Helsinki 2008 (Preamble 80) • ICH guidelines on Good Clinical Practice (Preamble 43) 	<ul style="list-style-type: none"> • Declaration of Helsinki latest version (Preamble 64) • ISO14155:2011 (Preamble 64)
Protection of personal data	<ul style="list-style-type: none"> • Personal data protection per Regulation (EC) No 45/2001 (now replaced by the General Data Protection Regulation (GDPR) 2016/679) • Protocol should describe arrangements for compliance, measures to ensure confidentiality, mitigation measures for security breach adverse effects (Annex I-D) 	<ul style="list-style-type: none"> • Personal data protection per Regulation (EC) No 45/2001 (now replaced by GDPR) • CIP should describe arrangements for compliance; measures to ensure confidentiality, mitigation measures for security breach adverse effects (Annex XV Chapter II, 4.5)
Protection of commercially confidential information (CCI)	<ul style="list-style-type: none"> • Protection of CCI, unless there is an overriding public interest in disclosure (Article 81, 4a) 	<ul style="list-style-type: none"> • Protection of CCI, trade secrets, intellectual property rights, unless disclosure is in public interest (Article 109, 1(b))



CE: Conformité Européenne; CIR: Clinical investigation report; CSR: Clinical study report; CTR: Clinical trial regulation; EC: European Commission; EU: European Union; Eudamed: European databank on medical devices; EudraCT: European Union drug regulating authorities clinical trials; EudraVigilance: European Union drug regulating authorities vigilance; IB: Investigator's brochure; IMPD: Investigational medicinal product dossier; ISO: International Standardisation Organisation; ICH: International Council on Harmonisation; MAA: Marketing authorisation application; MDR: Medical device regulation

^a in many instances, the CTR uses the terms study and trial interchangeably.

European Clinical Trials database [EudraCT]) will be avoided. Once the new portal and database are fully functional and implemented (expected to occur later in 2020), the current EudraCT and EU CT registry will be replaced, following a transition period.⁸

The European databank on medical devices (Eudamed), in existence since 2010⁹, has been operating in conjunction with the old directives; however, the database was never systematically used for investigations with medical devices. Through the MDR, the Eudamed structure is broadened and its use becomes mandatory under the responsibility and auspices of the EC. Another substantive change in the new Eudamed is the increased transparency of the investigations, requiring the database to be available for public access.

Public disclosure: clinical study application

The publicly accessible information and documentation used for the applications of clinical trials/investigations submitted via the EU portal/Eudamed will include information regarding the sponsor, clinical study protocol/clinical investigation plan (CIP) and their amendments, investigator's brochure (for both medicinal products and devices), and some sections of the investigational medicinal product dossier for medicinal products.⁸ There are exceptions as to what can be disclosed including protected personal data and commercially confidential information (CCI).

Though not clearly described in the legislations, decisions on publication and sharing of results are expected to be described in the clinical study protocol or the CIP as part of the clinical study application.

Public disclosure: clinical study results

Both the CTR and MDR require full disclosure of the clinical study results summary based on the clinical study report (CSR) and clinical investigation report (CIR), respectively. For medicinal products, the CTR requires a comprehensive summary of the clinical study results (technical summary) plus a summary that can be understood by laypersons (layperson summary also known as plain language summary). These summaries will need to be submitted to the forthcoming EU portal and will be available to the public via the EU database

after the study ends (12 months for studies with adults and 6 months for studies with participants 18 years or younger at the time of enrolment); *study end* is defined as the date of the last patient's last visit. The CSRs containing summary results of the study will be published 30 days after a marketing authorisation opinion is received (whether positive, negative, or if the marketing authorisation application is withdrawn by the applicant).

The MDR requires a full CIR and a summary of results that can be understood by the intended user (similar requirement as the layperson summary, above). These documents will be submitted to the Eudamed and made available to the public. Unlike the CTR, there seems to be no intermediate step of clinical study results summary posting under the MDR; a CIR is expected within one year of the end of the investigation, defined as the date of the last patient's last visit.

For clinical investigations, the MDR requires that each step, "from the initial consideration of the need for and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles," i.e., ISO 14155:2011 and the most recent version of the World Medical Association (WMA) Declaration of Helsinki (current version dated 2013). The CTR refers to the International Council for Harmonisation guidelines on good clinical practice and the 2008 version of the WMA Declaration of Helsinki. Both versions of the Declaration of Helsinki include clear recommendations on the registration of clinical studies and the publication of research results in publicly accessible platforms.

Personal data protection

The strict requirements to protect the personal data of study participants in documents that will be publicly accessible are mentioned in both the CTR and MDR. Both regulations refer to Regulation (EC) No 45/2001, which has now been superseded by the recently implemented General Data Protection Regulation (GDPR) 2016/679. Under the GDPR, the principle of

privacy by design or by default is a key requirement, i.e., all systems and processes should have personal data protection measures integrated into them.

Confidentially commercial information

The CTR and the MDR, respectively, consider the commercial interests of the "pharma" and "medtech" companies by providing possibilities to protect CCI, trade secrets, and intellectual property rights. However, there is a caveat in both regulations: protection of CCIs can be overruled if their disclosure is in the public interest. Experience with documents that fall under EMA Policy 0070 – which facilitates disclosure of numerous 'reports' of approved products – has shown that minimal CCI redactions are accepted by the EMA. Indeed, all redactions of CCIs need to be justified in writing and presented to the EMA for a decision; the EMA has the final word on the acceptance of a CCI to be redacted. It is anticipated that the principles for document redaction that apply to EMA Policy 0070 will also be used for the documents that are required to be disclosed by the MDR.⁸

And the twain shall meet

The CTR focuses mainly on investigational medicinal products (e.g., drugs and biologics) and mentions devices only in the context of medicinal product administration and delivery systems. The MDR, which postdates the CTR by three years, refers to the CTR three times. The MDR recognises that medicinal products and devices may occur together as combined products, a topic that is not addressed in the CTR. However, even outside of the context of combined products, the MDR states that "to ensure synergies with the area of clinical trials on medicinal products, the electronic system on clinical investigations [Eudamed] should be **interoperable** with the EU database to be set up for clinical trials on medicinal products for human use." This is presumably part of the EU initiative for standardisation and interoperability of all electronic health systems in Europe.¹¹ This

To ensure synergies with the area of clinical trials on medicinal products, the electronic system on clinical investigations [Eudamed] should be interoperable with the EU database to be set up for clinical trials on medicinal products for human use.

interoperability of the two electronic systems will address the information gap described earlier in our article and allow a more comprehensive record of clinical studies conducted in the EU (regardless of the product type), similar to what is available on ClinicalTrials.gov.

Similar contents, different impacts

We highlight above the similarities between the CTR and the MDR in terms of clinical studies, documentations, disclosure requirements, and the systems supporting such requirements. Yet, despite the similarity of their contents, the impact of the CTR and the MDR on their respective industries are very different. One reason for this

disparity is the large number and diversity of medical technology products that may have hindered previous efforts in the regulatory process harmonisation.⁷ There are approximately 500,000 medical technology products in Europe.¹² According to Boumans, “on average, more new medical devices enter the European market in a single day than new medicines in a year.”³ Another reason is that not only were the regulatory pathways for the two groups of products very different previously, the regulatory requirements in earlier legislations were clearly more stringent for medicinal products than for medical devices.¹³ With the passing of the CTR and the MDR, these requirements have been

brought to the same level of stringency. Thus, the difference in the impact on the two industries is due to the different baselines – the Directives – and the change in requirements that the new regulations brought with them (Table 2). For those who believe in the two parallel universes configuration, applying the rules governing medicinal products to devices was almost a quantum leap into regulatory space.

Are they really that different?

At first glance, medicinal products and medical devices are indeed like “different species”. There are inherent differences in their appearance, mechanisms of action, product development

Table 2. The impact of new regulations on the pharmaceutical and medical device industries

	Medicinal Products			Medical Devices		
	Directive ¹ 2001/20/EC + Paediatric Regulation 1901/ 2006 (Baseline)	Regulation ² 536/2014 (CTR)	Δ ³ and impact ⁴ on pharma industry	Directives ¹ 93/42/EEC and 90/385/EEC (Baseline)	Regulation ² 2017/745 (MDR)	Δ ³ and impact ⁴ on medical device industry
Clinical study conduct	Mandatory	Similar requirements, new application process	Small Δ Low to moderate impact (mainly timelines)	Not clearly required when following “equivalence” route	Mandatory for most device classes	Large Δ High impact
Clinical study documents	Mandatory	Similar requirements; more documents to disclose	Small Δ Low to moderate impact	Required but not clearly structured	Mandatory, with document requirements similar to pharma	Small Δ High impact
Clinical trial registration	Mandatory	Mandatory	Small Δ Low impact	Not required	Mandatory	Large Δ High impact
Clinical trial results disclosure	Partial disclosure required	Full disclosure mandatory	Large Δ Moderate to high impact	Not required	Full disclosure mandatory	Large Δ High impact

1 Directive: A “directive” is a legislative act that sets out a goal that all EU countries must achieve. Individual countries devise their own laws to reach these goals.

2 Regulation: A “regulation” is a harmonised legislative act that must be applied in its entirety across the EU member states.

3 Δ: Change from baseline (i.e., Directives and Paediatric Regulation 1901/2006).

Low Δ: no or minimal change in requirements; Large Δ: new requirements, substantial changes to previous requirements.

4 Impact is arbitrarily rated as low, moderate, or high, based on Δ and authors’ regulatory experience with the previous and new requirements.

process, and life cycles. But they also have much in common. They are products used as medical interventions in human patients. They have a medical purpose, i.e., to cure a disease, treat a condition or control and alleviate symptoms and pain. And their effectiveness and safety need to be demonstrated in clinical trials or investigations. It follows that the CTR and the MDR are also not so different after all, and a comparison of their requirements for clinical trials and investigations supports this inference (Table 1).

Both the pharmaceutical and medical device industries have had their share of efficacy scandals and safety mishaps.¹³ The lessons learned from such events have been used to refine regulatory requirements that should prevent the same mistakes from happening again. In the era of patient centricity, the type of product considered – be it medicinal product or medical device – does not really matter. The benefits and the risks to the patients through patient-focused medical care are of utmost importance, regardless of which universe they belong to.

It is likely that the transition to merge the two universes of medicinal products and medical devices will take some time. Nonetheless, the alignment of the CTR and the MDR requirements is paving the way in the direction of a single universe.

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The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

Conflicts of interest

Raquel Billiones is an employee of a pharmaceutical company. Kathy B. Thomas is an independent consultant to pharmaceutical industry on matters concerning clinical trial disclosure. The authors have no other conflicts of interest to declare.

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Publication of clinical trial protocols and statistical analysis plans on ClinicalTrials.gov

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Abstract

According to the final rule on “Clinical Trials Registration and Results Information Submission”, clinical trial protocols and statistical analysis plans have to be published on ClinicalTrials.gov. The requirement affects all applicable clinical trials with a primary completion date on or after January 18, 2017. Personally identifiable information, as well as any trade secret and/or confidential commercial information can be redacted, before documents are made public. This article reviews the limited available guidance on how to prepare the documents for publication and the key questions to be addressed.

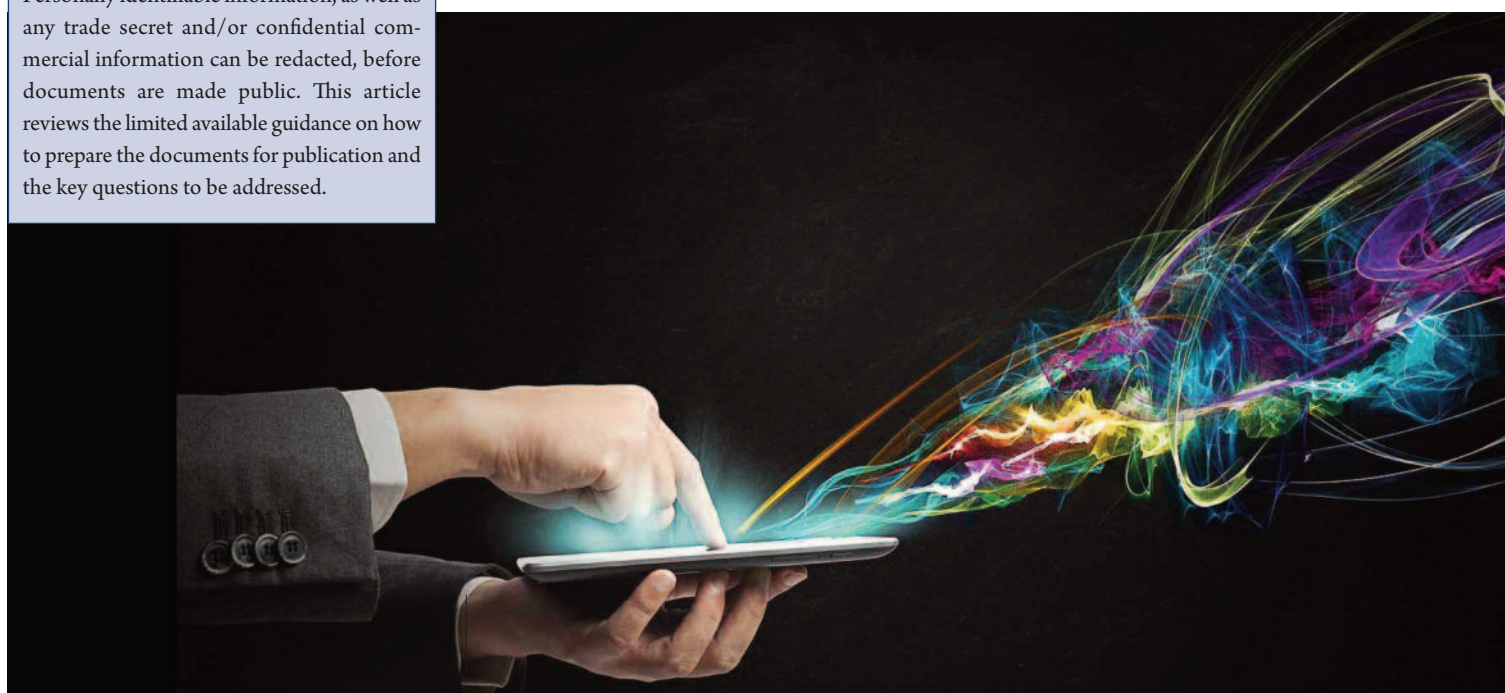
Once considered confidential documents, many clinical study protocols and statistical analysis plans (SAPs) are now publicly available on a variety of platforms: the Policy 0070 “Clinical Data” website of the EMA,¹ websites of some medical journals that follow the Recommendations of the International Committee of Medical Journal Editors, and clinical trial websites of a number of clinical research sponsors. However, following the implementation of the final rule on “Clinical Trials Registration and Results Information Submission”, the most comprehensive source of original study protocols and SAPs for recent studies is by now ClinicalTrials.gov. As of March 3, 2019, the ClinicalTrials.gov registry held more than 3500 records of interventional studies with protocols (and/or SAPs) publicly available. More than 93% of these studies had a primary completion date on or after January 18, 2017, the effective date of the final rule.² This demonstrates the large impact

that the final rule has already had.

Section 801 of the US Food and Drug Administration Amendments Act of 2007 mandates the submission of registration and results information for certain clinical trials. Further rulemaking was foreseen by the Amendments Act to clarify and expand the requirements. Accordingly, the final rule was issued in September 2016 by the US Department of Health and Human Services.³⁻⁵ This article focuses on the publication of study protocols and SAPs according to the final rule. The relevant key content of the Code of Federal Regulations is displayed in Figure 1. For a summary of the results-related requirements of the final rule, refer to Hanson.⁶

The results and document-related aspects of the final rule concern applicable clinical trials with a primary completion date on or after January 18, 2017. A study is considered an

The most comprehensive source of study protocols and SAPs for recent studies is ClinicalTrials.gov



applicable clinical trial, if it meets the criteria summarised in Figure 2. Primary completion date of a study is defined as the date that the final participant was examined or received an intervention for the purpose of final collection of data for the primary outcome.⁷ According to the final rule, all applicable clinical trials that need results posted also require the publication of the clinical trial protocol and the SAP (if not part of the protocol). For both documents, at least the most recent version, i.e., after the latest global amendment, needs to be posted.⁴

The results and document-related aspects of the final rule concern applicable clinical trials with a primary completion date on or after January 18, 2017.

Interestingly, the Proposed Rule had not stipulated the publication of the full protocol and SAP but had invited comments on the benefits and burdens of such a potential requirement. Following an assessment of the comments received, the US Department of Health and Human Services concluded that the benefits of making protocol and SAP publicly available would clearly outweigh the burdens on

responsible parties. The main advantages are cited as:

- Improves transparency and quality of reporting
- Is necessary for a full understanding of a study's results and replication thereof
- Safeguards against reporting bias
- Facilitates meta-analyses
- Improves the design of future studies
- Reduces unnecessary duplication of studies
- Promotes standardisation of protocol elements
- Avoids multiple individual requests for these documents.⁴

The default requirement is to make the protocol and SAP available at the same time as the results, i.e., within 12 months of the primary completion date. In certain cases, the results posting, and thus the publication of trial documents, may be delayed for up to two years. This is permitted, if the product was not yet initially approved by the FDA, when the primary completion date of the trial was reached. The delay is also possible, if a new use of the product (e.g., a new indication) has been filed with the FDA or is planned to be filed within one year. In exceptional cases, an extension of the submission deadline can also be requested for "good cause".^{4,7}

The protocol and SAP need to be made public at the same time as the results, i.e., within 12 months of the primary completion date.

When a responsible party fails to submit the mandatory registration and/or results information (now also including the protocol and SAP), the FDA can seek civil money penalties



of up to \$10,000 per day.³ Apparently, no fines have been imposed so far, for which the FDA has been heavily criticised by some transparency advocates.^{8,9} In September 2018, the FDA issued a Draft Guidance summarising their intention on how to implement the monetary penalties.¹⁰

§ 11.48 What constitutes clinical trial results information?

(a) For each applicable clinical trial, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, for which clinical trial results information must be submitted under § 11.42, the responsible party must provide the following:

... ..

(5) **Protocol and statistical analysis plan.** A copy of the protocol and the statistical analysis plan (if not included in the protocol), including all amendments that have been approved by a human subjects protection review board (if applicable) before the time of submission under this subsection and that apply to all clinical trial Facility Locations. The responsible party must include the Official Title

(as defined in § 11.10b(2)), NCT number (as defined in § 11.10a) (if available), and date of the protocol and the statistical analysis plan on the cover page of each document. The responsible party may redact names, addresses, and other personally identifiable information, as well as any trade secret and/or confidential commercial information (as those terms are defined in the Freedom of Information Act (5 U.S.C. 552) and the Trade Secrets Act (18 U.S.C. 1905)) contained in the protocol or statistical analysis plan prior to submission, unless such information is otherwise required to be submitted under this part. The protocol and statistical analysis plan must be submitted in a common electronic document format specified at <https://prinfo.clinicaltrials.gov>.

Figure 1. Excerpt from Code of Federal Regulations mandating the publication of clinical trial protocols and statistical analysis plans.

Relevant key content of Part 11 in Title 42, Chapter I, Subchapter A of the Code of Federal Regulations is shown.⁷

Abbreviations: U.S.C., United States Code



While many affected studies have publicly posted results and documents, the overall

Applicable clinical trials

- Interventional study, i.e., a clinical trial
- Any of:
 - At least one study site in the US or a US territory
 - Conducted under an FDA Investigational New Drug application or Investigational Device Exemption
 - Product manufactured, packaged, or labelled in the US or a US territory
- Product regulated by the FDA
- Not Phase 1 (for drug product) or not device feasibility study (for device product)

Figure 2. Definition of an applicable clinical trial per the final rule.

All four criteria must be met. For further details, refer to the National Library of Medicine checklist.¹⁵

compliance rate with the final rule leaves room for substantial improvement. The actual compliance in terms of timely posting can be monitored overall and for individual sponsors using the online tracker developed by the Evidence-Based Medicine DataLab at the University of Oxford, UK.¹¹⁻¹³

How to prepare documents for publication

The regulations concede that the responsible party may protect certain information through redaction, before making the trial documents public. Per the Code, the following may be redacted: “personally identifiable information, as well as any trade secret and/or confidential commercial information ... unless such information is otherwise required to be submitted under this part” (see Figure 1). The guidance on the extent and format of redactions is, at best, scarce. What is clear is that the responsible party, not the FDA, decides on the redactions and makes them. Also, “essential details necessary to understand the results” must not be redacted. Furthermore, although not expected, should personally identifiable information about

individual clinical trial participants be present, “it should be redacted”. The Agency reserves the right to provide “more specific guidance regarding redaction” later and to challenge a responsible party, if it appears that redactions are inappropriate.⁴

When approaching the redactions, responsible parties need to address many questions, some of which are listed below. The decisions are company-specific and affect, for example, the consistency of redactions on different public platforms and the effort needed to prepare redacted documents. Questions for consideration include: 1. Should redactions of personally identifiable information follow the same approach as employed for other transparency channels, e.g., EMA Policy 0070? 2. How much should be redacted as commercially confidential? Usually, product development is at an earlier stage when documents need to be published on ClinicalTrials.gov than for Policy 0070 publication. Therefore, more information may need to be considered commercially confidential than for Policy 0070. 3. Should copyrighted content, e.g., questionnaires or scales, be redacted? In contrast to the Policy 0070 “Clinical Data” website, no login or “acceptance of terms of use” is needed to view or download documents from ClinicalTrials.gov. Thus, the responsible party has no control over what a user of ClinicalTrials.gov might do with the documents. 4. Which style and format of redactions should be applied? 5. Should redacted documents on ClinicalTrials.gov be replaced by subsequent document versions with fewer redactions, once these become available on other platforms? Per the Code of Federal Regulations, there is no requirement to update the protocols and SAPs (unless for a protocol amendment).⁴ Further questions – for example, when to prepare the redacted documents, which functions to involve, how to decide on redactions, and which software to use – are largely independent of ClinicalTrials.gov.

The regulations require the NCT number, i.e., the ClinicalTrials.gov identifier, on the cover page of each document, if this number is available. In addition, the official study title and the date of the document must be stated on the cover page (see Figure 1). Given that a study protocol is normally finalised before the NCT number is assigned, this number is typically not present in the original protocol. Thus, extra cover pages may be added or the NCT number could be inserted on the title

Personally identifiable information as well as any trade secret and/or confidential commercial information may be redacted, unless such information is otherwise required to be submitted.

pages of the redacted documents. Finally, the Code states that documents “must be submitted in a common electronic document format” (see Figure 1). This is specified on the website of the Protocol Registration and Results System as the Portable Document Format Archival (PDF/A) file format.¹⁴

A cursory review of a few randomly selected studies conducted by 20 mid-sized and large biopharmaceutical companies revealed that the extent and format of redactions are quite variable. Some documents have no or almost no redactions, while others have full paragraphs or occasionally even full sections redacted. Sometimes the redactions follow the Policy 0070 style, other times simple black bars without overlay text are used. Overall, some common principles emerge, i.e., redaction of names and addresses of certain sponsor and vendor personnel and a tendency to redact exploratory endpoints and related analysis methods.

Conclusions

Writing clinical documents that are as transparency-ready as possible will save time and resources later, when these documents need to be made public. Documents without or with few commercially confidential items and with little personally identifiable information require no or only few redactions (or anonymisation via other methods). This not only helps with the final rule but generally facilitates the compliance with the divergent transparency requirements.

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The opinions expressed in this article are the author's own and not necessarily shared by her employer.

Conflicts of interest

The author is employed by Teva Pharmaceuticals International GmbH.

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Collecting metrics in medical writing – the benefits to you and your business

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Abstract

Collecting and using metrics may not be at the forefront of all medical writers' minds, but they can be an important asset to writers and managers, from freelancers to those working within companies, large or small. Keeping a record of pertinent details of writers' work and information about the department can

help plan, determine resources, set timelines, assess budgetary needs, respond to new business enquiries, and update curriculum vitae, to name but a few of the benefits. This article explains what medical writing metrics are and how they can be used to the advantage of writers and managers.

The Cambridge English dictionary defines metrics as "a set of numbers that give information about a particular process or activity".¹ Although the word "metrics" does not sound exciting and may even elicit groans of "oh no, what do I have to do?", collecting metrics can require relatively minimal effort for large gains. Whether you are a freelancer, a company employee, or manager, you may be aware of and be collecting at least some metrics already.

Typical metrics in medical writing are listed in Box 1. If you are collecting any of these then

you are hopefully already making the most of them. If not, read on to learn more about why metrics should be collected and how they can be used.

Why collect metrics?

Collecting metrics is essential for keeping on top of a business's activities. You may be asked a question about your work by business development, a client, or senior managers, such as how many documents of a certain type or therapeutic area have been written, how long it takes to write a certain type of document, or how many writers within the department have experience with a certain type of document and/or therapeutic area. When this happens, it is essential to be able to give an answer that is timely and accurate. This is where metrics come into play.

As well as providing information for enquiries, metrics can allow work to be planned and can ensure that the required headcount will

Box 1. Examples of metrics in medical writing

- Basic document information: client company name, therapeutic area, study phase, and start and end date of authoring
- Type of document, for example, protocol, clinical study report, paediatric investigation plan, manuscript, or abstract
- New business enquiries, wins, and losses
- Departmental headcount, including employees currently on a break from work and reasons (for example, parental leave, extended holidays, or sick leave)
- In global departments, distribution of workload across geographical regions
- Departmental skill sets, such as which types of document, therapeutic area, study phase, and study population, etc. have been written by which writers
- Utilisation – how busy individuals and the team are by tracking billable hours versus total hours (billable and non-billable)
- Profit and loss – which work was over budget, which was under budget, and why
- Timelines – whether projects were delivered on time, were completed early, or over-ran the planned timelines and why
- Lessons learned from completed work
- Findings from audits that involved medical writing projects or the department

be available to do the work at the right time. Perhaps you or your department has been steadily winning more work over the course of the past few months, but the headcount has not increased. Metrics that track new business wins can translate into the estimated number of writers needed in the department and hence influence – and importantly, justify – recruiting decisions. This sort of forward planning is essential for running a successful organisation. Metrics are the tool for reporting information to your managers, and yourself, and can give quantifiable evidence of your successes, not to mention areas for improvement. Regardless of what type of writing you do and the size or structure of your department, there will be metrics that will be useful and beneficial to you.

How can metrics be used?

Metrics can be useful in many ways. The simplest of tasks, such as noting client names, can show you the amount of new or repeat business. Likewise, tracking new business enquiries, wins, and losses can provide insight into your business development needs – a simple calculation of the proportion of wins and losses versus enquiries will show how successful you are at acquiring new work and whether you need to focus on improving your win rate.

For all writers, noting the start and

end date of the authoring time would show realistically how long it takes to write a given document and this, in turn, could be used to help to plan timelines for similar future projects. Realistic projections help to not only reduce stress but also provide clients with achievable expectations and make having to reset timelines during the course of the project avoidable. In addition, if you know you are beating your timelines regularly on certain projects or coming in under budget, show it with the metrics data. Metrics can highlight successes – that are proven with data – which you can share with your colleagues, management, or clients.

Likewise, and importantly, keeping a track of the hours spent on a project can be translated into money spent, and comparing the final cost with the original budget estimate can be translated simply into a profit or loss, a must for anybody in business. As each project is completed and hours and money spent is tracked, common loss-making work can be identified. For example, if a project involves writing patient narratives to support a clinical study report and the estimated time and budget needed

for each narrative is too low, the financial loss will soon stack up, especially if there is a lot of narratives to be written. Diligent medical writers will spot trends in the metrics and adjust the assumptions for estimating budgets and timelines before the project gets underway. Building up a record of the type of work, whether it was within the timelines and budget, and what could be done better next time will help avoid potential pitfalls on future, similar projects. This information, in conjunction with other metrics, such as whether the department was under-resourced, can help determine why, for example, a project exceeded its planned timelines.

By tracking data on how much time is being spent performing project work and other non-billable tasks (such as training, meetings not associated with a project or client, and general administrative tasks), the proportion of time spent on project work versus non-billable work (“utilisation”) can be calculated. Utilisation can be used to assess how busy writers or whole departments are. Low utilisation could prompt a push to win new business, whereas high utilisation could justify recruiting additional staff. Tracking future work when it is won can be used to predict the planned forthcoming workload and resource needs. Of course, there will always be surprises, with unplanned work arriving at the last minute. Supplementary to this would be tracking any extended staff absences, such as maternity leave or extended holidays.

In large, global departments, metrics capturing the type and count of projects or documents being worked on in each region can help managers map the distribution of the work. This can be used to target growth of the business in areas with smaller shares of the global workload. Senior departmental managers also benefit extensively from metrics, allowing, for example, informed decisions on budgetary needs (e.g., training requirements), identifying gaps in service offerings, planning, hiring, helping business development initiatives, and providing invaluable positive feedback to their employees. Metrics can also be an extremely useful internal selling tool within a large organisation, for example justifying the need for a new service

If you know you are beating your timelines regularly on certain projects or coming in under budget, show it with the metrics data.

Collecting metrics is essential for keeping on top of a business’s activities.

offering to executive management. Generating client-specific metrics can also provide further insight into the status of a key relationship (for both parties) and can be used to analyse key performance indicators. At the other end of the scale, for individual writers, keeping track of your own work information, such as types of document, phase, and therapeutic area, will provide details for a comprehensive and accurate curriculum vitae, which in turn, would “sell” you as a writer. If audits have been performed, tracking findings could create the basis of process improvement at the department level in order to avoid the same audit findings in the future. The usefulness of collecting different types of metrics will depend on the business you have and changes to the business over time. Keep in mind

that variations due to company expansion or diversification of the type of work performed could lead to changes in the requirement for – and the usefulness of – certain metrics.

How to collect metrics

The way that metrics are collected will be determined by what data are available and the format of the data. Firstly, the need for specific metrics should be identified – what information would be most useful if it was collected, and once identified, how it can be collected should be decided, using the least labour-intensive method. Making sure all possible existing sources of metrics data are explored is a must, before setting up new methods of collecting data. Care should be given in creating new methods of collection

so that the data can be used in the most efficient way – such as designing a spreadsheet with filters, conditional formatting, and calculations of total values (as required) set up from the outset. Decisions should be made about how much data needs to be summarised too; if the source information originates from email, think carefully about what needs to be carried across to your spreadsheet and what does not, to make the process of capturing the information as efficient as possible.

Box 2 provides some simple tips and tricks for collecting and using metrics.

Conclusion

You have useful data – metrics – at your fingertips. Collecting and using metrics will help you as a medical writer and will help your business, regardless of what kind of work you do or your role. Although starting to collect metrics can feel like adding another task to your already busy day, the benefits of their use will outweigh the effort and they will provide you with great insight into how you and your department or business are performing. Ultimately, the more you know about your own work, the more proficient you will be at dealing with enquiries and knowing what has happened, is happening, and will happen in the future.

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Conflicts of interest

The authors declare no conflicts of interest.

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Box 2. Tips and tricks for collecting and using metrics

- Explore the data-handling systems at your company – do you have access to software that summarises data for you already, such as headcount, financial data, or hours worked (often collected in timesheets)? If so, use it!
- Brush up on your Microsoft Excel skills – spreadsheets can be a great tool for collecting metrics. Just accessing the Help function within the Excel programme can show you how to perform the basics such as calculating row or column totals, using conditional formatting (to automatically change the colour of a cell, row, or column if it meets certain criteria), and calculating the difference between two dates.
- Create graphs – again, Excel’s Help function can show you how easy it is to use the data in your spreadsheet to create a graph that will enable you to visualise trends better than data in a tabular format.
- Create searchable databases for information – this will allow quick answers to be provided for any questions from clients or from within your organisation. Explore the use of software tools for metrics collection and presentation (for example utilising Tableau® dashboards).
- Keep on top of it – little and often works best. Don’t procrastinate about adding some data to your spreadsheet later, as you may not get around to it (or you will do it later but will forget some of the details you intended to input).
- Keep it streamlined – collect what you need to collect, and don’t collect what you don’t need to collect. Think about what you want to get from the data and don’t over-burden yourself or others by collecting information that doesn’t meet your needs. This is especially important if you are asking a team to supply their individual metrics in order to avoid unnecessary and unwanted additional effort from the writers. Routinely review the metrics you collect, to see if they are fit for purpose.
- Impress others – create accurate presentations using your metrics that show to your stakeholders (your manager, those enquiring about your business capabilities, other departments within your company) that you are on top of your numbers.
- Any process designed for metrics collection should comply with current data protection principles, or company legal policies (particularly if you are collecting any personal or confidential information). If appropriate, obtain approval to collate certain information and follow the basic tenets of lawful data protection: lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality.

Document management systems for medical writing



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Abstract

Clinical trial data are rightfully protected by robust regulations; given these requirements and increasing demands from clients, a validated and compliant electronic document management system is now a necessity for established medical writing organisations and contract research organisations. Even without this impetus, the improvements in administrative function, audit readiness, and team collaboration can justify the investment required.

Introduction

In a world where data security is increasingly under the spotlight; the old order of manually tracking file names with ever-increasing dates or versions on a file-share or drive is unlikely to meet client or auditor requirements moving forwards. This article provides an overview of the benefits and challenges observed after the implementation of an electronic document management system (eDMS) within the medical writing department of a large contract research organisation (CRO).



In a world where data security is increasingly under the spotlight; the old order of manually tracking file names with ever-increasing dates or versions on a file-share or drive is unlikely to meet client or auditor requirements moving forwards.

Background

ICON Medical Writing, in partnership with our vendor, implemented a cloud-based document management system using the Software as a Service (SaaS) model. This system was first installed in 2015. The goal was to comply with the FDA Code of Federal Regulations (CFR) Part 111 and EMA Good Manufacturing Practice (GMP) Annex 11 guidelines,² and to respond to the increasing document security requirements of clients.

Regulatory need

The FDA and EMA guidance set a high bar for the storage and tracking of electronic documents related to clinical trials. The FDA's 21 CFR part 11 requires that systems are validated, secure, auditable, and that records are stored and retained as accurate and complete copies in readable and electronic formats. It also specifies that compliant systems will support electronic signatures and limit system access to only authorised individuals.^{1,3} The EMA's GMP Annex 11 was revised in 2011 in response to the increased use of computerised systems and their increasing complexity. While many of the Annex 11 requirements and principles are similar to those included in 21 CFR part 11 (audit trails, electronic signature, document security), Annex 11 goes into additional detail around the use of third-party suppliers, the qualifications of IT infrastructure and the validation project phase.²

Document management systems have long been established within large pharma but there is increasing scrutiny to ensure that CROs also store working copies of their trial documentation to these standards. This is especially true for documents containing any protected personal data that may reveal sensitive medical information or the identities of trial participants, or confidential proprietary information, both of which are commonly found in documents authored by medical writers.

Implementation

Configuration

From our experience, it is highly unlikely that there will be complete alignment between the out-of-the-box configuration of the chosen system and the processes that are in place within your medical writing organisation. During implementation, it will be key to identify where the stock system configuration should be modified to fit in with these procedures and *vice versa*. It is important to maintain a long-term view; the essence of a procedure must be maintained but any system configuration changes that attempt to mimic previously manual procedures may result in imperfect compromises that negate the benefits of automation.

It is important to have intensive testing prior to implementation that includes input from writers with a variety of roles and experience

levels. We found that helped to identify where the system configuration and processes could be better adapted to fit with our department's way of working.

Training

A well-executed training programme is essential for the smooth introduction of a new eDMS into a medical writing department or organisation.

A combination of instructor-led training and detailed reference materials will give users the confidence needed to embrace the new system. The vendor providing the system is usually best placed to provide this training.

A successful training programme will teach writers how to work with the new system according to their previous writing preferences whilst maintaining compliance with the new procedures that govern the system. Establishing confidence in the system will prevent new users from reverting to legacy systems. The availability of these legacy systems may create a disincentive for users to fully buy-in to a new way of working so there would be benefits in ensuring access to these is revoked as early as practical.

Evolution

It is important to adapt and improve the configuration of the eDMS as the project matures. A critical challenge to the use of eDMS in a large CRO is the maintenance of inter-sponsor security when providing clients with access to their documents.

In our initial system configuration, this was achieved by storing each sponsor's documents in a separate sponsor-specific environment. This was very effective at maintaining security as new users needed to be provided with direct access to a sponsor's environment to see any of their documents; however, each new environment directly increased the level of administrative and technical support that was required.

In response to this, and after new functionality became available, the vendor and ICON redesigned the system configuration so that all documents could be stored in a single environment. This new environment utilises dynamic security that prevents sponsor users gaining access to the documents of another sponsor. A large revalidation and testing programme was performed to confirm the integrity of these

security measures before the new system went live. These changes generated beneficial reductions in administration time and an increase in general engagement as users now had all of their documents within a single location. With a true SaaS model and new innovations delivered on a scheduled basis, there are continual opportunities to improve processes.

Benefits

Collaboration

Automated workflows can track quality control (QC) reviews, capture the details of all QC participants, and allow for electronic signature. A record of all reviews is kept on the system; reports and audit trails can be exported from the system, if required. The introduction of workflows has allowed ICON Medical Writing to phase-out the use of hard copy QC forms, reducing the administrative burden associated with project filing. A significant advantage in the area of collaboration also comes from the very nature of SaaS solutions compared with legacy on-premise systems. It is easy to externalise and involve the sponsor organisations in the actual review process, leading to fewer review cycles with documents.

Pick up and play

One benefit from moving to an eDMS has been an improved ability to quickly start work on a new project. Detailed meta-data link documents to specific projects, clients or a therapeutic area, which improves the ability of a writer to step into a project and identify and work with the required documents with no loss of continuity. Automatic version management functionality and associated workflows provide easy access to all incremental document versions and a quick overview of their place in that document's development.

This is a significant step-up from a manual file system as even when writers are diligent and standardised structures are in place, an absence of project knowledge can make it hard to quickly get up to speed on a new assignment.

Inspection readiness

The implementation of an eDMS and robust processes around this can notably reduce the preparation time, compliance risk and stress around an upcoming client audit or regulatory inspection.

Replacing paper QC forms with review workflows removes the risk of missing signatures as the system will require the reviewer's electronic

signature before completion; comments can also be stored and responded to within the system. The version control ensures that all major and minor versions are clearly tracked and can be identified and provided to auditors, if requested. These systems also give users the ability to export an audit trail that details all actions taken with a document.

This increased visibility of the document development process provides auditors and regulators with confidence in the completeness of the data presented to them and reduces the overall time and effort associated with an audit.

Challenges

Rigidity

The validation process that is essential for regulatory compliance can also provide challenges. Some of the flexibility afforded by manual systems has to be relinquished when working within the structure of a validated system. Configuration changes can take longer to implement because of the need to update specification documents and conduct formal testing.

Organisations without an in-house validation department may want to consider their approach for maintaining their chosen system's validation and regulatory compliance when changes are required to the configuration. This will assist in keeping the system current and allow for adaptation as their needs change. However, it should be recognised that SaaS solutions come with the advantage that the system owners no longer need to invest significant efforts in the lower levels of validation such as Installation and Operational Qualification that were traditionally associated with on-premise systems.

Managing change

Any large-scale change to the daily workings of an organisation will present challenges; medical writers are certainly not immune to this. The importance of fine-tuning the initial configuration and a well-planned training programme have been discussed; these will ease the transition, but it is also important to understand that writers will take time to adapt to the new system and additional support may be needed. An important part of this process is the communication of a well-defined plan for transitioning work to the new system. With the support of the vendor, this can be further simplified through the use of their expertise in delivering materials to support your change management approach.

Conclusion

A validated and 21 CFR part 11- and Annex 11-compliant eDMS is now a necessity for established medical writing organisations and CROs. Even without the impetus from clients, the improvements in administrative function, audit readiness, and collaboration can justify the investment required.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by ICON Plc or EMWA. This article has been written independently of ICON Medical Writing's eDMS vendor; however, the vendor was given an opportunity to review and provide comments.

Conflicts of interest

The author is employed by ICON Plc.

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Author information

Brendan Thorne has been a medical writer at ICON Plc since 2010 and is the business lead for the eDMS. Brendan gave a presentation entitled "Collaborating in the Cloud – A New Way of Working with Clients" to the 2016 Vendor European R&D Forum in Copenhagen.



Winner of the Geoff Hall Scholarship Essay Competition

The Geoff Hall Scholarships are given in honour of a former president of EMWA. Geoff was a very special person, an extremely valued member of EMWA, and a very good friend to many EMWA members. He firmly believed that the future of EMWA lies in our new and potential members, and so it's a very fitting legacy that we have the scholarship awards in his memory.

The scholarships are awarded annually on the basis of an essay competition, and the title of this year's essay was "The medical writer: partner or servant?" This year the scholarships committee decided to award only one scholarship, to Abbie Fearon.

Abbie received her PhD in tumour biology in

FOR CORRESPONDENCE



Lisa Chamberlain James

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2015 from Barts Cancer Institute, in London, England. The research focused on the dissection of drug resistance mechanisms in endometrial and breast cancer. She then moved to Switzerland to take up a role as a postdoctoral research scientist at the Eidgenössische Technische Hochschule Zürich (ETH), a science, technology, engineering and mathematics university in Switzerland, and Abbie is still there today. At the ETH, Abbie works on delineating the mech-

anisms involved in liver repair and regeneration. She also has a real love of science communication and is now focused on combining her research career with scientific writing for the general public.

Abbie's winning essay is presented opposite, and we wish her the very best at the start of her very promising medical writing career. For those of you inspired to pick up your laptop, the title for the next essay competition is "How would you go about identifying a predatory journal?" The submission deadline is September 30. More details are available on the EMWA website.

I hope to read your essays soon!

**Bestest,
Lisa**



The medical writer: Partner or servant?

From an academic who took communication for granted

I'm an academic scientist. I work in a lab and often forget about the world beyond the fume hood. As a molecular biologist, it's easy to become consumed with the behaviour of your cells without worrying too much about what the outside world thinks of your work. Well, that's not completely true; we're always worrying about what fellow scientists would make of our findings and the questions they'd ask if peer reviewing our papers. What the average person on the street would think of our data is not usually at the top of our agendas. However, one evening away from the lab, whilst still a PhD student, it was forced to the top of mine.

Over a beer, a partner of a friend of mine casually dropped into conversation that he would never give money to a cancer research charity. His explanation was simple: these charities have already received lots of donations and have achieved nothing. Giving them any more money was simply a waste. In his opinion, my days toiling in the lab could be much better spent elsewhere. As a cancer researcher, I was a little annoyed (to put it mildly), but then, after talking with him, I came to realise that I was part of the problem.

The missing link

I was an enthusiastic scientist who clearly loved her work, but I obviously wasn't explaining its significance. It's difficult to really accurately explain complex concepts and ideas in an easy to understand way. It doesn't help that scientists rarely receive any training in science communication. It could be argued that including such

training as a matter of course in a scientist's education would be beneficial across the board. Perhaps some of us would be more successful at getting those precious research grants if we could explain what we do a little better.

Research is both time consuming and expensive. Really expensive. How can we expect people to give generously to donation tins and fun runs to pay for our next experiment when we haven't explained why it is so important? There's also the small matter of making sure governments understand the relevance of basic research to society and so keep giving money to institutions to fund it. Bridging that gap is essential.

Enter the medical writer

Since that conversation in the pub many years ago, articles explaining new research discoveries are becoming more widespread in general publications. The importance of a communicator who can take technical language and make it engaging to the lay reader is of paramount importance. Here, the medical writer can take the reins.

The diversity of roles in this profession reflects the diversity of instances in which research and big data need to be communicated. These range from explaining the results of clinical trials to patients as well as doctors, to explaining how a charity's funds were used to support groundbreaking research that could one day form the basis of a cure for a disease. And there is so much in between. The difference between well and poorly communicated research could be the difference between whether or not a patient

understands the risks involved in taking their medication, or a company's decision to support and raise large sums of money for one particularly charity or another.

There are a variety of routes one can take to the end destination of medical writer. Some are traditionally trained writers with a passion for science, some clinicians who are multitasked and find an outlet for their creativity in communication, and then there are those like me; career scientists who found that explaining their own work and that of others was just as exciting as being at the bench. But, no matter what the journey, all serve a common goal: sharing their enthusiasm for medicine and basic science with the rest of the world.

How to be both

I'd like to have another conversation with the same man in the pub now that I am better equipped to explain my research to him. Sadly, this is not possible as he's no longer my friend's partner and so doesn't talk to either of us. But, it is thanks to him in some part that my interest in, and appreciation of, medical writing and communication was piqued.

Medical writers are the bridge between the lab and the outside world. In this capacity, writers play a dual role; to partner with researchers to communicate their work with the people it will affect, and to be of service to the public. After all, we each deserve to know what our charity donations and taxes fund, as well as where our next medication will come from.

Abbie Fearon

Regulatory Matters

A brief look at biosimilars in the United States

The first recorded use of a biologic was by Edward Jenner in 1796.¹ Fast forward another century, and in 1922, 14-year-old Leonard Thompson received the first dose of insulin.² From a humble beginning through the process of punctuated equilibrium, biochemists through the ages have built on those early discoveries. Now there are in excess of 250 approved marketed biologics in the US formulary, including vaccines. Biologics encompass vaccines, blood components, allergenics, somatic cell lines, tissues, peptides, antibodies, and more.³

The approval process for new or novel biologics is costly and time consuming. On the whole, biologics come with a hefty price tag for patients. As with small-molecule drugs, generic biologics could encourage competition and decrease prices. The need for generic biologics and an abbreviated approval process is necessary; however, unlike small-molecule therapeutics, a biologic is generally a complex milieu.

Simply put, the bioequivalency rules that apply to small-molecule therapeutics do not work for biologics.

In an effort to bring down the costs of biologics, the FDA enacted the Biologics Price Competition and Innovation (BPCI) Act, signed into law by President Obama in 2009. The EMA had established comparable rules in 2005. The intent of the BPCI legislation was to provide a path forward for the creation of “generic” or interchangeable/biosimilar biologic drugs analogous to the current process for small molecules. Extrapolating, the net effect should be greater patient access and lower-priced biosimilar drugs.

The first biosimilar drug approved for use in the United States was ZARXIO® (filgrastim-

sndz) in 2015. Without discussing the reasons behind the delayed adaptation of the BPCI Act, the latest printing of the FDA “Purple Book” lists 18 interchangeable/biosimilar drugs licensed for use in the United States (see Table 1).¹

The use of biosimilars in Europe has lowered prices and, as a result, improved patient access. In some cases, availability of biosimilars has lowered the price of reference material, limiting sales of the biosimilar itself. As most biosimilars in the US market have been approved in the past 2 years, it is still too early to tell if the BPCI Act will result in significant cost savings to patients. However, the European data are encouraging. It is probably safe to say there will be price decreases in the US market and improved patient access as the BPCI Act gains more traction in the United States.⁴⁻⁵

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Table 1. Interchangeable/biosimilars licensed for use in the United States¹

Product	Proprietary Name	Date of Licensure
adalimumab-adaz	Hyrimoz	October 30, 2018
adalimumab-adbm	Cyltezo	August 25, 2017
adalimumab-atto	Amjevita	September 23, 2016
bevacizumab-awwb	Mvasi	September 14, 2017
epoetin alfa-epbx	Retacrit	May 15, 2018
etanercept-szsz	Erelzi	August 30, 2016
filgrastim-aafi	Nivestym	July 20, 2018
filgrastim-sndz	Zarxio	March 6, 2015
infliximab-abda	Renflexis	April 21, 2017

Product	Proprietary Name	Date of Licensure
infliximab-dyyb	Inflectra	April 5, 2016
infliximab-qbtx	Ixifi	December 13, 2017
pegfilgrastim-cbqv	Udenyca	November 2, 2018
pegfilgrastim-jmdb	Fulphila	June 4, 2018
rituximab-abbs	Truxima	November 28, 2018
trastuzumab-dkst	Ogivri	December 1, 2017
trastuzumab-dttb	Ontruzant	January 18, 2019
trastuzumab-pkrb	Herzuma	December 14, 2018
trastuzumab-qyyp	Trazimera	March 11, 2019

News from the EMA

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The articles included in this section are a selection from the European Medicines Agency (EMA)'s News and Press Releases archive from January 2019 to March 2019. More information can be found on the Agency's website: www.ema.europa.eu



New safety features for medicines sold in the European Union

February 8, 2019 – As of February 9, 2019, most prescription medicines and some over-the-counter medicines for human use supplied in the European Union (EU) are required to have a unique identifier (a two-dimension barcode) and an anti-tampering device on their outer packaging. The anti-tampering device is a safety feature that shows whether the packaging has been opened or altered since it left the manufacturer, thereby ensuring that the content of the packaging is authentic. These mandatory safety features are a key measure of the Falsified Medicines Directive which is part of the EU's strategy to strengthen the security of the supply chain of medicines.

Falsified medicines are fake medicines that are passed off as real, authorised medicines. In June 2011, the EU strengthened the protection of patients and consumers by adopting a new Directive on falsified medicines for human use. The Directive introduced new harmonised, pan-European measures, structured around four pillars:

1. Tougher rules on import of active substances;
2. Strengthened supply chain and requirements for wholesale distributors;
3. A common, EU-wide logo to identify legal online pharmacies;

4. Obligatory safety features (i.e. the unique identifier and an anti-tampering device on the outer packaging of medicines).

The fourth pillar on safety features was the final aspect of the Falsified Medicines Directive to be addressed, and this safety feature has now become mandatory.

The safety features are implemented through a delegated regulation that comes into application on 9 February 2019. It will apply in all EU/European Economic Area (EEA) Member States, except for Greece and Italy, who have until 2025 to update their already existing tracking systems.

The safety features will help protect European citizens against the threat of falsified medicines, which may contain ingredients, including active ingredients, which are of low quality or in the wrong dosage and could potentially put patients' health at risk. The unique identifier and the anti-tampering device on the packaging of the medicines will guarantee medicine authenticity for the benefit of patients and will strengthen the security of the medicine supply chain, from manufacturers to distributors to pharmacies and hospitals.

Manufacturers will upload the information contained in the unique identifier for each individual medicine to a central EU repository. The repository is part of an end-to-end medicines verification system introduced by the regulation. Depending on the source of the medicine, wholesalers will also need to scan medicines at different points in the supply chain to verify their authenticity. Pharmacies and hospitals will then scan each medicine at the end of the supply chain to verify their authenticity and check them out from the repository before dispensing them to patients. Although the safety features are now a legal requirement, medicines that were released for sale or distribution without the safety features before 9 February can still be dispensed.

Also, a new reporting form is available on European Medicines Agency (EMA)'s website to be used by pharmaceutical companies when notifying EMA of any suspected falsification of their centrally authorised medicines. The new form is specifically for notifications related to suspected and confirmed falsified medicines and suspicious offers and is an important step in streamlining processes for reporting and investigating falsifications of centrally authorised medicines.

European Union and Switzerland to improve information-sharing on good manufacturing practice through use of EudraGMDP database

February 21, 2019 — The Swiss Agency for Therapeutic Products (Swissmedic) has started in 2019 to enter information on Good manufacturing practice (GMP) compliance as well as on manufacturing authorisations related to Swiss manufacturers into the EU's EudraGMDP database. This applies for all new or renewed manufacturing authorisations and the related GMP certificates issued using new templates (similar to those of EMA). This will allow replacing the current practice of issuing paper documents, i.e. GMP certificates for certain regulatory procedures and therefore should lead to easier information-sharing and efficiency gains for all stakeholders.

The EudraGMDP database is the EU's database on manufacturing, import and wholesale-distribution authorisations, and GMP and Good distribution practice (GDP) certificates. A public version of the database has been available since 2011 and gives public access to the information in the database that is not commercially confidential or contains personal data. This

means that the GMP compliance status of manufacturing facilities can be readily verified online by all stakeholders, including importers, manufacturers and regulatory authorities.

This latest development is part of the mutual recognition agreement (MRA) between the EU and Switzerland, operational since June 2002 and most recently updated in August 2017. The latest amendment introduced the provisions on data entry to EudraGMDP by the Swiss authorities. Swissmedic has 'read and write' access to the data base and will be entering GMP compliance information on Swiss manufacturers, including those exporting to the EU. As a consequence, the regulatory requirement to provide original paper GMP certificates issued by EU or Swiss authorities will be replaced by either the provision of a reference to an entry in EudraGMDP or by means of a downloadable file or printout from the data base.

The details of the specific applicability of this measure depend on the respective regulatory procedures, e.g., as regards importation or



marketing authorisation, and are clarified in relevant notices of each party. In cases where a certificate of GMP compliance cannot be accessed via the EudraGMDP database, the document will have to be requested following the "traditional" procedures directly from the competent authority which inspected the manufacturer in question.

EMA offers 'read and write' access to EudraGMDP to the regulatory authorities of all countries with which the EU has an MRA. Since 2013, the Japanese authorities also enter data into EudraGMDP which allows waiving the need for paper GMP certificates for certain procedures.

New add-on treatment for patients with severe asthma

March 1, 2019 – EMA's human medicines committee (CHMP) has recommended granting an extension of indication to Dupixent (dupilumab) as an add-on maintenance treatment for adult and adolescent (12 years and older) patients with certain forms of severe asthma.

Asthma is a chronic lung disease caused by the interaction of genetic and environmental factors. It causes airways to narrow and swell and

to produce mucus. The main symptoms are coughing, wheezing, shortness of breath but severe asthma attacks can even lead to hospitalisation. Currently, there is no cure for asthma and treatments available are used to control the symptoms (reliever) or to reduce the frequency and severity of the attacks (controller). Therapeutic options are limited for patients with severe asthma whose symptoms cannot be controlled with the available treatments such as high dose inhaled corticosteroids.

Dupixent is a human monoclonal antibody that reduces inflammation observed in the airways through inhibition of the signalling of two key proteins (interleukin-4 and interleukin-13). This represents a novel mechanism of action to the available therapeutic options in severe asthma patients. Dupixent is already approved in the EU for adult patients with atopic dermatitis who are candidates for systemic therapy. The CHMP's opinion recommends to extend the indication to add-on maintenance treatment for adult and adolescent (12 years and older) severe asthma patients with type II inflammation characterised

by increased blood eosinophils and/or raised exhaled nitric oxide measured by FeNO test and inadequately controlled by inhaled high dose corticosteroids plus another asthma medicinal product.

The benefits and safety of Dupixent have been studied in three pivotal trials including a total of 2,888 patients. In the clinical trials conducted, Dupixent demonstrated benefit to patients by reducing severe asthma exacerbations and improving lung function. The most common side effects of Dupixent are infections, eye disorders (conjunctivitis and related conditions) and injection site reactions.

The opinion adopted by the CHMP at its February 2019 meeting is an intermediary step on Dupixent's path to patient access in this new indication. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.



First treatment for rare disease characterised by high levels of triglycerides in blood



March 1, 2019 – EMA has recommended granting a conditional marketing authorisation (CMA) for Waylivra (volanesorsen), the first medicine for the treatment of the familial chylomicronaemia syndrome (FCS). FCS is a rare genetic disease that prevents the body from breaking down fats (lipids). Patients with this condition have extremely high levels of triglycerides in their blood. This causes a range of symptoms including for instance severe abdominal pain, potentially fatal attacks of acute pancreatitis, hepatosplenomegaly, diabetes, lack of concentration, memory loss and fat-filled spots on the skin (called xanthomas).

There is currently no authorised medicine available to treat this rare disease. Patients need

to strictly limit their fat intake through diet, but this is not always feasible and sufficiently effective to reduce the level of triglycerides and prevent pancreatitis. Existing lipid-lowering medications are only minimally effective to reduce triglyceride levels in patients with FCS and there is an urgent unmet medical need for new treatments to help patients to manage this disease.

The benefits and safety of Waylivra were investigated in a phase III clinical study involving 66 patients with FCS. Data from this study showed that levels of triglycerides in the blood of patients treated with Waylivra decreased on average by 77% after 3 months' treatment, compared to an increase of 18% in the placebo-receiving control group. The observed substantial

reduction in levels of triglycerides is expected to lead to a reduction in the incidence of potentially life-threatening pancreatitis. The most common side effects are reduced platelet counts and injection site reactions. A number of cases of severe platelet reduction were observed in the Waylivra trials, which may result in an increased risk of bleeding. To manage this risk, a number of additional risk minimisation measures will be implemented including strict dosing guidance based on regular platelet monitoring and specific information to patients and their carers on this potential risk. As part of the CMA, the applicant is also required to conduct a study that further investigates the safety and efficacy of the medicine and the feasibility of implemented risk minimisation measures.

CMA is one of the EU's regulatory mechanisms to facilitate early access to medicines that address an unmet medical need. Conditional approval allows the Agency to recommend a medicine for marketing authorisation in the interest of public health where the benefit to patients of its immediate availability outweighs the risk inherent in the fact that additional data are still required.

FCS was granted an orphan designation in the EU in February 2014. At the time of orphan designation, it was considered that the condition affected less than 1 in 100,000 persons. As always at the time of approval, this orphan designation will now be reviewed by EMA's Committee for Orphan Medicinal Products (COMP) to determine whether the information available to date allows maintaining Waylivra's orphan status and granting this medicine ten years of market exclusivity.

EMA confirms omega-3 fatty acid medicines are not effective in preventing further heart problems after a heart attack

March 29, 2019 – EMA has confirmed that omega-3 fatty acid medicines containing a combination of an ethyl ester of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a dose of 1 g per day are not effective in preventing further problems with the heart and blood vessels in patients who have had a heart attack. This is the outcome of a re-examination requested by some of the companies that market the medicines

concerned, following EMA's original recommendation in December 2018. This means that these medicines should no longer be used in this way. However, they can still be used to reduce levels of certain types of blood fat called triglycerides.

The review concerned omega-3 fatty acid medicines containing a combination of EPA and DHA and focused on the medicines' use in patients who have had a heart attack. EPA and

DHA are commonly found in fish oils. Omega-3 fatty acid medicines are taken by mouth and have been authorised for use after a heart attack in combination with other medicines, in several EU countries since 2000, at a dose of 1 g per day. At the time of their authorisation, available data showed some benefits in reducing serious problems with the heart and blood vessels.

EMA's committee for human medicines, CHMP, has re-assessed the evidence

New add-on treatment to insulin for treatment of certain patients with type 1 diabetes

March 1, 2019 – EMA's human medicines committee (CHMP) has adopted a positive opinion for Zynquista (sotagliflozin) intended as an adjunct to insulin for certain patients with type 1 diabetes mellitus. Zynquista is a small molecule with dual inhibitor activity on SGLT1 and SGLT2. It works in the kidneys to prevent reabsorption of glucose from the urine and in the proximal intestine to delay and reduce glucose absorption into the blood stream, which helps lower the blood sugar level. This medicine is the second SGLT inhibitor for the treatment of type 1 diabetes to be recommended for authorisation.

Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus who have failed to achieve adequate glycaemic control despite optimal insulin therapy. Patients considered for this treatment should fulfill certain requirements and should have a body mass index (BMI) higher than 27 kg/m².

Type 1 diabetes is an autoimmune disease in which the immune system mistakenly attacks the insulin-producing beta cells in the pancreas. Without insulin, the body cannot maintain proper blood glucose levels. Patients with type 1 diabetes require lifelong insulin therapy.

In spite of improvements in insulin, its methods of administration and monitoring of blood glucose, a proportion of patients with the disease are unable to achieve or maintain recommended blood sugar levels with insulin alone. Hyper- and hypoglycaemia and weight gain are common and patients' life expectancy is still significantly reduced compared to the general population, mainly due to the increased risk of heart disease. Thus, there is a need for new

therapies as an adjunct to insulin therapy, to better manage blood sugar levels and other cardiovascular risk factors.

The CHMP's positive opinion is based on data from three phase 3 studies including 1,853 patients with type 1 diabetes mellitus. The main benefit of treatment with sotagliflozin in patients with type 1 diabetes is its ability to improve glycaemic control. Other effects include weight and blood pressure reductions and reduced variability of glucose levels.

Despite precautionary measures during treatment with sotagliflozin, there is a considerable increase in the risk of diabetic ketoacidosis (DKA), a potentially life-threatening complication. Because the increased risk is of concern,

the CHMP recommends limiting the use in type 1 diabetes mellitus patients as follows: treatment should only be considered in overweight or obese patients with a BMI higher than 27 kg/m². Use of Zynquista is not recommended in type 1 diabetes mellitus patients with low insulin requirements. During treatment with Zynquista, insulin therapy should be continuously optimised to prevent ketosis and DKA and the insulin dose should only be reduced to avoid hypoglycaemia. This treatment should only be initiated and supervised by specialist doctors. Patients should be able and committed to control ketone levels in their body. They should be educated about risk factors for DKA and how to recognise its signs and symptoms.



accumulated over the years on these medicines for this specific use and consulted additional experts in the field. It concluded that, although there are no new safety concerns, the effectiveness of these medicines in preventing recurrence of problems with the heart and blood vessels has not been confirmed. EMA concluded that the marketing authorisations of these medicines should be updated to remove this use.



Getting Your Foot in the Door

Editorial

In this June edition of GYFD, I'd like to share a diagram developed by my colleagues at the Swiss Association of Pharmaceutical Professionals (SwAPP). The diagram serves as a road map for those looking for their place in the healthcare industry. Can you pinpoint those areas where medical writers can get their foot in the door?

Also featured here is the inspiring career journey of Sushma Materla from a postgraduate student to highly experienced medical writer. Happy reading!

Raquel Billiones

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important role at any given time point of drug development and an essential liaison collaborating with multiple stakeholders like regulatory bodies, patients, caretakers, healthcare professionals, researchers, reimbursement bodies, clinical trial teams, and the general public, etc. Therefore, medical writing is an art of narrating science, tailored to the reader.

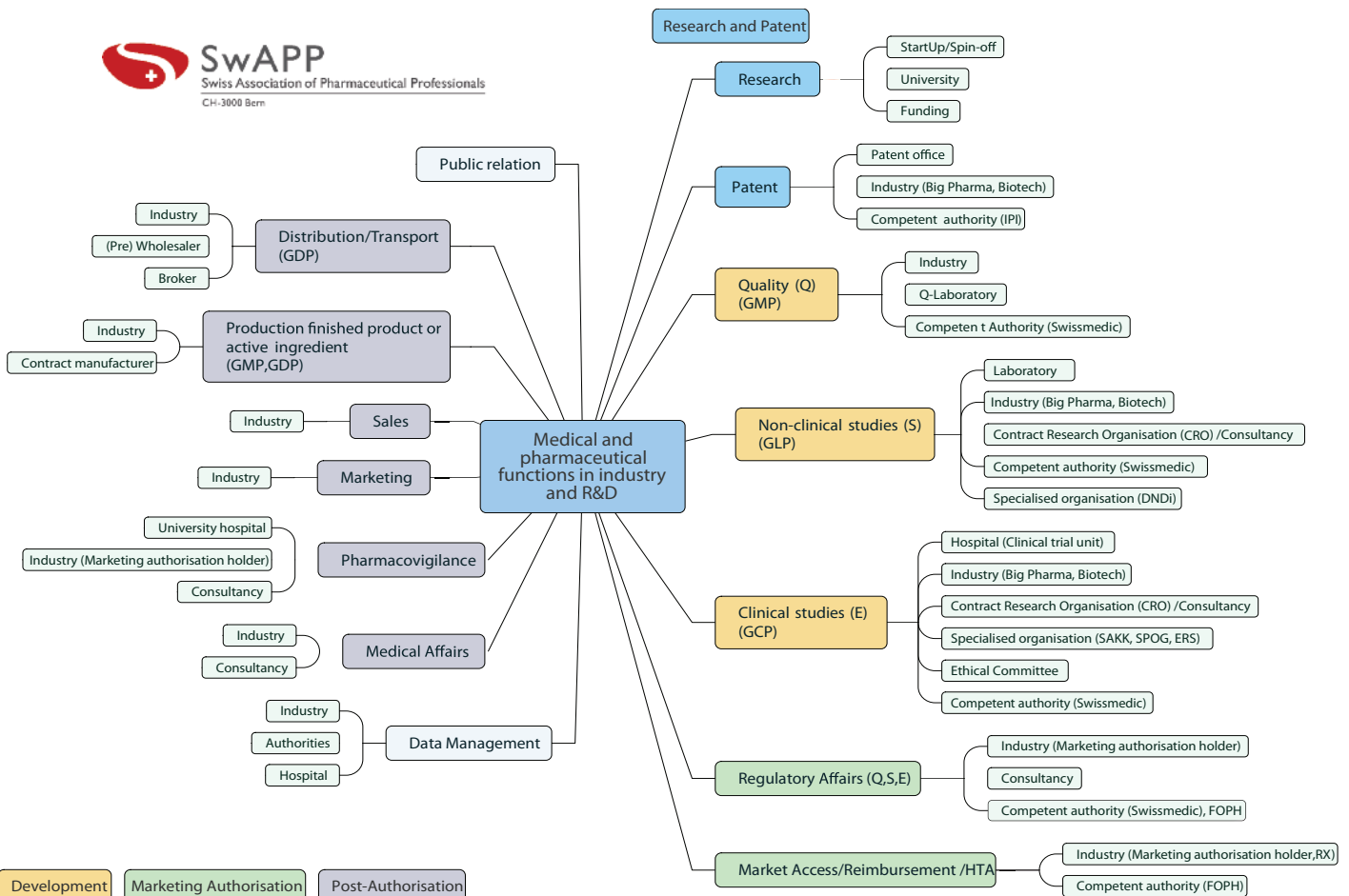
Choosing and chasing a career path certainly isn't easy but as a first step, one needs to be well-informed and passionate to pave their way towards their field of choice. The essence of this article is to guide students or professionals in choosing or building a career path into medical writing. The intent is to provide valuable insights to incite thoughtful introspection about one's preferences for a fulfilling career and sustain the

Medical writing: A walk through my career journey

Scientific advances have come a long way through centuries, yet drug development appears to be in its nascent stages owing to the dynamic ethical and regulatory environment. Its growing popularity over the last few decades has attracted students, academicians, and professionals from various biomedical backgrounds into trying their hands across different fields within drug development. With ample

opportunities comes the challenge to identify an appropriate field that best suits one's academic background, passion, and goals in their career journey. One of the critical areas of drug development is "documentation"; and medical writing is one of the key aspects of documentation that demands vast knowledge of disease areas and extensive skills not limited to writing. A medical writer (MW) plays an

If it wasn't documented, it didn't happen.



Medical and pharmaceutical functions in industry and R&D © SwAPP 2018. (Reprinted with permission)

momentum in building expertise. This is only a basic guidance based on my personal career journey limited to regulatory writing in a corporate pharmaceutical company setting.

Ask yourself: Why medical writing?

More often than not, students' aim is more to grab a job offer than to choose one. It is inevitable that the industry looks for experienced professionals that are best fit for the role. So, it might be very difficult to be amongst the chosen one to get a job of your choice. Nevertheless, there are ample opportunities that companies offer such as summer internships, trainee programmes, campus placements, walk-in interviews, career fairs, and recruitment drives. With a range of options, one should be aware of the extent to which you would be willing to invest your time and efforts in landing yourself a job of choice. To do this, it is critical to introspect on a few key points to understand your interest in medical writing. As a start off, ask yourself these simple questions:

- Does data interpretation interest me?
- Have I enjoyed semester assignments or thesis writing?
- Am I good at converting volumes of data into clear, concise, and meaningful messages?
- Am I keen on keeping abreast with new research trends?

If your answer to these questions is a definitive yes, you might want to consider going into the medical writing field.

When clinical research began as a formal course in India during the mid-2000s, I had no clue on what it was all about. With an inquisitive mindset, I have chosen to take up the 2-year postgraduate course in this field at Cranfield University, UK. During my course work, I realised that I enjoyed reading literature, research trends, and writing my assignments and thesis more than actually doing the project itself. In one of my orientation classes, I attended a session on different job profiles in the pharma and clinical research organisation (CRO) industry. That was when the idea of medical writing struck with me deeply and I knew this is what I wanted to pursue.

Does educational background matter?

The most commonly asked question is, does the area of one's educational background, degree or course matter in pursuing their ambition of a medical writing career? Theoretically speaking,

As we enter an "era of data transparency", the role of medical writing gains more importance as a "communication catalyst" throughout the drug development process.

this does not impact your abilities to be a MW as long as you are from a field relevant to biomedical science and have the potential skills that the role demands. As competition is tough for every field, landing a medical writing job doesn't come easy. Your additional competencies are what give you an edge over other potential candidates to showcase not only in your resume but also during an interview. To build such competencies, one could consider taking up courses related to medical writing, drug regulatory affairs, pharma-covigilance, communication skills, etc.

On the other hand, professionals with sufficient experience in other domains (pharmacovigilance, clinical operations, data management, etc.) might want to explore new horizons within clinical research. This is when the question is a bit different: "Would my experience count to transition laterally into the medical writing domain?" Of course, the answer is a "yes", but it depends on two things:

- First, the duration of a candidate's experience in the current role. A lateral shift might mean descending a level below regardless of the experience one may have had and especially when the intended job demands high technical and functional expertise.
- Second, the level of experience that the job demands. This is certainly challenging for candidates making a lateral move. Therefore, it becomes imperative to understand the job description in depth to be able to justify how their current experience would enable them to perform the job better and quicker than the other potential candidates for the role. This comes with ease when one gains the knowledge of different roles in a project team and understands how to connect their interdependencies.

With growing curiosity in medical writing, I decided to take up a certification course in medical writing during the summer break after my first semester of postgraduate course. I spent nearly 4 weeks together on Google to find a good one amongst a very few institutions which offer such a course. Medical writing was a new concept at that time in my city. I did not regret spending

my holidays doing this course instead of enjoying with my family and friends. I completed this certification course at a medical and marketing communications agency in Hyderabad, India. During the course, I was consistently encouraged by my mentor to explore various domains within medical writing. It also taught me in depth the broad aspects of medical writing unlike the postgraduate programme which focused on clinical research in general.

After completing my postgraduate degree, I revisited my mentor for guidance on job searches, who connected me to some of the MWs in the industry. Despite many referrals and attempts, there was no luck even in getting an interview call. At that time, there was no LinkedIn but there were many job portals. After a few months, I managed to get a few walk-in interview calls, went into direct walk-in interviews and recruitments drives. Yet during the final rounds, I was rejected multiple times by many big and small companies due to a lack of industry experience. This is a default reason that freshers hear from a recruiter. That's when my mentor offered me a job at the same agency where I completed my certification course to handle some of their healthcare writing projects. I couldn't thank him enough and I kick started my career journey in medical writing.

An array of opportunities!

Medical writing offers different areas of expertise which one can steer into. A few of them include regulatory writing, publication/scientific writing, pharmacovigilance writing, clinical writing, medico-marketing communications, health economics writing, scientific journalism, etc. Having all these options to choose from allows one to evaluate professional interests in relation to one's educational background or current domain. More often than not, this is by mere chance rather than a choice that people end up being a MW, probably because of lack of guidance or lack of pursuit. With a rapidly evolving regulatory environment and increasing volumes of "big" data, there is an exponential



growth of medical writing consultancies; therefore, demand for MWs in the market continues to rise. This is the key factor that makes us more empowered than ever to take advantage of choosing a field of expertise within medical writing. Apart from these, the unique advantage of this field is the feasibility of freelancing, unlike any other field within drug development.

After a few months in my first job, I realised that I wanted to purpose my educational background into a more relevant role and chose to explore regulatory medical writing. Just in time, I had a friend who informed me of an internship opportunity at Novartis, Hyderabad. Though I was sceptical of leaving a full-time job for a temporary internship, I took a leap of faith with a hope that my skills wouldn't go unnoticed. I performed well in the interview and finally managed to grab the role of a scientific writer-intern.

Stepping in was a temporary relief but my chances of getting a full-time job after the six-month internship within the organisation was uncertain. It was by chance that I made it to a permanent position. I could never have imagined an informal lunch meeting with my skip level manager turned out to be an informal interview; I only realised this after I was offered the permanent position following a formal interview. I was later told that the reason to hire me was not only my dedication to learn and perform but also my transparency. This was when I learnt that 'integrity' matters both personally and professionally.

Building your career blocks: Enhancing expertise

Making it big careerwise starts with small building blocks to gain the required level of skills to perform the daily job. A simple suggestion is to focus on preparatory reading at any given time point for any kind of project, as this takes precedence over actual writing itself. When we want to keep it short, simple, clear, and concise, we need to process large volumes of information and resynthesise to tailor for the audience of interest. In the end, remind yourself the intended outcome of the document you are writing: what do you want your reader to perceive and what action do you expect them to take? Amongst the many skills required, being meticulous with an eye for detail is the primary attribute one must possess to be a reliable MW.

Career survival and progress comes not only by gaining expertise but also by having the passion to sustain the learning curve. Over the due course,

Being more than a medical writer enables us to shirk the team's perception of our role from a mere "service partner" to a value adding "strategic partner".

gaining experience and expertise becomes naturally important in building career blocks. Some of the options one could consider include leading or contributing to cross-functional initiatives, pilot projects, trainings, conferences, current trends/news, regulatory updates, executive courses, courses with medical writing associations, workshops, coaching and mentoring programmes, informal collaborations, networking, volunteering, etc.

During my tenure at Novartis, I started with short and simple documents like safety narratives and public disclosures and moved on to develop simple Phase 1 to 2 clinical study reports. With advice from my manager and coach, I moved into writing development safety update reports, periodic safety update reports, and risk management plans. As I gained experience with safety documents, I took up complex documents like CTD clinical modules, i.e., summary of clinical safety, summary of clinical efficacy, and clinical overview. While these helped me gain technical expertise in regulatory medical writing, I also actively led and contributed to a few cross-functional initiatives for process streamlining, delivered global trainings, conducted and attended writing workshops, got involved in mentoring programmes, handled vendor management, and led as a "dedicated programme MW" for a compound etc. I attended medical writing conferences to enrich my knowledge and network which gave me an opportunity to be a speaker at a DIA medical writing conference in 2017.

Being a strategic partner

Having to collaborate with multiple contributors in the team requires a MW not only to display writing skills but also to gain their trust to be considered as a valuable and reliable partner. Writers may rarely become authors, but that should not hinder us from displaying our authoring potential as long it is in our purview. Of course, this requires going the extra mile by providing strategic inputs to the project teams; for example, providing expert input on templates, regulatory requirements, processes and workflows, data interpretation, and alternative ways to resolve project issues, etc. Initially, this might seem quite challenging but eventually it comes with experience and in-depth background on project requirements, knowledge of the compound or therapeutic area, and expertise on the document type. Trust me when I say no good performance review feedback gives me more happiness than a direct positive feedback from teams on my strategic contributions beyond writing.

Creating the balance: writing and management

Most MWs enjoy writing and continue to be happy in their individual contributor roles while some move into management roles as they progress in their career. The two roles might seem mutually exclusive but management skills are equally vital for a MW to possess and enhance. Every writing project demands people and project management skills to gather required inputs, tracking milestones, facilitating meetings, collaborating with multiple stakeholders, managing review cycles, etc. Therefore, it is essential to balance the two skills to enable on time completion of high quality deliverables. This is especially important for freelancers because they are their own writers, managers, and accountants.

Pre-define your own success indicators

As one continues to gain experience, it is not uncommon for one to aim for a managerial or an operational position. Not many are aware that this is not the only path to move ahead in the medical writing field. This is a unique field that offers multiple levels of senior roles into functional/technical area like subject matter experts, expert consultants, coaches or trainers, business managers, client/portfolio managers, or project managers. Therefore, before embarking further, one might want to carefully introspect on the reasons for choosing a particular role, keeping in view one's forté.

Currently, I am working as a consultant lead medical writer. After nearly 10 years of experience as a medical writer, I do not regret eschewing a managerial position unlike many of my peers. Career success is subjective and is pre-defined by self. So far, I consider myself a successful MW and continue to do so. My satisfaction lies in accolades from my teams and peers. In the end, I take pride in making a positive impact in patients' lives and companies' future.

The human tendency is to compete for everything because we are programmed to be eternally dissatisfied with whatever we acquire. Conflict is a way of life and it is no different in a professional life. One must realise that career success is not dictated by corporate competition but by your own career goal. Setting this goal and revisiting it regularly comes from one's passion, ambition, and perseverance to be a successful MW.

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Veterinary Medical Writing

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Editorial

With veterinary treatment options becoming more diverse and advancing rapidly, the demand for veterinary medical writers is growing. Currently we are a growing group of

vets in EMWA and we look forward to welcoming more colleagues to our community. Coming from a clinic, research institute or position within a local authority, vets bring a lot

of different experiences to the table of medical writing. Jennifer Freymann is one of us and was kind enough to share her experience on communication and transparency with us.

Transparency on controversial topics: What medical writing can learn from vets

I have a background in laboratory animal science, and I was happy to find interesting ties to medical writing. One good example is the relatively new interest in open communication about animal experimentation. Although animals are (and will be in the future) desperately needed in research, animal experimentation is still a controversial topic. This is in part due to a lack of information and animal rights activists have used this to incite concerns and rejection of animal experimentation. To approach the problem and raise awareness, a growing number of research institutes engage in an open dialogue with the general public. In the UK, institutes can sign the *Concordat on Openness on Animal Research* and thereby commit to a transparent communication about animal experimentation. Following Britain's example, more and more research facilities in Europe speak openly about the research they conduct. The announcement of a clear commitment to animal experimentation on an institute's website is a great first step towards more transparency. Open days for the public provide a meeting point for scientists and laymen. Such events are a great opportunity to answer questions and explain face-to-face the research that is done.

Translating information

Speaking from my own experience during open days, I was often confronted with a mixture of scepticism, curiosity, prejudice, and justified criticism. You need to provide facts and reasonable information to discuss the necessity, advantages and limitations of animal studies with an interested public.

Providing clear and easy-to-understand information will sound very familiar to medical



writers. Speaking about animal experimentation is a form of medical communication: the ability to explain science, medical advances, and procedures to a lay audience is essential; we act as a translator, giving everyone the information they need in the right language. Communicating in an often emotionally charged discussion certainly sharpens your tools.

Where medical writers can gain insights

Besides open communication, systematic reviews are another field where animal experimentation and medical writing can benefit from each other. As an important element in evidence-based medicine, systematic reviews are well known in clinical research. Since animal experimentation

is the basis for a majority of this research, the need for systematic reviews here is undisputed. The Systematic Review Centre of Laboratory Animal Experimentation (SYRCLE) in Nijmegen, the Netherlands, provides a lot of valuable advice, guidelines and tools on systematic reviews in pre-clinical research. The goal is to improve quality and reproducibility of animal studies; however systematic reviews can not only point towards new hypothesis, but also help to avoid unnecessary experiments.

There are so many other links between veterinary medicine and medical writing. I am excited and inspired to discover them together with you!

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Teaching Medical Writing

The teaching of medical writing has arrived!

How far does the academic medical world recognise the teaching of medical writing? Does PubMed include articles on courses, techniques, or material for the teaching of medical writing to health personnel or scientists? Teaching of medical writing is not commonly included in university programmes,¹ so perhaps it does not figure in academic publications. Furthermore, the EMWA journal *Medical Writing* is not indexed in PubMed.

I decided to see how many articles would be generated by a simple PubMed search of articles published over the course of 1 year, limited to free full text available in English (apologies to non-native English speakers, but in fact it did not change the number of articles) (Table 1). Many of the 109 articles generated discussed medical education in general, treatment of specific illnesses or symptoms (e.g., tremor, difficulty writing), clinicians' prescribing skills, administrative issues, research leadership, or scientific competencies, and a few discussed the quality of hand-written operative notes, medical writing techniques (such as hedging), ghostwriting, collaborative writing, and peer review.

Six articles dealt with the teaching of medical writing. Three papers provided writing advice for medical students and scientists, and the other three reported on the effects of specific writing programmes or interventions.

Teachers' advice to medical students and scientists

Gottlieb et al.,² provide a "primer for junior academics" targeted at trainees in emergency medicine, but the advice is relevant for all

academic medical writers. The authors describe the typical content and structure of journal articles (Introduction, Methods, Results, Discussion), the use of journals' author guidelines and reporting guidelines (the EQUATOR network), and the importance of a cover letter and of ensuring that your own work is identifiable (e.g., by obtaining a unique identifier through ORCID). They also discuss authorship roles and author order. The aspects I found particularly helpful for teaching purposes were:

- Two main strategies for determining the order of authors: the "sequence-determines-credit" approach (more common in the medical field) and the "equal contribution" approach (more common in other scientific fields)
- A detailed section on choosing an appropriate journal, with information about how to check whether a journal is indexed in an NLM database (including PubMed and Medline) and how to use the SCImago Journal and Country Rank index (SJR; based on the Scopus database³) to identify and rate journals in specific fields. (I found 41 open access journals in immunology and allergy, each with an SJR quality ranking, the H index, citation numbers, country of publication, and percentage of international collaboration. In my teaching, this will be a useful addition to the JANE server⁴ that I usually tell students about.)
- Tips on how to "survive" the peer review process: e.g., preparing a point-by-point response to a decision letter and (highly recommended sometimes!) the value of waiting 1 to 2 days before responding "to let

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any strong emotions pass and allow you to focus on the scientific components of the paper" (p.1001).

- How to identify predatory open access journals that change publication fees without providing any significant editorial or publishing services (and may even change fees for the withdrawal of a paper from review if an author discovers its predatory nature). Tables 3 and 4 in the paper list criteria for determining the legitimacy of a journal and the features of a predatory journal. (Unfortunately, these are now necessary topics in medical writing courses for authors in the health sciences.)

Iskander et al.,⁵ write from 30 years' experience with a scientific writing course for public health students and professionals. They mention similar points to Gottlieb et al., but have additional items:

- As an early step in drafting your article, write out the "take-home message" and share it with co-authors for their review and comment. This helps to ensure agreement on relevant structure and content of the manuscript.
- If you have not already planned your tables and figures at the protocol stage, consider starting the Results section by drafting the figures and tables, then develop one to two sentences that summarise each one. You are more likely to focus on the most relevant results for the research question – linked to the take-home message.
- The Abstract should not be written in a hurry

Table 1. Search history in PubMed on teaching medical writing

Search	Add to builder	Query	Items found
#5	Add	Search ((writing[Title/Abstract]) OR medical writer*[Title/Abstract]) NOT case report[Title/Abstract] Filters: Free full text; Publication date from 2018/03/01 to 2019/02/28; Humans; English	109
#4	Add	Search medical writing Filters: Free full text; Publication date from 2018/03/01 to 2019/02/28; Humans	149
#3	Add	Search medical writing Filters: Publication date from 2018/03/01 to 2019/02/28; Humans	256
#2	Add	Search medical writing Filters: Publication date from 2018/03/01 to 2019/02/28	1,057
#1	Add	Search medical writing Study types: Clinical study/trial + Comparative study + Evaluation studies + Meta-analysis + Review	11,090

at the last minute! It helps a reader to decide whether to read further, so make it count. Review your completed manuscript to identify the main aspects of the methods and results and a clear conclusion.

Peterson et al.,⁶ offer “10 simple rules” to help scientists improve their writing productivity, including these useful reminders:

- It may help you to write more regularly if you develop your own “triggers” for writing, e.g., music, a brisk walk, or making a cup of tea.
- When you ask for feedback on your writing, make it clear what sort of feedback you want – on the whole text or a specific section? On the structure only? Or the grammar as well?
- You need time to reflect on your writing, so instead of delaying until the last minute, make a start and work on it regularly.

Evaluating the effects of writing programmes or interventions

Duncansen et al.,⁷ investigated the publication outcome and skills development among 50 first-time researchers who participated in “writing bootcamps” in rural Australia between 2012 and 2015. The researchers had a weekly group teleconference for 6 weeks then two follow-up teleconferences within 3 months. The homework was working on own text and providing written feedback to each other. Despite possible self-selection by those more interested in writing for publication or with research findings worthy of publication, more of the programme participants (52%) submitted manuscripts to peer-reviewed journals (of which 42% was published) than did non-participants (15%). The participants reported increased confidence in scientific writing and had valued the support from their peers, especially the giving and receiving of feedback on their writing.

Sahoo and Mohammed⁸ described an educational writing programme for Malaysian medical students aimed at developing critical thinking skills. The focus of the 4-week programme was on justification and reasoning in writing research proposals. The 188 students made a literature search, developed relevant research questions for a clinical study, and were then randomly divided into small groups to write a research protocol. The students’ written



comments on their learning process make interesting reading. They clearly enjoyed the tasks (referring to the assignments as “fun”) and found the group work useful (“I could learn better by sharing my thoughts”). The authors recommended the inclusion of writing modules in the core medical curriculum – structured in a collaborative learning format but with reflective practice embedded – to foster the skills of critical thinking and collaboration.

Ruscetti et al.,⁹ set out to develop a method to assess the quality of quantitative writing for their biology students at a Californian university and ended up with a useful educational tool. They analysed ‘quantitative comparison’ statements in the literature (e.g., “Average height was 25% higher in Group A than in Group B.”) and concluded that such statements need four elements (4C): *Comparison* (Group A vs Group B), *Calculation* (25% higher), *Context* (average height), and *Clarity* (the first three elements are in the same sentence with no redundancy or contradiction). The authors initially used these four rules to give feedback to the students on their writing but have since used them in teaching, for example, in writing exercises to practise sentence construction.

Conclusion

PubMed certainly does include articles that describe medical writing courses or that evaluate writing interventions for medical and scientific researchers. The six articles I identified were written by authors at different institutions in various countries and were published in a range of medical and scientific journals. I found the

content relevant for my own teaching, and I hope that others will also find it useful. I would be interested to hear from any reader who has other experiences or suggestions for teaching medical writing that they would like to share. In the meantime, I will continue to review PubMed now and again for relevant articles.

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Conflicts of interest

The author declares no conflicts of interest.

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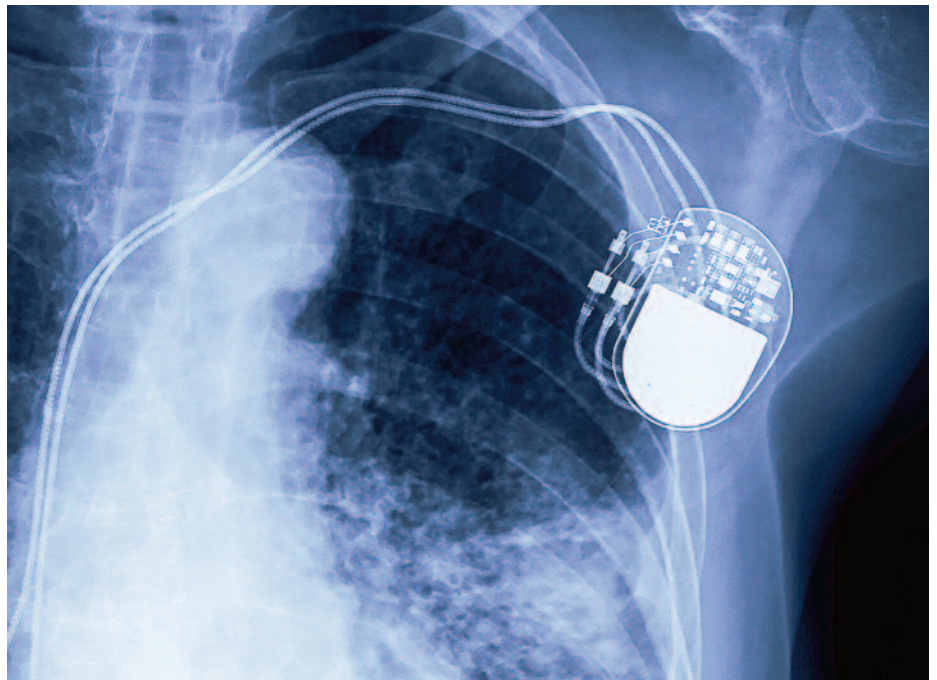
The next medical device scandal: Medical device files – my personal view (Part 2)

In the last issue, I started to share my opinion on the recently published “implant files”.^{1,2} As this topic could be discussed endlessly, I focused on an article in a German newspaper, the *Süddeutsche Zeitung*, that provided a summary about the “10 facts to know about the implant files”.³ In Part 1,² the first five “facts” were discussed, and this part will focus on the remaining assertions, which are indicated in the subheadings below.

“Frequently, devices are implanted that are not or barely tested”

The article reported that patients do not know how an implant has been certified and that the majority of implants are introduced to Europe without premarket clinical studies. Medical device approval is theoretically possible through the principal of equivalence and clinical studies can be avoided in cases where similar or “equivalent” products are already available on the market. From 2020 onwards, manufacturers can only submit CE dossiers for equivalent devices if they have the same information for the equivalent device that the manufacturer has and explain how and why it is equivalent. But the loophole remains in effect and new devices, if approved, can be sold without being clinically tested in humans.

As stated in my last article,² it is true that approval to distribute a device (“CE-certification”) has in the past often been based on limited clinical data. This is one of the reasons why the new, more rigorous device regulations were developed. Clinical Evaluation Guidelines (MEDDEV 2.7/1 revision 4) were published in June 2016 and the Medical Device Regulation (MDR 2017/745) was published in May 2017 (and will be in full effect after a 3-year transition period starting in May 2020). Both documents add new levels of



scrutiny and demand more clinical data for CE-certification and post approval data for CE-mark retention and renewal. Of note, the intensification/expansion of the equivalence approach is already in force as this was modified in the MEDDEV 2.7/1 rev 4 (June 2016) criteria.

The new MDR will require that clinical study reports be published and made available to the public (together with a lay summary), so that patients and interested parties can be informed about the clinical study results that led to CE-certification. Rather than reporting shortcomings of the past which have been amended – the authors of the implant files should have informed the readers about this prospective opportunity.

So, in short, this section of the article talks about a past situation that has changed since MEDDEV 2.7/1 Rev 4 and which will further improve once the MDR 2017/745 is fully

applicable. Regarding the still existing CE approval loophole: Yes, in rare circumstances, the equivalence approach can still be used to obtain CE-certification, because sometimes it indeed makes sense, e.g., if the product changes are only minor, can be sufficiently evaluated using preclinical data, and with planned formal post approval follow-up studies, particularly in low to medium risk devices.

Most of the studies are financed by the industry

The report states that even if there are studies, they are barely independent. Frequently authors have financial relations to the manufacturer of the devices. Furthermore, most of the studies are funded by the industry. And physicians say that studies that are negative “disappear”.

The sentence “even if there are studies” implies

that there are barely any studies, which is no longer the case. Meanwhile, for innovative, high risk devices, it is nearly impossible to receive CE-certification without data from clinical studies.

Related to financial interest: It is true that many clinical investigators may have a financial relationship to the manufacturer of the device, but:

- This must be declared in medical society presentations or publications as a “conflict of interest statement”.
- Furthermore, in clinical investigations (syn. clinical studies) investigators have to disclose any conflict of interest, e.g., using a “financial disclosure form”.⁴ These forms are commonly submitted to the ethic committees and competent authorities along with other professional details of the investigators. If an investigator has declared such an interest, it needs to be justified as to why this does not influence his participation in the clinical study.
- Financial contracts for clinical studies are commonly negotiated with the institution, as it is not allowed to directly pay investigators in most of the European countries.
- Notably, only the work performed is allowed to be reimbursed and the payments need to reflect “fair market value”.
- In most European countries financial contracts for clinical studies are supervised at a national or local institutional level. For example, in France, the Conseil National de l'Ordre des Médecins (CNOM, French Medical Council) needs to review and approve each contract between the industry, investigators, and all other involved health care professionals prior to study commencement at the investigation site. Furthermore, in most European countries, relevant parts of the contract (such as payment details) need to be submitted along with the study application to the competent authority.
- In relevant clinical studies leading to CE-certification, separate contracts are often made with independent data safety monitoring boards, clinical event review committees, and core laboratories, adding another level of independency. Of course, in the end, those committees are paid by the sponsor for the services they render, but in my experience, they are well aware of their responsibility.

Unfortunately, the authors neglected to inform the readers about positive developments such as the US⁵ Sunshine Act, which also appears to be implemented in some form in the pharmaceutical industry.⁶ Although there has been no pan-European Union agreement on the

appropriate standards of transparent payment disclosures, many EU member states have enacted Sunshine Act provisions including France, Portugal, Belgium, United Kingdom, Denmark, Romania, Latvia, Turkey, Slovakia, and Greece. Anticorruption/transparency laws are also in place in Croatia, The Netherlands, Germany, Italy, Poland, Slovenia, Sweden, and Spain.⁷⁻⁹

The statement that the majority of studies are funded by the industry is true. But for premarket and mandated postmarket studies, this is not voluntary. I can imagine that companies, particularly small start-ups who depend on external funding, would welcome someone else paying for their premarket trials which generally cost several million Euros. For postmarket registries, it is already common to have national registries, e.g., for transcatheter implantation the FRANCE registry,¹⁰ the TVT registry in the US,¹¹ the GARY registry in Germany,¹² or for stent placement the Scandinavian SCAAR registry.¹³ In addition to the current national registries, article 108 of MDR2017/745¹⁴ encourages the use of registers and databanks that shall contribute to the independent device evaluation, so it is expected to see even more in the future. Notably, these registries frequently have poor follow-up compliance as it takes tremendous efforts and very thorough study oversight to ensure good follow-up compliance, so a mix of manufacturer initiated and national registries may be a good future post market data collection scenario.

That studies with negative results disappear is a statement that I do not agree with from my experience. To be published in peer-reviewed journals, medical device clinical trials must be posted on platforms such as clinicaltrials.gov and both positive and/or negative outcomes have to be published. Approximately 2 years ago, there was some discussion that only around 50% of studies were reported, but it turned out that the analysis algorithm only identified studies as being reported if the associated clinicaltrials.gov number was displayed in the abstract or method section and that many more studies have in fact, been reported.

Also, anyone who has been involved in publication knows how difficult it is to have negative results published (unless it is something truly relevant with clinical consequences). Journal editorial committees are interested in maintaining their readership with clinically relevant results. In my personal experience, the trial with the least interesting results, e.g., a trial that reported no difference between the groups (hence negative for the study sponsor), required submissions to at least five different journals and

took more than 2 years to get published.¹⁵

Unfortunately, the reporters missed the opportunity to inform the reader that trial results are available on clinicaltrials.gov (where results can be posted in case they are not published or where a link to the respective publication should be posted). Furthermore, from 2020 onwards, the MDR-requested database should be in place and clinical study results can be accessed there.

If something goes wrong, the patient often is not informed about it

This has been true in the past, has been identified, and the new MDR 2017/745¹⁴ intends to fix this situation. Through the EUDAMED (European Database on Medical Devices) database, relevant information about a device will be centralised. Information about device certification, clinical studies and lay summaries, clinical study reports or summary of safety and performance of implantable class III devices will be accessible (see article 33 MDR2017/745 for further details). Moreover, for implantable devices, patient implant cards need to include a link to the manufacturers website that will need to contain current product information in lay terms (see article 18 of MDR2017/745 for further details).

So, this statement refers to the past, will likely be resolved soon, and again fails to provide the reader about options to obtain information.

Regulatory authorities rarely react

In Germany, neither the Federal Ministry of Health nor the competent authority BfArM provided the information about which product has caused most deaths in the past 10 years as they claim these are “confidential information”.

Frankly speaking, the information about which product has caused most deaths in the past 10 years is irrelevant. As detailed in Part 1, a device relationship is already claimed as soon as a relationship cannot be reasonably excluded. With this, the number of “device-related deaths” also correlates with the existing patient comorbidities. For instance, in the aortic transcatheter PARTNER US study,¹⁶ 19.6% of patients that were classified as high risk and inoperable died from cardiovascular causes within one year. This sounds like a very high rate of death however, the randomised comparator group that received standard therapy (medical therapy) had a 1-year mortality of 41.9%. Everything has to be seen in context.

Regulatory authorities rely on the fact that in case of failure, the manufacturer recall their device or provide safety warnings. Since 2010, this occurred

around 10,000 times, but there were only 6 recalls from the authorities during this time.

These numbers seem to show that the majority of medical device companies take their responsibility for patient safety and device quality very seriously. Furthermore, it is logical that manufacturer recalls are higher than recalls from the regulatory authorities for the following reasons:

- Companies know their product best and usually receive the relevant information first, therefore it is logical that they start the recalls first.
- There are frequent actions and “prophylactic” recalls initiated by companies before something happens.
- A company can freely recall their device whenever they want, but the competent authorities need to provide a respective justification.

As stated in Part 1, there is still room for improvement for notifications of incidents outside of clinical studies, but this is not in the hands of manufacturers or notified bodies, but those who should report those events (mostly physicians). Patients themselves have the option to report such incidents to the competent authorities, but are frequently not aware of it. Sadly, the opportunity to inform the readers about this option was missed.

The medical device lobby is blocking changes

The European Commission and parts of the European Parliament wanted to implement stricter rules since years, but there was no change in the system despite year-long negotiations. Still private notified bodies instead of national authorities decide over the certification of new medical devices. If the device is useful does not need to be proven.

In 2012, based on the discovery of the fraudulent use of non-medical grade silicone in breast implant, the European Commission called for “immediate actions – tighten controls, increase surveillance, restore confidence”.¹⁷ Only 4 years later, MEDDEV 2.7/1 revision 4 was released with stricter requirements, and the more comprehensive MDR¹⁴ has been released in 2017, which will be fully applicable in 2020.

Regarding notified bodies as private entities: As I already explained in Part 1, notified bodies cannot act in a legal vacuum. The national authority is responsible for setting up and carrying out the necessary procedures for the assessment and designation of conformity assessment bodies under a Mutual Recognition

Agreement (MRA) or under the CETA Protocol on Conformity Assessment. Furthermore, independent Expert Panels under the supervision of the European Commission are involved in the review of class III and implantable devices. Whoever is interested, can read MDR Annex VII¹⁴ “Requirements to be met by notified bodies”.

That it does not need to be proven that the device is useful is incorrect. MEDDEV 2.7/1 rev 4 has strengthened the necessary justifications to show that the device is a safe state of the art device including extensive material and function tests as well as a specific literature search.

Summary

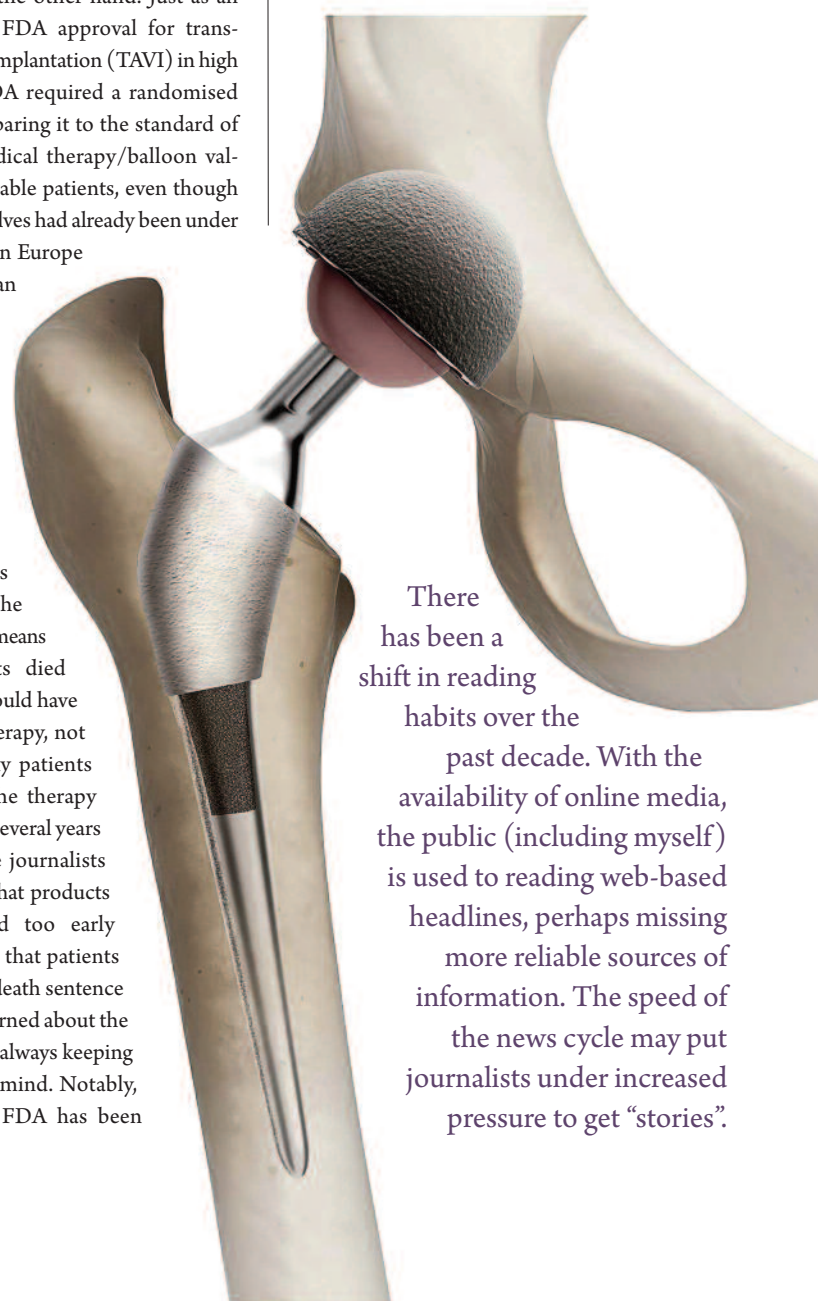
In general, it is important to understand that it is impossible to find the perfect balance between product safety/security and innovation. Previously, the US was stricter than Europe. While that led to increased security and fewer events for patients on one hand, it led to a delay in life-saving therapies on the other hand. Just as an example, to obtain FDA approval for transcatheter aortic valve implantation (TAVI) in high risk patients, the FDA required a randomised controlled trial comparing it to the standard of care, which was medical therapy/balloon valvuloplasty for inoperable patients, even though transcatheter heart valves had already been under study and approved in Europe and large European registries had been initiated, which means a substantial amount of clinical data was available. In the US-trial, the 1-year mortality in the comparator group was 20% higher than in the TAVI-group,¹⁶ which means that several patients died even though there would have been an adequate therapy, not to speak of the many patients who died because the therapy was not available for several years in the US. The same journalists who now complain that products have been provided too early would have reported that patients are randomised to a death sentence if they would have learned about the situation in the US – always keeping a selling headline in mind. Notably, since then, the US FDA has been

working on a new process facilitating the introduction of innovative medical devices.¹⁸

The journalists also cite physicians that have concerns regarding industry. During my career, I also came across such physicians. However, having a strong business acumen, I always had the opinion that – the sooner I know about a potential problem – the sooner I can fix it, hence preventing potential (financial) harm. Building a best-in-class product through thorough oversight is the best assurance for profit.

To conclude, it is important that journalists and other people critically assess and challenge the status quo. However, just hunting for headlines and biased reporting is a missed opportunity. As a reader, I want to be provided with facts and want to develop my own opinions rather than being fed the opinions of others. Worst is that opportunities to inform the public about sources of reliable information have been missed.

There has been a shift in reading habits over



There has been a shift in reading habits over the past decade. With the availability of online media, the public (including myself) is used to reading web-based headlines, perhaps missing more reliable sources of information. The speed of the news cycle may put journalists under increased pressure to get “stories”.

the past decade. With the availability of online media, the public (including myself) is used to reading web-based headlines, perhaps missing more reliable sources of information. The speed of the news cycle may put journalists under increased pressure to get “stories”. While I do not know how to change this in the future, I do hope that we will find a way back to balanced reporting.

Whoever is interested in further reading can access an interesting executive summary of an interview with Bernasconi, MedTech Europe, at <https://bit.ly/2F51HsT>.

Acknowledgement

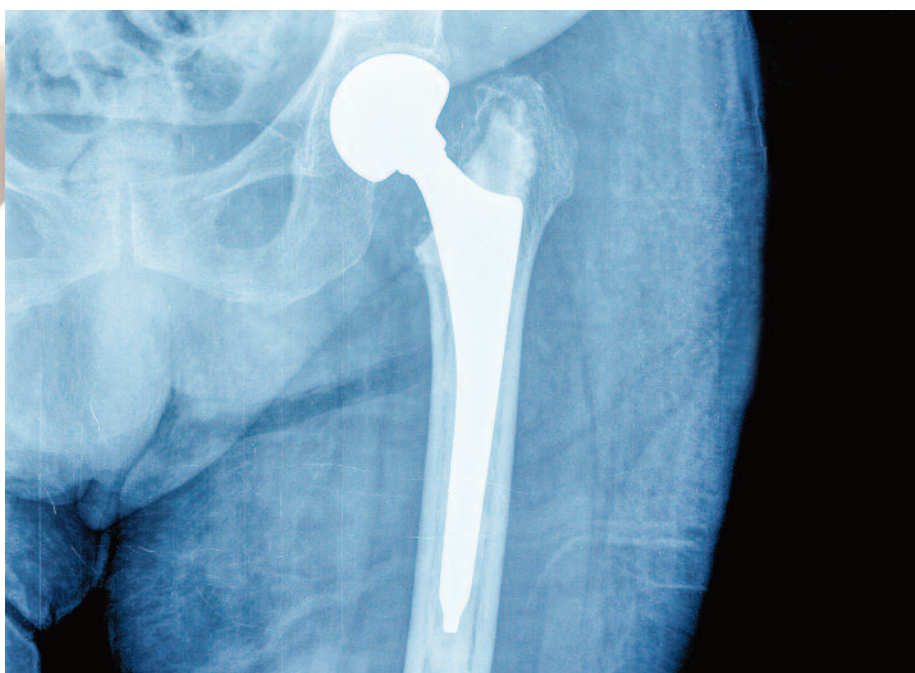
For this article, I was again supported by Monica Meyer who reviewed it and provided practice-based input from her more than 30 years of experience in the medical device industry, as Director Clinical Research Europe and as director of a global medical writing team.

Conflict of Interest

The author acts as a medical writer and consultant in the medical device industry and owns shares in Edwards Lifesciences.

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My First Medical Writing

Editorial

In this release of My First Medical Writing, we welcome one of the first articles written by Robin Sachdeva. Robin finished his PhD at Heidelberg University in Germany, and he is passionate about reading and writing about

diabetes. Fortunately, since we started working together on this article, he transitioned from being an “aspiring medical writer” to being hired as a research scientist in Canada. He is now involved in designing clinical trials, preparing

comprehensive final reports, and writing manuscripts. It has been a great pleasure to share this journey with him, seeing him grow in his writing skills, and now publishing his first article in *Medical Writing*.

One drug, many benefits: Promising outcomes from a new class of antidiabetic drugs

Can you imagine how much damaging power a glucose molecule possesses? In patients with diabetes, long-term high blood glucose levels can lead to limb amputation, blindness, kidney dysfunction, or cardiovascular disease. Such an uncontrolled increase in blood glucose can be due to the autoimmune destruction of pancreatic β cells (type 1 diabetes) or insulin deficiency combined with insulin resistance (type 2 diabetes).

There have been many approaches to treat diabetes and its associated complications. The first-ever commercially available antidiabetic agent was insulin.¹ Most antidiabetic drugs seek to lower blood glucose levels by increasing either insulin secretion by the pancreas or insulin sensitivity and, therefore, can lead to potentially fatal hypoglycaemia.

Sodium glucose co-transporter-2 (SGLT2) inhibitors, the most recently developed class of antidiabetic drugs, act independently of the insulin pathway. SGLT2 inhibitors include empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin. Canagliflozin was the first to be approved in 2013 and, as of 2019, four drugs of this class have been approved by the FDA. These molecules act in the kidneys where they block SGLT2 proteins, which are the prime mediators of renal glucose reabsorption in the proximal tubules (Figure 1). Consequently, by removing excess glucose from the blood, SGLT2 inhibitors maintain normal blood glucose levels.²

The most stunning result from clinical studies is that SGLT2 inhibitors confer cardiovascular benefits to patients with diabetes.^{3,4} In contrast to other antidiabetic drugs, the use of SGLT2 inhibitors reduce cardiovascular-related mortality

risk in patients with type 2 diabetes.⁵ Because SGLT2 inhibitors do not affect insulin secretion or action, unlike other antidiabetic drugs (e.g., sulfonylureas), they have low risk of inducing hypoglycaemia. In clinical trials, SGLT2 inhibitors reduced fasting blood glucose and HbA1c levels that are the markers most commonly used for diagnosing diabetes.⁶ Interestingly, SGLT2 inhibitors can cause weight loss and blood pressure reduction, probably by increasing glucose and sodium secretion.⁷

Although these clinical studies are promising, SGLT2 inhibitors may cause urogenital tract infections by increasing urinary glucose levels. SGLT2 inhibitors may also increase the risk of stroke and diabetic ketoacidosis (i.e., high blood ketone levels), although the mechanisms are not fully understood.^{8,9} SGLT2 inhibitors can be prescribed alone (monotherapy) or in combination with other antidiabetic agents (e.g., metformin) for patients who cannot substantially reduce their glucose levels with only one drug.¹⁰

SGLT2 inhibitors act *via* a novel mechanism to control blood glucose levels. Although SGLT2 inhibitors can cause diabetic ketoacidosis and urinary tract infections, they can still be used in carefully selected patients. In the future, these inhibitors may be utilised for diabetic patients with hypertension, but

more clinical studies will be needed to verify benefits other than their ability to normalise glucose levels.

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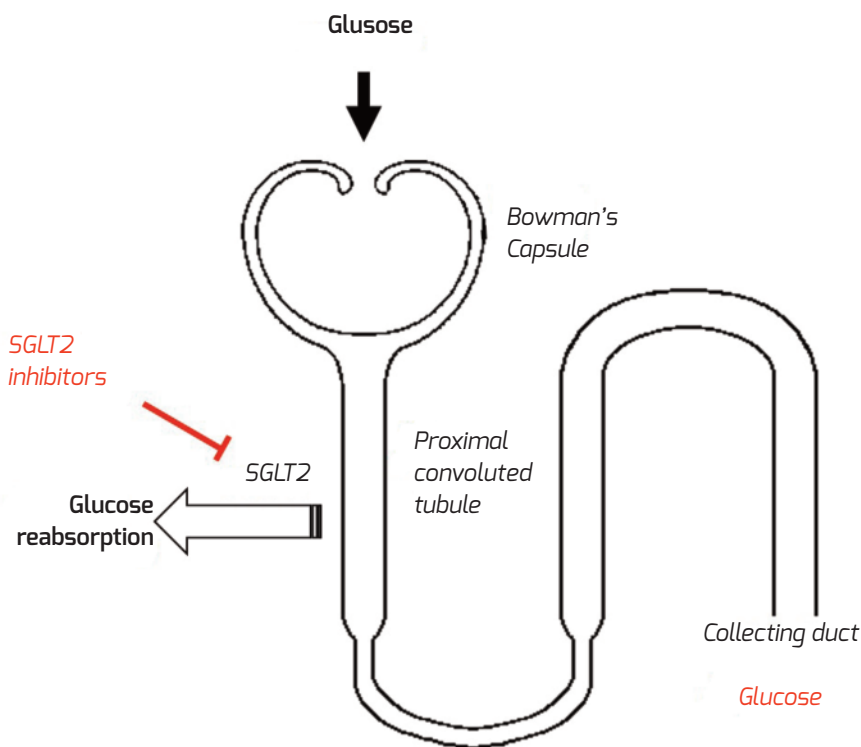


Figure 1. Mechanism of action of sodium glucose co-transporter-2 (SGLT2) inhibitors in a nephron.

Under physiological conditions, most of the glucose in the blood is filtered through the Bowman's capsule and reabsorbed by SGLT2 proteins present in the proximal convoluted tubule. SGLT2 inhibitors normalise blood glucose levels by blocking glucose reabsorption and inducing the elimination of glucose through urine.

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SECTION EDITOR



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Better writing can boost the impact of publications

The title of an opinion article in *Proceedings of the National Academy of Sciences* (PNAS) asks: “How can we boost the impact of publications?” The title also provides a quick answer: “Try better writing”.¹ The three authors, from the University of Adelaide, Australia, developed a writing index to assess clarity, creativity, and narrative structure. They measured 11 components and described their rationale for including them:

1. Word count is the most apparent component of an abstract. Longer abstracts include more ideas, but this can come at the expense of clarity.
2. Setting gives context by placing the research in a time or place.
3. Narrator refers to authors who refer to themselves in the first person.
4. Conjunctions provide links between different ideas.
5. Signposts provide a clear structure or order for ideas.
6. Punctuation marks link ideas in nuanced ways, enabling the author to direct the

reader’s attention.

7. Consistent language reduces complexity by using consistent terminology.
8. Parallel phrasing reduces complexity by using a consistent sentence structure.
9. Hedging uses qualifiers (e.g., largely, has the potential to, may) to dampen the confidence of statements.
10. Acronyms shorten phrases to save space, but they also reduce the clarity of the phrase’s meaning.
11. Noun chunks are strings of multiple consecutive nouns. Noun chunks connect objects or ideas in ambiguous ways.

The authors analysed abstracts from 330 papers published in 2012 and 2013 from three disciplines: environmental science ($n=48$), social science ($n=41$), and medical science ($n=44$). They recorded the number of citations for each paper as of July 2018 as indicated in Scopus, and the 2017 Scopus Cite Score of the journals.

Influential articles (those earning 100 to 1000

cites) had more positive writing components and were thus written more with the reader in mind. For instance, highly cited articles were short; used first-person narration; placed findings in context by providing a setting (e.g., “in the world’s oceans” or “over the past 20 years”); linked ideas by using conjunctions (e.g., “therefore” or “conversely”), punctuation marks (e.g., semicolons and dashes), and consistent terminology; and avoided excessive acronyms and awkward noun chunks.

This brief paper (2.5 pages) is interesting because of the originality of the score, but the sample is small, and the conclusions deserve confirmation and more clarity. The score should be better validated, and their concept of “writing with the reader in mind” deserves a definition.

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Significance (not just statistical): The debate must go on

More than 800 researchers have signed a petition calling for the abandonment of “the entire concept of statistical significance”.¹

The poor quality of statistical analysis and reporting in research articles has been widely documented. Probably half of articles have statistical problems. Regularly, papers call attention to the need for improved statistical practices. In early 2019, a petition signed by more than 800 researchers and published by the journal *Nature* called on researchers to retire the idea of statistical significance in papers.¹ The article stated: “... Eradicating categorisation will help to halt overconfident claims, unwarranted declarations of ‘no difference’ and absurd statements about replication failure when the results from the original and replication studies are highly compatible.”

They are not calling for a ban on the use of *P* values. Instead, the authors write: “We must learn to embrace uncertainty. One practical way to do so is to rename confidence intervals as

‘compatibility intervals’ and interpret them in a way that avoids overconfidence.”

This article has been very controversial. John Ioannidis provides a brief thoughtful commentary. He notes that “a low barrier such as $P < 0.05$ is typically too easy to pass. Hence, one option is making the barrier more demanding.”

Ioannidis provides a useful summary of the petition:

The petition proposes retaining P values but abandoning dichotomous statements (significant/nonsignificant), suggests discussing “compatible” effect sizes, denounces “proofs of the null,” and points out that “crucial effects” are dismissed on discovery or refuted on replication because of nonsignificance. The proposal also indicates that “we should never conclude there is ‘no difference’ or ‘no association’ just because a P value is larger than a threshold such as 0.05 or, equivalently, because a confidence interval includes zero,” and that categorisation based on other statistical measures (e.g., Bayes factors) should be discouraged. Other recent articles have also

addressed similar topics, with an entire supplemental issue of a statistics journal devoted to issues related to P values.

The brief commentary by Ioannidis deserves a careful reading because all the arguments are clearly presented.² There is a debate between statisticians and clinicians, and Ioannidis’ position is: “Significance (not just statistical) is essential both for science and for science-based action, and some filtering process is useful to avoid drowning in noise.”

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The dominance of men in the publication game

We have a lot of data on the prevalence of men in the publishing system. We know that men outnumber women on journal editorial boards. In early 2019, two articles contributed to the literature on the imbalance. Here are the summaries of these articles:

Gender inequalities among authors who contributed equally¹

We analyzed 2898 scientific papers published between 1995 and 2017 in which two or more authors shared the first author position. For papers in which the first and second authors made equal contributions, mixed gender combinations were most frequent, followed by male-male and then female-female author combinations. For mixed-gender combinations, more male authors were in the first position, although the disparity decreased over time. For papers in which three or more authors made equal contributions, there were more male authors than female authors in the first position and more all-male than all-female author combinations. The gender inequalities observed among authors who made equal contributions are not consistent with random or alphabetical ordering of authors. These results raise concerns about female authors not receiving proper credit for publications and suggest a need for journals to request clarity on the method used to decide author order among those who contributed equally.

This paper has a footnote: †These authors contributed equally to this work; author order was determined both alphabetically and in order of increasing seniority.

Gender differences in peer review outcomes and manuscript impact at six journals of ecology and evolution²

The productivity and performance of men is generally rated more highly than that of women in controlled experiments, suggesting conscious or unconscious gender biases in assessment. The degree to which editors and reviewers of scholarly journals exhibit gender biases that influence outcomes of the peer-review process remains uncertain due to substantial variation among studies. We test whether gender predicts the outcomes of editorial and peer review for >23,000 research manuscripts submitted to six journals in ecology and evolution from 2010 to 2015. Papers with female and male first authors were equally likely to be sent for peer review. However, papers with female first authors obtained, on average, slightly worse peer-review scores and were more likely to be rejected after peer review, though the difference varied among journals. These gender differences appear to be partly due to differences in authorial roles. Papers for which the first author deferred corresponding authorship to a coauthor (which women do more often than men) obtained significantly worse

peer-review scores and were less likely to get positive editorial decisions. Gender differences in corresponding authorship explained some of the gender differences in peer-review scores and positive editorial decisions. In contrast to these observations on submitted manuscripts, gender differences in peer-review outcomes were observed in a survey of >12,000 published manuscripts; women reported similar rates of rejection (from a prior journal) before eventual publication. After publication, papers with female authors were cited less often than those with male authors, though the differences are very small (~2%). Our data do not allow us to test hypotheses about mechanisms underlying the gender discrepancies we observed, but strongly support the conclusion that papers authored by women have lower acceptance rates and are less well cited than are papers authored by men in ecology.

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Writing and science: A special issue of *Written Communication*

The January 2019 issue of *Written Communication: An International Quarterly of Research, Theory, and Application* focuses on the topic of writing and science. All six papers and the editorial are of interest. In their introductory editorial, Wickman and Fitzgerald note:¹

Scientific texts are evolving in response to emergent needs and media affordances. While time-honored genres still very much influence the publication and circulation of research, scientists are developing new and hybrid ways to communicate their work...

The actors involved in scientific research and communication are also evolving. Citizen science initiatives in particular emphasise the increasingly distributed work of knowledge making, and digital media continue to transform how we conceptualize boundaries between

scientific communities and lay publics. Such developments invite further exploration of writing as a means whereby scientists enroll participants into their inquiries and circulate information for specialist and nonspecialist audiences alike.

Here is a brief look at the six papers in the issue, as summarised in an article introducing the editorial:

1. **“I think when I speak, I don’t sound like that”: the influence of social positioning on rhetorical skill development in science** explores how a young woman of colour negotiates the process of learning and being enculturated into the disciplinary discourse of biomedical science. This study shows us, in the author’s words, how “traditionally

marginalised individuals negotiate academic and disciplinary boundaries” through writing.

2. **“Registered reports: genre evolution and the research article”** examines how registered reports respond to current exigencies in academic publishing and intervene in the ongoing evolution of the research article. This hybrid genre is shaping the way researchers in the life and psychological sciences conceptualise, undertake, and communicate their work.
3. **“Compressing, expanding, and attending to scientific meaning: writing the semiotic hybrid of science for professional and citizen scientists”** investigates how a group of biologists employ different semiotic resources, and make strategic choices, when composing documents for specialist and nonspecialist audiences, including citizen scientists. This text shows how the work of inquiry gets distributed in a contemporary media environment.
4. **“Writing and conceptual learning in science: an analysis of assignments,”** undertake a systematic analysis of writing to learn scholarship with particular emphasis on concepts employed in empirical studies of writing to learn science. The authors suggest that meanings attached to writing are critical for promoting effective research and classroom instruction.
5. **“Linguistic injustice in the writing of research articles in English as a second language: data from Taiwanese and Mexican researchers”** methodically examines the “linguistic burden” placed on scientists who publish in English as a second, third, or additional language – a form of “linguistic injustice” that has real, and measurable, effects on individual writers.
6. **“How do online news genres take up knowledge claims from a scientific research article on climate change?”** explores how expert information related to climate change gets recontextualised in online news genres. Following the textual trajectory of a single research article over the course of one year, this paper shows how different genres mediate “uptake” and how expertise moves and gets transformed across texts and contexts.

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Good Writing Practice

Syntactic inter-sentence distraction

Omission: Continuity markers

Introduction

Paragraph lengthiness and complexity cause a continuity inexplicity (discontinuity), which can be lessened by using forecasting and backcasting markers of the information pattern. Thus, omission of such continuity markers (e.g., a subheading) impedes immediate comprehension. In this article, examples of continuity marker omission are analysed according to the section of a journal article (experimental, contextual), the conceptual component therein, and the type of omitted marker.

Experimental section

Part 1 – Materials and methods section: method

Example: omitted subheading

At the Chilao study site (San Gabriel Mountains, California), after soil temperature measurement (LaMotte Chemical dial thermometer), small samples of soil (2 m intervals) were collected (trowel), placed into a bag, dried, and mixed. A few table spoons of soil were dried (to the nearest ounce), heated (4 h, 550°C), reweighed (25°C), and the amount expressed as a percentage of total weight.

A LaMotte Deluxe Turf Lab Soil Kit (Model TL-2) was used to determine the following: nitrate nitrogen (mixed acid reagent and nitrate reducing reagent); phosphorus (NF extracting solution and charcoal suspension); potassium (K solution); iron (iron reagent #1 and #2); calcium and magnesium (Schwarzenback EDTA titration method). Nitrate, phosphorus, and iron were measured colorimetrically.

Revision

Collection and processing – At the Chilao study site (San Gabriel Mountains, California), ...

Chemical analyses – A LaMotte Deluxe Turf Lab Soil Kit (Model TL-2) ...

Notes

In the Example, the omission of in-text subheadings results in an inexplicit shift from one research activity (collection and processing) to another (chemical analyses). Inclusion of the subheadings facilitates continuity between dense paragraphs of different types of information.

Part 2 – Materials and methods section: method

Example: omitted determiner

Three hepatoma cell lines were used in this experiment.

Revision

The three hepatoma cell lines were used in this experiment.

Notes

Without *the*, it would seem that the noun phrase three hepatoma cell lines (probably mentioned in the Introduction section) is mentioned for the first time, avoiding not only its prior mention but its importance in context. The definite article, a marker of uniqueness (e.g., the sun), also denotes that a noun was previously mentioned and, thus, known to the reader and the author. The definite article thus functions as a marker of continuity, intra- and especially inter-sentence. Therefore, a continuity gap can occur if the definite article or a stronger type of determiner is missing.

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In addition to articles, pronouns (indefinite, demonstrative) and numbers can function as determiners.

Part 3 – Materials and methods section: method

Example: omitted determiner

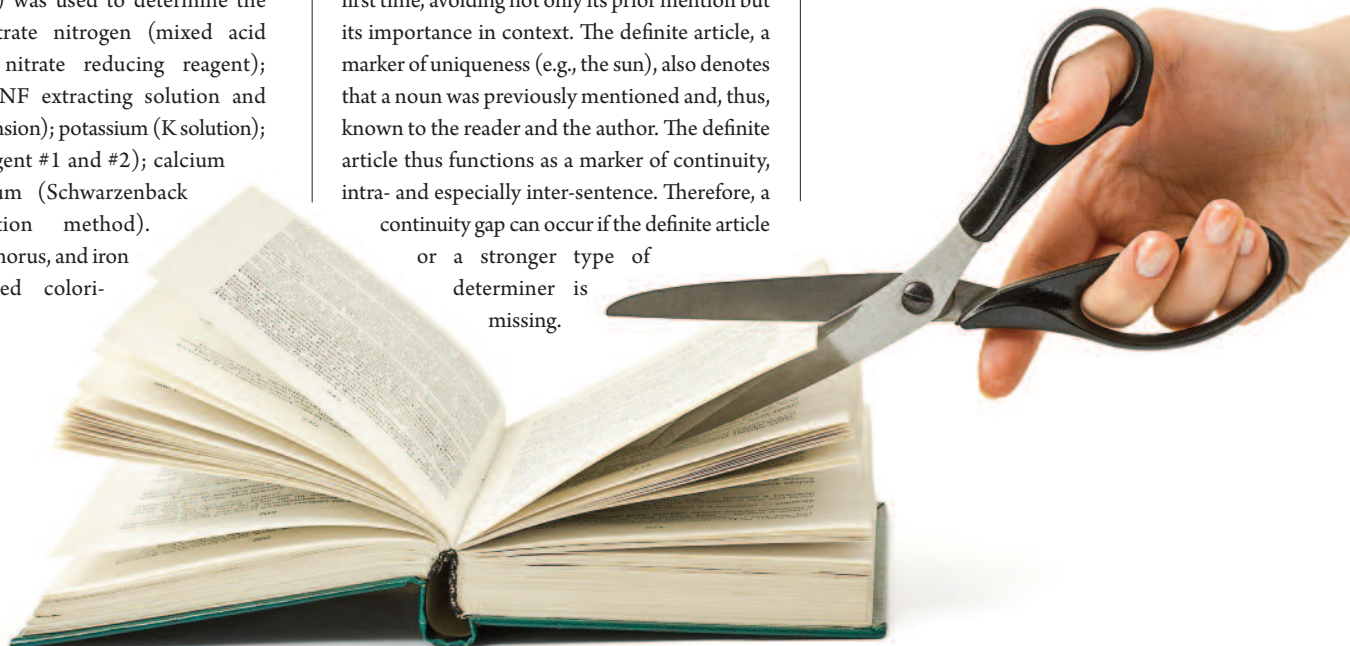
Many studies were performed in vitro.

Revision

Many **of the** studies were performed in vitro.

Notes

Without *of the*, there is no denotation that the studies were previously mentioned. The usage of *the* alone as in *many the* is unconventional. Other indefinite pronoun determiners that require *of* are *none* and *some*. In contrast, *all the* sounds conventional, but *all of the* would be consistent with usage of the others.



Contextual sections

Part 1 – Introduction section: research problem pertinent background

Example: omitted end-of-sentence appositives

To obtain the best performance from processors, two essential assistants can be considered. The compilers maximise the parallelisation and balance workloads. The interconnects among clusters improve the processor performance by overcoming the partitioning overhead as inter-cluster communications.

Revision

To obtain the best performance from processors, two essential assistants can be considered: **compilers and interconnects among clusters**. The compilers maximise the parallelisation and balance workloads. The interconnects among clusters improve the processor performance by overcoming the partitioning overhead as inter-cluster communications.

Notes

Forecasting the assistants (*compilers and interconnects among clusters*) as appositives at the end of the first sentence provides explicit continuity to the second and third sentences. This forecasting improves inter-sentence continuity.

Part 2 – Introduction section: research problem pertinent background

Example: omitted determiner

Bacteria can spread quickly from cavities to apical through straight root canals of baby teeth, resulting in infected bone and periodontal tissue. Infection will impair craniofacial development.

Revision 1

Bacteria can spread quickly from cavities to apical through straight root canals of baby teeth, resulting in infected bone and periodontal tissue. **The** infection will impair craniofacial development.

Revision 2

Bacteria can spread quickly from cavities to apical through straight root canals of baby teeth, resulting in infected bone and periodontal tissue. **Such** infection will impair craniofacial development.

Notes

Inclusion of a determiner fills the continuity gap between the first and second sentence. Some continuity is provided by echo of the word *infected* as *infection*. In Revision 1, further continuity is provided by *the*. In Revision 2, the indefinite pronoun determiner *such* renders the continuity explicit. Usage of the determiner *this* (or *that*)

would be a little less emphatic. Thus, there seems to be a hierarchy of determiner-elicited continuity marking: *such* > *this/that* > *the*.

Summary

Forecasting markers (subheadings; end-of-sentence appositives) facilitate comprehension in paragraphs common to a Materials and Methods section. However, backcasting markers (determiners *the, such*; indefinite pronouns *many of the*) cohere text in all sections of a journal article.

Omission of forecasting or backcasting markers diminishes paragraph continuity, resulting in impeded immediate comprehension.

The taxonomic nomenclature of omission indicates the revision option: addition of the omitted forecasting marker (subheading, end-of-sentence appositives) or backcasting marker (determiner) if they indeed minimise impeded immediate comprehension. Furthermore, there is a sub-option for the usage of determiners: the hierarchy of emphasis among the indefinite backcasting determiners *such* > *this/that* > *the*.

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Save the date:
**EMWA Conference in
the Czech Republic**
PRAGUE
May 6 to 9, 2020

<https://www.emwa.org/conferences/future-conferences/>

Regulatory Public Disclosure

Editorial

Keeping up with regulatory public disclosure (RPD) globally is a challenge for us all. This regular RPD section of *Medical Writing* and EMWA's RPD Special Interest Group (SIG) help you stay ahead of the game through information sharing.

Although the EU lull in RPD continues with clinical data publication activities suspended since October 2018 (<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/support-industry-clinical-data-publication>), RPD activities elsewhere have gained pace.

Health Canada (HC) concluded their "Public Release of Clinical Information" consultation and issued a final regulation with final guidance on March 12, 2019 (see box for links). Broadly, the HC guidance is aligned with EMA Policy 0070 guidance with the intention of streamlining sponsor effort. Clinical information is now publicly available via the HC Clinical Information Portal (see box for link). The portal contains clinical information on a few products from volunteer organisations in advance of the March 12 "in force" date, and afterwards, drug submissions data will be posted as each review is completed. Proactive device data disclosure will start in 2021, aligning with EMA's intended timetable. Further, drug and device data that is already "available on request" will be publicly posted. A MEW open access feature article – a deeper dive into the HC guidance – is planned for the second half of 2019. In the meantime, Christopher Marshall says neatly summarises the take-home points for us in his short "nutshell guide" to the Health Canada guidance.

Vivli – a platform offering clinical trial data sharing management capability and functionality – is spotlighted by Raquel Billiones. If you know of other such platforms, please be in touch.

This quarter, we are incredibly lucky to have two excellent feature articles. In the first, Sybille Eibert explains the FDA final rule requirements for publication of protocols and statistical analysis plans on ClinicalTrials.gov. Sybille navigates the limited guidance on redaction of personally identifiable information and confidential commercial information prior to publication, and highlights some key questions (p. 81). Our second feature article, brought to us by Raquel Billiones and Kathy Thomas, is a bold challenge to the idea that the drug products and devices worlds are vastly different. The two worlds collide when the Clinical Trial Regulation (CTR) and Medical Device Regulation (MDR) are interrogated in the context of clinical studies and public disclosure (p. 74). The authors tenaciously support the case for medical writers interchanging between the regulatory drug and device arenas.

In March 2019, the Budapest Working Group (BWG) – the developers of CORE Reference – concluded a line-by-line review of the November 2018 TransCelerate clinical study report (CSR) template – i.e., the template that cites CORE Reference and ICH E3 as key developmental resources. Following the BWG's preliminary higher-level review findings (<https://www.core-reference.org/news-summaries/core-reference-statement-on-transcelerate-csr-template/>), the team submitted a paper describing more detailed

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findings to an open access peer-review journal in May 2019. We hope to have our work published later in 2019. A summary of and link to our article will appear in *Medical Writing*.

Finally, it was a pleasure to meet those of you who came to the RPD SIG meeting at EMWA's May 2019 conference in Vienna. We are delighted to welcome Miriam Kremser who kindly volunteered to join the RPD SIG Committee and help out with resource management. We also discussed ideas that we hope to develop into articles and resources in the coming months. There is an easy way for you to help with written content... if you plan to attend a relevant conference – for example, DIA's December 2019 Clinical Trial Disclosure and Data Transparency Conference (<https://www.diaglobal.org/conference-listing/meetings/2019/12/clinical-trial-data-transparency-conference>) – consider contributing a short article about your conference experience and what you learned.

As usual, relevant clinical trial transparency and disclosure information will be shared via multiple outlets – this regular RPD section, through www.core-reference.org emails (sign up at: <http://www.core-reference.org/subscribe>), and through EMWA News Blasts.

Kind regards, Sam

A nutshell guide to the Health Canada guidance on public release of clinical information

- Clinical information released for drugs will be:
 - Clinical overviews (M2.5), clinical summaries (M2.7.1 - 2.7.4), and CSRs
 - CSRs = single report with the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products,

technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output.

- Clinical information released for devices will be:
 - Summaries and detailed information of all

clinical studies and investigational testing that provided evidence of safety and effectiveness for medical devices.

- Individual patient records will not be publicly released with other clinical information.
- The publication process has five phases – initiation, submission, review, finalisation, and publication

- Health Canada targets uploading of the redacted and anonymised package within 120 calendar days of process initiation
 - Issuance of the positive regulatory decision triggers the publication process
 - Issuance of negative decision triggers publication 31 calendar days after the date of the notice, but may be halted if a Letter of Intent for Reconsideration is submitted.
- Redacted documents that were previously accepted by EMA Policy 0070 may be submitted.
- Use of the EMA specifications on redacted text are permissible in finalised documents. (See Box for links).

Christopher Marshallsay



Status updates – from regulatory regions



An introduction to the vivli.org data sharing platform

Vivli.org is one of a number of platforms offering an alternative to the perhaps more widely known CSDR (clinicalstudydatarequest.com). The National Academy of Medicine recently wrote about the launch of the Vivli platform (<https://nam.edu/moving-data-sharing-forward-the-launch-of-the-vivli-platform/>).

Vivli hosted a meeting in Tokyo on May 13, 2019, that included roundtable discussion with experts in privacy and transparency of clinical trials on the theme “One Year On: GDPR and Its Implications for Data Disclosure and Data Sharing”.

Raquel Billiones

Canada

Public disclosure guidance and portal:

- Health Canada released final guidance on the “Public Release of Clinical Information”: <https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/profile-public-release-clinical-information-guidance/document.html>.
- Clinical information on drugs and medical devices is publicly available via the HC Clinical Information Portal: <https://clinical-information.canada.ca/search/ci-rc>
The HC “Public Release of Clinical Information” consultation is concluded: <https://www.canada.ca/en/health-canada/programs/consultation-public-release-clinical-information-drug-submissions-medical-device-applications.html>

Europe

1. The role of big data for evaluation and supervision of medicines in the EU is being assessed (<https://www.ema.europa.eu/en/news/role-big-data-evaluation-supervision-medicines-eu>). Stakeholders are invited to

submit feedback and observations on the recommendations to inform the upcoming work of the group.

2. Opinion 3/2019 (January 23, 2019) (https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_opinionctrq_a_final_en.pdf) concerning the “Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR) (art. 70.1.b)” by the European Data Protection Board is a legal “opinion” that should be shared widely in the clinical research industry, including amongst legal departments. Review of standard Informed Consent Template and Protocol Template texts for appropriate wording is recommended.

United Kingdom

4. In the event of a “no-deal” Brexit, the UK Government’s “Guidance on the registration of clinical trials for investigational medicinal products and publication of summary results” (<https://www.gov.uk/guidance/guidance-on-registration-of-clinical-trials-for-investigational-medicinal-products-and->

publication-of-summary-results) published March 20, 2019, will become applicable.

This guidance contains information about registration of clinical trials, publishing trial results and future requirements if the UK leaves the EU without a deal. Remember that until the UK's exit from the EU is clearer (date and manner of exit), this guidance represents the UK's preparedness position in the event of a "no deal" only.

4. The UK government has announced that a national clinical trial transparency strategy will be published before the end of 2019. The statement marks a significant step towards ensuring that all clinical trials conducted in Britain will be registered and will publish their results. Read TranspariMED's summary report on the status of the strategy (<https://www.transparimed.org/single-post/2019/02/25/UK-government-promises-national-strategy-to-boost-clinical-trial-reporting>).

... from the journals

In this IAPP article (<https://iapp.org/news/a/does-anonymization-or-de-identification-require-consent-under-the-gdpr/>), experts Khalid El Amam and Mike Hintze article, make the case that consent is NOT required to anonymise or de-identify clinical trial data.

CORE Reference

- CORE Reference (available for download from <http://www.core-reference.org/core-reference/>) identifies each point in an ICH E3-compliant CSR where anonymisation considerations should apply. Downloads approach 20,000 (June 2019)
- CORE Reference has a News Summaries page: <https://www.core-reference.org/news-summaries> where relevant regulatory and disclosure news is posted periodically. Stay one step ahead and receive these updates in "real time" by signing up at: <http://www.core-reference.org/subscribe>



Resources

1. EMA's invaluable reference to describe their end-to-end process for the journey of a centrally-authorised EMA medicine from lab to patient <https://core-reference.us13.list-manage.com/track/click?u=c2b68d727a3b5cd76327cee23&id=d989b6ae35&e=79858c7e19>.
On page 14, there is a great summary titled: "What information is publicly available during the evaluation of a new medicine and once a decision has been made?" complete with relevant web links.
2. Read EMA's EudraCT and EU Clinical Trial Regulation (CTR) Q & A document https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf
The 32-page long 84 Q & A covers general, protocol, and results information, the EU CTR, and paediatric clinical trial information (protocol and results).
3. PhUSE White Paper (March 14, 2019) titled "Retrospective versus proactive anonymization of narratives": <https://www.phusewiki.org/docs/Deliverables/Narratives%20White%20Paper%20Version%202.pdf>
This 17-page PhUSE White Paper by Rashmi Dodia and Gregory Campbell focuses on two approaches to produce anonymised narratives – retrospective and proactive. The retrospective section addresses challenges faced with qualitative methods (e.g., redaction) and the impact on data utility. Desirable features of a tool or software solution for redaction are included on page 10. In the proactive section, the needs for modern solutions and skills enhancement in order to meet Policy 0070 requirements are discussed. Suggestions on how to operationalise proactive anonymisation are also offered on page 15. All PhUSE white papers are available at: <https://www.phuse.eu/white-papers>
4. EMWA RPD SIG members' page: <https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/>
Subpage for disclosure-related regulatory news updates: <https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/regulatory-news-emwa-newsblast/>



Laura A. Kehoe
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Out on Our Own

Welcome readers,

Back in 2016, the Out on Our Own editors reached out to groups in European countries who had established informal medical writers' gatherings. It was great to see that groups had appeared in Germany, France, the UK, and the Netherlands. Here, I asked the Berlin group and the Netherlands group to give us a recap on their gatherings. Paul Walufa, original author back in 2016 and based in Berlin, provides a summary of the advantages of

these groups. Maya Raghunandan, who is still in the lab as a post-doc but being tempted by a medical writing career, gives her view on the gatherings that are taking place in the Netherlands. Lastly, Viviana Moroso offers a different perspective on networking, within the Erasmus programme. She explains how it's not all about students, and that the Erasmus programme provides a great opportunity for young entrepreneurs; and medical writing is fast becoming a hot topic. So, if you're a medical writer sitting at

home as a freelancer or home-working, or even employed and keen to meet other medical writers, search social media platforms like LinkedIn and Facebook to see if there's an informal gathering near you. The gatherings offer a supportive networking opportunity where people with similar interests can share ideas and experiences or ask questions. And if you can't find a group, why not establish one and let us know how it goes. Happy networking!

Laura A. Kehoe

Informal gatherings: A perspective from the Berlin and Brandenburg group

Positive from the start

Following the introduction of the concept of informal gatherings as a way to expand networking activities among freelancers; we formed the Berlin and Brandenburg group. Our first meeting was on the July 14, 2016. The turnout was great, and the meeting proved not only to be an opportunity to establish new contacts but also to reunite with former colleagues. The general feeling was that this was an opportunity many colleagues had wanted to have, and it was finally here with us!

A supportive lot

Our group is composed of writers with a wide range of experience, a blend which has proved to be an asset. Through discussions, colleagues have benefited a great deal from each other. This has not only been restricted to sharing information and knowledge on how to tackle issues related to writing from a freelance point of view but has also extended to supporting each other in business through referrals and providing contacts from whom newbies could find placements. In light that some members have switched to regular employment, whenever their old clients contact them for freelance jobs, the information is shared in the group's mail list.

The general feeling was that this was an opportunity many colleagues had wanted to have, and it was finally here with us!

From freelancers' gathering to medical writers' meeting

From the first meeting until today, both freelancers and colleagues in regular employment attend the informal gatherings. For the sake of inclusivity and to adapt to our situation, we as a group, decided to officially transform our

informal gathering from a freelance group to a general medical writers' informal gathering group. This was to ensure that everyone felt welcome. Additionally, we saw it as a way for freelancers to get business and contacts from colleagues in regular employment. Having the two groups together was an opportunity to exploit establishing reliable business relations between the freelancers and their colleagues in regular employment.



Point of contact on professional issues

Having a group account on LinkedIn (<https://www.linkedin.com/groups/8553972/>) has enabled members to support others wanting to get into the medical writing field as well as those who wish to get information on training to further their medical writing knowledge. The possibility to have face-to-face meetings through informal gatherings has, in addition, provided opportunities to meet with such colleagues not only to continue with the conversation but also to provide an opportunity for the new members to network and to know their colleagues in Berlin and its environs.

Informal but still professional

Our gatherings also provide opportunities to discuss issues about the profession as a whole. We have had very insightful discussions on a wide range of topics, ranging from new regulations in the industry, how to deal with expensive paid-

access published articles and databases, and sharing of business, just to name a few. Discussions also take place on our LinkedIn page in the form of posts and updates.

In addition, we use the gatherings to encourage colleagues to join EMWA in order to advance their knowledge in medical writing and interact with other medical writers at an international level.

Merely an opportunity to get out of routine

The informal meetings have provided an occasional chance for medical writers to break away from the home-work-home routine. This is even more beneficial to those in home-based settings whether as freelancers or simply remote workers in regular employment. Medical writing is such a demanding career with many high-pressure moments, and endless deadlines make it at times difficult for one to get out of their routine. The socialising aspect of our meetings

has been refreshing and quite enjoyable. Many times, we have ended up listening to in-depth and interesting talks like the scientific aspects of winemaking and history of Berlin from a totally different perspective; topics which are far from medical writing but enriching in their way.

Conclusion

Looking back, it has been a rewarding and fulfilling experience to be part of the informal gathering organising team. As a group, we strive to meet quarterly to continue providing an avenue to network, unwind and share professional information as medical writers in Berlin and Brandenburg, Germany. To know the exact dates of our next meeting, kindly access our LinkedIn page and feel free to join us in more of our gatherings to come.

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The SciMed Writers Network: Fostering local medical writers' camaraderie in the Netherlands

While hopping between continents for different academic jobs, I have observed a new trend: a global lack of scientific awareness, varying from anti-vaccination rallies to climate change denial. Is this really the world we live in? And I guess this is what led me to start science blogging: the feeling that I have the responsibility to effectively communicate science and spread scientific awareness. Blogging has also led me to other projects, including some medical writing and editing – all of which I have really enjoyed alongside my research. But would I like to write as a career? Before dropping my pipette and picking up a laptop for good – I wanted to learn more about what “medical writing” really meant.

I knew that having a solid professional network would be an integral part of the job search process and could probably also help me break into the field. To explore my options, I joined EMWA and connected with some members face-to-face and online. Every EMWA member I spoke to highly recommended the bi-annual EMWA meetings. It is indeed a great way to meet people, but the meetings are only held twice a year, and I knew that I would likely only stay in touch with other members online.



From left to right: Gabriela Plucińska, Jackie Johnson, and Mariella Franker – Organisers of The SciMed network

I wanted to also connect with a local professional network. This would make it possible to grab a coffee sometime with experienced writers. And

that's how I stumbled upon the Netherlands SciMed Writers Network (SMWN).

I'm told that the idea for a local Netherlands-



Organiser Sally Hill conducts her session on writing tips for medical writers, while the workshop attendees take notes.

based networking group all started at the EMWA Barcelona Conference where three fellow EMWA members – Gabriela Plucińska, Jackie Johnson, and Mariella Franker – brainstormed over Spanish tapas about having a structured way of staying in touch with their ‘virtual’ colleagues and connecting with others in the local medical communication, pharma and biotech industries. Shortly thereafter, the trio decided to organise a drink and a bite at a local café in Amsterdam. Though very informal, this was a great success with 14 people attending. At this first meeting, they recruited another organiser, Sally Hill, an experienced writer and volunteer for other groups in the Netherlands. Together, they set the wheels in motion for the Netherlands SciMed Writers Network’s first workshop.

Interactive, informative, and fun meetings

To my surprise, when I joined the online Facebook group (<https://www.facebook.com/groups/2058710307712882/>), there were already nearly 60 members. Therefore, I was quick to sign up for a place at the first live workshop on *Storytelling in Science*, held at the public library in Amsterdam in October 2018. I had heard about it on the LinkedIn (<https://www.linkedin.com/company/scimed-writers-network/>) and Facebook groups, and there was a lot of interest from the other members.

The event started with a session given by Frederike Schmitz titled “Storytelling in Science Communication”. Frederike explained to us, “If you want facts to resonate with your audience, you’re better off telling them a story. But how do you start? First, you have to know your audience.”

This is easy to say, but harder to act upon, which is why Frederike got us standing up and practising elements of theatre improvisation, in order to get us thinking about connecting with our audience.

The next session, led by Sally Hill, highlighted some useful writing tips that were simple and could help make text more readable. Of course, there was plenty of time for networking and interacting with other writers over coffee. All in all, it was a great afternoon, and I learned a lot! After attending the event, I felt invigorated – thanks to an excellent platform to communicate freely with like-minded peers.

Structured yet informal setting

What stands out the most to me about this network is the structured yet informal nature. The frank and casual interactions during the event allowed me to be more myself and less nervous than I usually feel at such gatherings. It was fantastic to meet people from such diverse backgrounds in the group: from fresh graduates to experienced medical writers. It is also nice to see such a mix of careers and companies represented. Some attendees were freelance writers, and others worked for local companies, many of which I had not previously heard of.

New colleagues and opportunities

Although it’s still in the early days, I think the SMWN will surely grow. Since the first networking event, I’ve been able to keep in touch with other members via the active Facebook and LinkedIn groups. Here, the members regularly

share information on potential writing opportunities from their respective networks. This also provides a great platform for seeking expert advice for those venturing into a new aspect of medical writing.

Sally Hill agreed: “I’m really enjoying being part of this network and meeting other medical writers as well as young scientists thinking of transitioning out of academia. Since writing is not an obvious career path for people with science qualifications, the network is an excellent way of hearing more about it.” Even for the professional medical writers in the group, networking continues to be an indispensable resource for staying employed and learning about new publishing mediums.

When describing the goal of the group, Jackie said, “the goal is to connect med writers and other related professionals in the Netherlands and surrounding areas. We are not a business, and we are not looking for profits from our events. We just have a genuine interest to have skill sharing events and meet other like-minded professionals in our country.”

What’s next?

The organisers have been conducting regular polls in the Facebook group to check what discussions and workshops would be the most beneficial for future sessions. Following a more informal networking meet-up in January, they are currently organising a spring workshop in May on the theme “Medical Writing as a Career”.

It has been inspiring to meet fellow medical writers face-to-face and talk about the day-to-day of medical and scientific writing, similar to what might happen in a real office setting. This local group is already helping to create new business opportunities and forge new friendships. So, I recommend that if you are thinking of starting your own local medical writing meet-ups – go for it!

Acknowledgements

Thank you to Jackie Johnson and Sally Hill for help drafting and editing this article. Thank you to the SMWN organisers for the invitation to write this article.

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The Erasmus programme Not only about students, new entrepreneurs can benefit too

Since I first moved to the Netherlands in March 2007 for my master's internship, I was asked many times "are you an Erasmus student?". No, I was not. But I got the feeling that the Erasmus programme was the most popular way to move around Europe to study, train, and get new experiences as a young student.

Now, 12 years later, after my third move to yet another European country, and shortly after starting my own medical writing and editing business, I was asked: "Do you want to join the Erasmus programme?" My first thought, of course, was that I am too old to take part. But I was wrong because this specific Erasmus has nothing to do with my actual age, but rather with the age of my business. It turns out I should not only associate "Erasmus" with the world of students and universities. This is an opportunity for new entrepreneurs who plan to start a business or have started their own business in the past 3 years.

Briefly, the Erasmus for Young Entrepreneurs is a cross-border exchange programme that gives

new or aspiring entrepreneurs the chance to learn from experienced entrepreneurs running small businesses in other participating countries. The exchange of experience takes place during a stay with the experienced entrepreneur, which helps the new entrepreneur acquire the skills needed to run a small firm. The host benefits from fresh perspectives on his/her business and gets the opportunities to cooperate with foreign partners or learn about new markets. The stay is partly financed by the European Commission and can have a duration from 1 to 6 months. This and much more information can be found at the website www.erasmus-entrepreneurs.eu/.

But don't worry, you don't have to plan everything alone. You will get help from a "local contact point", who will guide you through the experience from the very early steps. You can find all available contact points on the website too. Also, on YouTube you can find several short reports of successful Erasmus experiences in different fields.

Since I am now located in a rather remote area

in the North of Sweden (Luleå), where I have no concrete opportunities to learn from other businesses or experienced entrepreneurs, this seems a great option to start with the right foot.

My "local contact point" told me from the beginning that the field of medical writing has been rather uncommon within the Erasmus for Young Entrepreneurs programme until now. Well, I thought, maybe if more of us, EMWA members, know about this programme, many more opportunities will open up in the near future! A chance for both young and experienced entrepreneurs to exchange knowledge and ideas, to train and maybe create precious collaborations.

Let's hope that from now on medical writers become a much more popular category in the Erasmus programme!

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Upcoming issues of **Medical Writing**



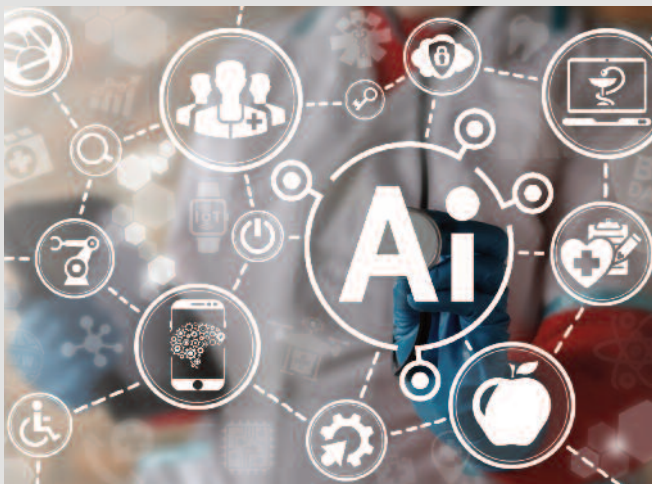
September 2019:

Trends in medical writing

The medical writing industry is growing and evolving at a fast pace, and we need to keep up with the trends. From public disclosure to global medical writing, find everything you need to know in this issue.

Guest Editor: Somsuvru Basu

The deadline for feature articles is June 10, 2019.



December 2019:

Artificial intelligence & digital health

Technological innovation is overtaking all industries, and medicine is no exception. Artificial intelligence and digital health are growing trends. As medical writers, we must understand and communicate these advances and know how they will affect our profession.

Guest Editors: Evguenia Alechine and Martin Delahunty

The deadline for feature articles is September 9, 2019.



March 2020:

The data economy

In an increasingly digitised world, data are economic assets that are becoming the lifeblood of the world economy. Medical writers need to know how the data economy affects the development of healthcare products and should understand which big data repositories are reliable, the specialized data analysis approaches needed, and the issues around big data protection.

Guest Editor: Raquel Billiones and Sam Hamilton

The deadline for feature articles is December 10, 2019.

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If you have ideas for themes or would like to discuss any other issues, please write to mew@emwa.org.



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