



Medicines with a 'well established use'

by Iain Colquhoun

Question: What do menthol, hexylresorcinol, amylmetacresol, camphor, cetalkonium chloride, turpentine oil (to name just a few from a long list) have in common?

Answer: All are drugs with a 'well-established use' (WEU).

The regulatory definition of this will follow, but a literal interpretation is easily justified by considering the dates when some of these compounds were first isolated or developed. For example, menthol and camphor have been widely used for flavouring and medicinal purposes for centuries [1,2], but little studied until the 1920s [3]; both are still widely used in over-the-counter (OTC) products, mostly topical, with 40 products listed for camphor and 109 for menthol [4]. Hexylresorcinol was first studied around 1924 [5], and amylmetacresol around 1930 [6,7]; both are still widely used in antiseptic throat lozenges that have annual worldwide sales of many millions of packs.

This article will describe the regulatory background and guidance available when working with a drug with a WEU. While many generics and herbals may be regarded as drugs with a WEU, their specific requirements vary in some respects from WEU drugs, and they will not be discussed in detail here.

Regulatory background

As medical writers, most of us are, or have been at some point, involved in writing clinical study reports (CSRs). Clinical studies are most often undertaken to evaluate a new chemical entity or a new indication for an existing compound, sometimes for a high-profile disease condition that may seriously affect the health and welfare of millions of people world-wide. We have ICH guidance available that has been specifically written for this scenario, telling us how we should present the evidence for safety and efficacy from clinical studies in the common technical document (CTD) format.

However, not all drugs on sale are supported by clinical studies: in 2007 the EU pharmaceutical products market (at consumer prices) was estimated to be worth €195,254 million [8], of which €30,652 million (15.7%) was due to the sale of non-prescription OTC products. For many of these products no clinical trial may ever have been carried out. Drugs that have been on the market for many years often have very slim dossiers, at least in the UK, because after The Medicines Act of 1968 came into force, those medicinal products on the market on or before 01 September 1971

were granted 'product licences of right' (PLRs), and for those marketed before 1964 little was required in the way of safety and efficacy data [9]. If a MAH (marketing authorisation holder) now wishes to vary the licence or submit an application for a marketing authorisation (MA) in a new territory, a new dossier is clearly required; but how does one demonstrate the required safety and efficacy of the product without clinical and pre-clinical studies?

If the active compound(s) falls into the category of drugs 'with a well-established use', as many ingredients of older OTC products do, there is an alternative application route that allows the dossier to be based upon a bibliographic review of the published evidence on the safety and efficacy of the actives. The current criteria for WEU status have a convoluted history, but were first defined in Directive 65/65/EEC Article 4.8.(a)(ii), which states (after being amended)[10]:

'The applicant [*for a MA*] shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate...by detailed references to published scientific literature presented in accordance with the second paragraph of Article 1 of Directive 75/318/EEC [11] that the constituent or constituents of the medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety;'

Paragraph 2 of Article 1, Directive 75/318/EEC, simply states that

'Where...reference to published data are submitted, the provisions of this Directive (75/318/EEC) shall apply in like manner'.

'Like manner' understandably gave rise to some confusion, and Directive 1999/83/EC [12] specifically sought to clarify the meanings of 'bibliographic applications', 'well-established use' and 'bibliographic reference' by inserting a new Section I in Part 3 of the Annex to Directive 75/318/EEC [11]. Note that the current version of this revised Annex is to be found in Directive 2003/63/EC [13].

Part II of the revised Annex (page 32) [13] finally provided detailed guidance on preparing a 'bibliographic application' and made clear that 'specific rules' must be applied to demonstrate a well-established medicinal use with established safety and efficacy. In essence, the main factors to be taken into account are:

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- a) to establish a well-established medicinal use, the period of time from the first systematic and documented use of that substance as a medicinal product in the European Community must be not be less than one decade;
- b) the documentation should assess all aspects of safety and efficacy, and must include a review of the relevant literature, including pre- and post-marketing studies and published scientific literature including epidemiological studies. All available evidence, both favourable and unfavourable, must be presented, and the use of particular sources of information justified;
- c) if information is missing, justification will be required as to why an acceptable level of safety and/or efficacy can be supported;
- d) the non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing;
- e) post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

Two aspects of this advice are sometimes forgotten: firstly, the exhortation to report supportive and unsupportive data, and to justify the data and sources, and secondly the encouragement to include epidemiological studies. The need to report positive and negative data is self-evident, but is frequently given a very light touch: there are different ways of doing this, but my own is to present the 'bad' news first, and conclude with the 'good' news. The lack of rigorous clinical trial data gathered in accordance with Good Clinical Practice (GCP) guidelines is also a common issue: all one can say is that the studies being presented were not conducted to GCP guidelines, but to the standards of the time, and comment upon how this affects the quality of the data.

The mention of observational studies is interesting, given the current tendency to view any correlations arising from them with suspicion! At the risk of being labelled subversive, it is worth pointing out that there is a school of thought that is supportive of observational studies, and I recommend the following short articles, the first being of a more serious nature [14] and the second humorous—but instructive [15], and most elegantly and wittily written!

The writer's tasks

For drugs with a WEU the writing tasks are not, in principle, different from more modern drugs licensed via a standard application: updates to old dossiers, new dossiers, variations to existing MAs, renewals to MAs, and periodic safety update reports (PSURs). Of those tasks, that of creating a new dossier is one that occurs whenever the MAH wishes to apply for a MA in a new territory and only has a pre-1971 dossier.

Fortunately the revised Annex provides considerable detail as to the content of the bibliographic CTD, and some points not covered in the Annex are now answered in the current Question and Answer (Q&A) document [16]: for example, two points on which MAHs have been unsure are (i) whether it is adequate to submit only Overviews or are Summaries also required, and (ii) should the data from the references be tabulated? The Q&A document answers both those questions with:

'Summaries may not be necessary for very old, well-known substances, but a proper justification will be required. Overviews always have to be provided.'

The assumption is that tabulations occur predominantly in Summaries, but when reporting old studies, there is a very definite limit to which one can extract data, and I frequently find that an Overview, with some limited tabulation, is the more appropriate way to present the limited data available.

Other requirements may arise: one that demands a particularly thorough and detailed literature search is 'switching' (i.e. changing the legal classification) the class of product licence from prescription only (POM) to pharmacy (P) or from P to general sales list (GSL = OTC). As required in EC Directive 2001/83/EC Article 71[17], before a medicine can be switched from POM to P, it must not:

- present a danger to human health if used without the supervision of a doctor;
- be widely used incorrectly (including risk of abuse), and as a result present a danger to human health;
- require further investigation of activity and/or side-effects;
- be normally prescribed by a doctor for administration by injection.

Before a medicine can be switched from P to GSL it must be shown that it:

- can with reasonable safety be sold or supplied without the supervision of a pharmacist.

Guidance is provided by the MHRA on their web site [18] and in a guidance note [19]. As these products are already licensed, efficacy data are only required when indications, dosages or age ranges differ from the authorised product. It is the safety profile that the application is built around, and for all the reasons discussed above, this again will depend upon evidence from a literature review supporting the MAH's existing safety database.

Recently, the Paediatrics Regulations [20] required MAHs to submit safety and efficacy data relevant to the paediatric population for all marketed products with a paediatric indication. Again, the written submission for many WEU products, whether a CTD overview or an old-style expert statement (still being written although contrary to the available guidance), had to rely upon a detailed literature review supplemented by post-marketing data.

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So when, as a medical writer, you are looking to expand your activities, remember that there is more to medical writing than CSRs, and that the humble literature review still has a major role to play! And that role is probably more important for medical devices, but that is another story!

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A chamber of rogues in drug development

Marcia Angell, former editor of *The New England Journal of Medicine*, begins her review of three books that relate practices of grave concern in drug marketing by referring to Senator Charles Grassley's investigation of the ties between the pharmaceutical industry and academic physicians. She says he has not had to look far and gives her own list of recent ethics transgressions arising from cooperations between opinion leaders and the pharmaceutical industry (www.nybooks.com/articles/22237).

Senator Grassley's investigation of Wyeth's ghostwriting policies is reported at:

<http://links.mkt1066.com/ctt?kn=49&m=3815998&r=Mjk1Mjg3MDA5MAS2&b=0&j=MTA2MTUyNTAyS0&mt=1&rt=0>

Note also that the 7th February 2009 issue of the *BMJ* has a debate presented from different perspectives on how relations with the drug industry, academia and healthcare professionals should be reframed.

Grammarians who rule by whim ...

Jan Freeman of the *Boston Globe* cautions against the above [1] in her 'The Word' column, very much in the vein of the myths about English that I have tried to dispel over the past few years in *TWS*. If you do not know it already, I'm sure that as a *TWS* reader, you will find the column not only entertaining but also informative. The following link leads you to a selection of her recent articles:

http://www.boston.com/bostonglobe/ideas/jan_freeman/

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Reference:

1. <http://www.iht.com/articles/2008/12/28/opinion/edfreeman.php> accessed 12 January 2009.