



The world of medical devices—serving two masters

by Art Gertel and Nancy J Stark



Many of us who have worked in the Medical Writing profession and have been associated with the Pharmaceutical Industry, cut our teeth in the world of DRUGS.

The research, development, and registration of other medical interventions, such as vaccines and devices, were always considered to be ‘lightweight’ in comparison to drugs. Devices, in particular, seemed to us to require much less diligent research, certainly less monitoring, and only simplistic evaluations of therapeutic safety and efficacy.

This may, in part, be due to an increasing interest in the development of drug-device combinations to enhance the delivery of already approved medications; the advent of more sophisticated diagnostic tools (eg, assays for the early detection of disease); development and design of more biocompatible materials, allowing the implantation of indwelling devices; and, of course, the ever-present spectre of product liability and associated litigation.

In the USA, devices are usually handled under the authority of the Center for Devices and Radiological Health (CDRH). A notable exception to this is devices that involve blood collection or analysis. These are the purview of the Center for Biologic Evaluation and Review (CBER).

What is a ‘device’?

The term ‘device’ is defined as instruments, implements, machines, and other things that are intended for use in diagnosing diseases or other conditions and in treating disease in humans. Also, items that are intended to affect the structure or function of the body of humans or other animals are considered devices. Essentially, devices do not depend on being metabolized or on chemical action to achieve their primary intended effects.

Medical devices initially were subjected to regulation in the USA, based on the Federal Food, Drug and Cosmetic Act (FD&C Act) in 1938. However, until 1976, there were no requirements that devices be reviewed or approved before they were distributed commercially. Device regula-

tion was defined by the FDA&C Act’s misbranding and adulteration provisions, and device regulation was “after the fact” because the Agency had no authority to keep unsafe products from entering commerce. Finally, in 1976, Medical Device Amendments gave the FDA authority to require premarket review.

The key feature of the 1976 Amendments was a classification scheme that placed all devices into one of three classes (Class I, Class II, or Class III). Although Congress intended that Class III devices be subject to the highest level of regulation, which requires product-by-product approvals prior to marketing, and that Class II devices comply with FDA-issued performance standards—resulting in what would amount to a generic premarket approval process. However, this level of oversight never materialized! FDA did not issue any performance standards for Class II devices, and did not require manufactures to submit premarket approval applications (PMAs) for the vast majority of Class III devices that were on the market prior to the 1976 Amendments.

In the past five years, however, there has been a change in the way that regulators in the United States have addressed the requirements for the development of devices.

Class I: Those for which “general controls” reasonably assure safety and effectiveness. If there is insufficient information to demonstrate that general controls are adequate, must meet the following criteria:

- It is not purported to be life-supporting or life-sustaining;
- It is not intended for a use that is of substantial importance in preventing impairment of health; and
- It does not present a potential unreasonable risk of illness or injury.

Class II: Those for which Class I controls are inadequate and there is evidence that “special controls” reasonably assure safe and effective use.

Class III: Those for which there is insufficient information to show that either Class I or Class II controls can provide reasonable assurance of safety or effectiveness.

As a result, Congress was placed in the position of either forcing the FDA to comply with the original intent of the 1976 Amendments, or altering the law’s approach. Congress chose the latter path, and passed the Safe Medical Devices Act of 1990 (SMDA). Instead of relying

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Table 1 Examples of differences:

TOPIC	ICH	Ref	ISO	Ref
QA/QC	sponsor responsible for implementing & maintaining QA/QC control systems w/SOPs to ensure compliance with protocol, GCP, other regs.	5.1.1-5.1.4	The sponsor "shall ensure ... through a quality system" –without giving detail as to what that system should include	Part 1-8.1
Transfer of Obligations	sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor	5.2.1-5.2.3	only mentions CROs in passing, as an example of an additional party to be listed in the final report	Part 1 – C.13.c
DSMB	establishment of an independent data monitoring committee	5.5.2	Not addressed	
e-Data Handling		5.5.3	Not addressed	
Archiving	original copy of data should be archived before transformed during processing	5.5.4	Not addressed	
Data Ownership	sponsor may not be the 'owner' of the data	5.5.6	Not addressed	
Data Retention	2 years	5.5.8	Not addressed	
Transfer of Ownership of Data		5.5.10	Not addressed	
Financial Agreements	allows the protocol to substitute for agreement between sponsor & investigator; suggests a separate agreement on financial matters	5.9	requires unique, written agreement between sponsor & investigator; silent on financial matters.	
Good Mfg. Process	investigational product must be "manufactured in accordance with any applicable GMP"	5.13.1	literature summary, list of materials & components, intended clinical performance, summary of relevant pre-clinical data, summary of previous clinical experience, list of International Standards complied with, & results of the risk analysis—presented in Investigator's Brochure. These data are intended to support the safety and appropriateness of the investigational device and substitute for compliance with Good Manufacturing Practices [3] .	Parts 1-7.2
Access to Source Data	Sponsors should obtain agreement in writing for monitors, auditors, IRBs, & regulators to have direct access to source data/ other trial documents. Should verify that subjects have consented to such access.	5.15	only mentions 'direct access' indirectly	
SUSAR Reporting	sponsor should expedite reporting of all serious & unexpected adverse drug reactions (i.e., adverse device effects) to other investigators, other IRBs, and to regulators	5.16.2	requires sponsors to report all serious adverse device effects & all other SAEs to regulators, ethics committees, & safety monitoring committees and to other principle investigators See Figure 1, below	Parts 1-8.2h, i
Central Monitoring	when conducted in conjunction with procedures such as investigator training and meetings; allows for statistically controlled sampling for selecting data to be verified	5.18.3	Not addressed	
SOPs	sponsor's established written SOPs required	5.18.5	Not addressed	
Audits	devotes an entire section to defining purpose & frequency of audits, having SOPs for auditing, how to conduct audits, audit certificates, & that audit reports should not be requested by regulatory authorities	5.19.1-5.19.3	one sentence on auditing: "The clinical investigator(s) shall allow auditing of their clinical investigation procedures"	Part 1-6.12
Protocols	Basically, same as for ISO Exception: allows for description of 'stopping rules' or 'discontinuation criteria' for individual subjects, parts of trial, and entire trial	6.4.6	Basically, same as for ICH Not addressed	
Source Data	provides for data to be recorded directly on CRFs (i.e., no prior written or electronic record of data). These data are considered to be source data and shall be identified in the protocol	6.4.9	doesn't provide for this possibility, yet certain forms are commonly completed by contemporaneous interview and are both source document and CRF	
Early Discontinuation	specify in protocol the criteria for discharging subjects from a trial early; ie, for noncompliance	6.5.3	Not addressed	
Investigator's Brochure	purpose of an IB is to provide investigators with information to facilitate compliance with the protocol; contents are pharmaceutically oriented, eg, "highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, & clinical information available"	7.1 7.2	ISO asks for a more device-oriented content: a literature summary, list of materials & components, intended clinical performance, summary of relevant pre-clinical data, summary of previous clinical experience, list of International standards complied with, & results of the risk analysis	Part 1-7.2
Essential Documents	comprehensive list of documents that should be kept during conduct of a clinical trial, and designation of who should keep them	8	Not addressed	

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on premarket approval or performance standards as the premarket means of protecting the public, Congress accepted the FDA’s reliance on premarket notification as the primary safety and effectiveness screen for devices. Specifically, Congress took the FDA’s guidance on 510(k)—which requires persons who intend to market devices to notify the FDA at least 90 days before introducing a device into interstate commerce—and, essentially, turned it into law, with some additions (which apply to Class II and Class III devices):

- currently marketed medical devices may be used as predicates;
- premarket notification must include a summary of safety and effectiveness that describes substantial equivalence between the newer and predicate devices;
- conduct reasonable searches of all known or available information regarding the new and predicate devices;
- certify to FDA that an appropriate search was completed and submit a summary of all adverse safety and effectiveness data for both the new and predicate devices.

The FDA Modernization Act of 1997:

FDAMA changed many Agency practices, including the elimination from premarket review of those devices that did not really require FDA review before marketing.

FDAMA imposed numerous deadlines for CDRH to make significant changes to its programs, issue regulations, and produce guidance documents. The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) imposed even tougher performance goals on CDRH in exchange for payments from industry to supplement review costs. More recently, FDA has increased the rigour to which devices are subjected. They seem to be moving toward standards that more closely reflect those required for drug and biologic applications. This resulted in the ‘rude awakening’ among some device developers that times have changed. Sometimes, there were no Standard Operating Procedures (SOPs), no organized system for conducting animal safety tests or conducting clinical studies in humans. The companies most affected were start-ups and European manufacturers attempting to enter the US market.

While drug development and approval processes have referenced the (ICH), the processes for devices are caught between two worlds: that of ICH, and that of ISO.

Import/Export:

The international movement of devices is an area of growing interest for manufacturers and regulatory authorities in various countries. Under the FD&C Act and in conjunction with the Department of Treasury (US Customs Service), FDA controls the movement of devices to and from the USA.

Current status:

While drug development and approval processes have referenced the International Conference on Harmonisation (ICH), the processes for devices are caught between two worlds: that of ICH, and that of International Organisation for Standardisation (ISO). Companies with experience in the ICH context must assess applicability of these standards to the world of devices. This is not always self-evident, since ISO and ICH do not agree on some requirements and, often, ISO is silent on issues that are emphasized in ICH, as shown in Table 1, above.

ICH-GCPs: Applicable to devices?

The ISO 14155 standards for the Clinical Investigation of Medical Devices were written for the purpose of clinically investigating devices [1]. Now 10 years old, the ICH Good Clinical Practices (ICH-GCP, E6) were written for the purpose of clinically investigating pharmaceuticals [2].

This may present a dilemma for those who are preparing to register devices, as the original purpose of these guidances had different foci. For device manufacturers who decide to conduct their first-in-man trials in Europe, the question of which document to follow can be difficult one. Following ISO 14155 is easier, and will bring the device to market in Europe faster, but the data may be of limited value in the USA. The converse is true with respect to following the ICH-GCPs.

Figure 1. The Venn diagram describes the reporting requirements of sponsors in medical device clinical trials, as required by ISO 14155, 2003

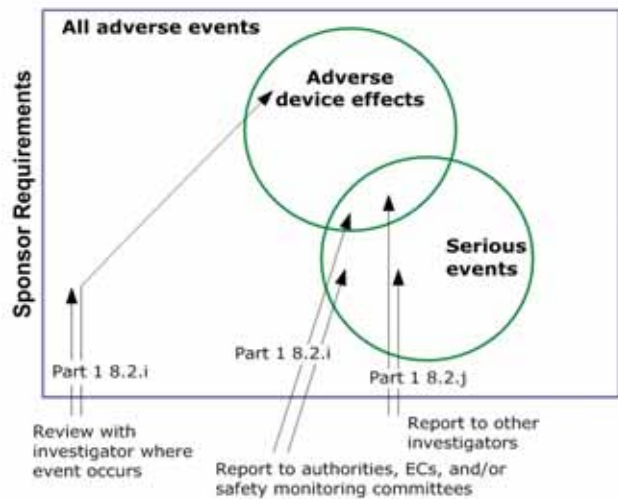


Figure 2. Responses of 26 medical device manufacturers re: adverse event collection procedures

AEs Collected:	US Sites	EU Sites	ROW Sites
Only Device AEs	3	3	2
All AEs	10	11	3
Mixed AEs	5	7	3

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Responsible and rational adverse event reporting is a continuing problem for all device sponsors. Most sponsors, regulators, investigators, and IRBs agree that ISO is too restrictive and the US Part 812 is too confusing. An informal survey of device manufacturers in October 2006 showed that most sponsors collect ALL adverse events regardless of whether or not the event is device-related [4].

Recommendations:

Don't follow either ICH or ISO. Instead, write your own standard operating procedures for international trials, using ISO as a base and adding ICH components as necessary. If you do this methodically, you'll have procedures that meet FDA requirements, but don't place unjustified burdens on unsuspecting European investigators.

Conduct your first-in-human and pivotal clinical trials in Europe or other developing nations, where it is usually easier to get clinical trials started. Choose countries with investigators trained in western medicine, ample subjects for participation, and an interest in implementing FDA-accepted trials.

Write a clinical quality system for yourself, methodically basing it on the ICH-GCPs compared to ISO 14155 and ISO compared to ICH, and incorporate checkpoints for host country regulations. Become familiar with the International Ethical Guidelines for Biomedical Research Involving Human Subjects [5]. Be absolutely ethical in the conduct of the trials.

Watch this space:

A new ISO Draft International Standard (DIS), is expected to be issued by mid-2008: ISO-DIS 14155—*Clinical Investigations in Humans of Medical Devices—Good Clinical Practices*.

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1. ISO 14155 Parts Clinical Investigation of Medical Devices for Human Subjects—Parts 1 and 2, February 15, 2003.
2. ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice—E6, May 1, 1996. See www.ich.org.
3. 21 CFR Part 812 takes a similar approach, asking for a Report of Prior Investigations and a statement as to the extent of compliance with good manufacturing practices.
4. The following survey question: "Of the medical device or device-combination clinical trials you conducted in 2006, did you collect only device related adverse events, all adverse events, or a mix of adverse events according to a plan your company developed?" was emailed to 100 companies outside of the United States and 200 companies within the States. The table is based upon 26 responses received within the first 5 days.
5. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Council for International Organizations of Medical Sciences (CIOMS), Geneva, Switzerland
See http://www.cioms.ch/guidelines_nov_2002_blurb.htm

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The following is quoted from the website <http://www.inklingmagazine.com/inkycircus/detail/you-too-can-author-a-computer-science-paper/> and runs under the title: You too can author a computer science paper!

"I've been hearing a lot of grief from my scientist friends about having to write research papers or submit or edit them, etc.

Here's a silver bullet—if you're in computer science that is. SCIgen randomly generates an entire computer science research paper (complete with graphs and figures) at the click of a button. All you have to do is fill in the five author fields.

For example, the trio behind inky circus came up with a paper titled On the Visualization of Hierarchical Databases.

Here's the abstract. Can I just say, who knew we had it in us?

In recent years, much research has been devoted to the visualization of XML; however, few have deployed the investigation of spreadsheets. Given the current status of classical archetypes, end-users daringly desire the refinement of the partition table. We construct a heuristic for autonomous information, which we call Emu. Such a claim is usually an extensive mission but fell in line with our expectations.

As you can see the results are pretty spiffy—which explains how three randomly generated papers made their way to the World Multiconference on Systemics, Cybernetics and Informatics in Orlando in 2005."

The site also has a 13-minute film clip about the hoax.

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