Medical Device and Diagnostic Industry 101

Carey Smoak, Roche Molecular Systems, Inc., Pleasanton, CA

ABSTRACT

Medical devices and diagnostics are increasingly important industry to the healthcare industry. The number of devices approved by the FDA has increased by 52% in the past decade. While devices are important in and of themselves, they are also increasingly more and more important in pharmaceutical research including diagnostic imaging used to monitor therapies, devices used to deliver drugs and diagnostic tests to determine if a patient will respond to a particular therapy. Devices are different from pharmaceutical products in terms of the FDA approval process, the use of CDISC standards and types of studies.

INTRODUCTION

This paper will cover basic information about the medical device and diagnostic industry, including the importance of devices, differences between medical devices and pharmaceutical products, regulatory approval of devices, CDISC and types of studies. Changes in medical device regulations may be in the works. The FDA has asked the Institute of Medicine to conduct a review of the approval process for devices which should be completed in 2011 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm183497.htm February 14, 2010).

In this paper, the term devices to refer to both medical devices and diagnostic products.

THE IMPORTANCE OF DEVICES

Devices in and of themselves are important. For example, devices like heart stents may save peoples' lives and blood screening instruments that tests for the presence of HIV to help to keep the blood supply safe.

Table 1 shows that during the past decade, the number of device approvals (PMAs – Pre-Market Approvals) by the Center for Devices and Radiologic Health (CDRH) at the FDA has increased from 488 in the year 2000 to 740 in 2009 – an increase of 52% (http://www.fda.gov/cdrh/pmapage.html January 27, 2010).

Table 1: Number of PMAs Approved by CDRH During the Last Decade

Year	Number of PMAs Approved
2009	740
2008	776
2007	683
2006	704
2005	497
2004	438
2003	532
2002	551
2001	556

2000	488

Not only are devices important in and of themselves, but also when used in conjunction with therapeutic products. For example, contrast agents in imaging devices may monitor therapeutic agents. Drug eluting heart stents may treat cardiovascular disease. Diagnostic assays may determine if a therapeutic product will work in a patient. This last area includes targeted therapies and companion diagnostics in which a diagnostic test may identify when a targeted therapy may work in a particular patient.

DIFFERENCES BETWEEN THE MEDICAL DEVICES AND PHARMACEUTICAL INDUSTRIES

The information in Table 2 is based upon a paper by Greg Campbell (2006) at CDRH and has been previously published (Smoak 2008b).

Table 2: Differences between the Medical Device and Pharmaceutical Industries

Medical Devices	**Pharmaceutical**
A medical device is anything that is not either a drug or a biologic product.	A pharmaceutical product is a drug or a biologic product.
The mechanism of action for medical devices is usually physical.	The mechanism of action for pharmaceutical products are usually chemical or biological.
Medical devices can be therapeutic, diagnostic or something else.	Pharmaceutical products are usually therapeutic.
Medical devices are invented.	Pharmaceutical products (new chemical entities) are generally discovered.
Medical devices can be altered during clinical development and once on the market a newer, improved version may be in development. Consequently, the life-cycle of a medical device may be as short as a couple of years.	Pharmaceutical products are usually on the market for many years.
Medical devices are approved through the Premarket Approval (PMA) application process and a single confirmatory study is often sufficient for approval.	Pharmaceutical products are approved through the New Drug Application (NDA) process and drug development is characterized by Phases I through IV clinical trials.
There are more than 25,000 medical device companies registered with the FDA.	There are relatively few pharmaceutical companies.
There are tens of thousands of medical devices.	Pharmaceutical products numbers in the thousands.
Medical device companies are usually small (the median size is less than 50 employees).	Pharmaceutical companies tend to be large.

The differences in terms of approval process by the FDA, CDISC and Types of Studies are explained in more detail in the following sections.

APPROVAL PROCESS FOR DEVICES

Medical devices are approved by two branches at the FDA – CDRH (Center for Devices and Radiologic Health) and CBER (Center for Biologics Evaluation and Research). CDRH handles all device submissions except for HIV devices and blood screening devices which are handled by CBER.

CDRH

Devices are classified as I, II or III is based "on the *intended use* of the device and also upon *indications for use*" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm, November 25, 2009).
Table 3 shows examples of Class I, Ii and III devices (http://www.devicewatch.org/reg/reg.shtml, November 25, 2009).

Table 3: Device Classification

Classification	Description	Examples
I	Generally, these are simple devices with minimal risk to the user.	enemas, crutches, elastic bandages, bedpans
II	These devices pose a moderate level of risk to the user.	condoms, intravenous administration sets, sutures, inflatable blood pressure cuffs
III	These devices pose a serious level of risk to the user, mostly because they are implants or sustain life.	implantable pacemakers, blood vessel stents, breast implants

Devices at CDRH are approved through either the 510K, PMA or IDE process. In general, class I and II devices can be approved by a 510K submission, while a class III device requires a PMA submission. IDE (Investigational Device Exemption) approval allows a device to be used in support of a 510K or PMA submission.

New devices cannot be used in clinical trials in human subjects without prior permission. The application process for this approval is called an IDE. IDEs are covered by 21 CFR Part 812. Per the FDA (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm November 25, 2009):

> "An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA."

510(k) submissions usually compare a new device to a predicate device (a predicate device is defined as a legally marketed device) to demonstrate that the new device is substantially equivalent to a predicate device. 510K products are covered by 21 CFR Part 807 Subpart E. Per the FDA (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm November 25, 2009):

> "A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent."

The FDA generally has 90 days to clear, question or reject a 510(k) application. 510(k) products are "cleared," not "approved" by the FDA. Device manufacturers may not advertise that 510(k) products are "approved" by the FDA.

PMA (Pre-Market Approval) submissions are used to demonstrate to the FDA that a new or modified device is safe and effective. The standard for PMAs is higher than the requirements for 510(k) submissions. PMAs are covered by 21 CFR Part 814. Per the FDA (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm November 25, 2009):

> "Product requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device."

The FDA generally has 180 days to approve, question or reject a PMA application. The FDA "approves" PMAs and manufacturers may advertise them as such.

CBER

Devices at CBER are also approved by either the 510K or PMA process as described above. In addition, some devices may require a Biologics License Application (BLA). BLAs are covered by 21CFR 600-680 and are needed

when interstate commerce is involved
(http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/default.htm November 25, 2009).

CDISC (CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM)

Currently, SDTM (Submission Data Tabulation Model) is not completely configured to allow medical device and diagnostic companies to submit data to the FDA in CDISC. Therefore, existing domains need to be modified and new domains need to developed. In May, 2006 an SDTM Device sub-team formed to begin reviewing SDTM domains and developing new domains (Smoak 2007). In February, 2009 the CDASH (Clinical Data Acquisition Standards Harmonization) team joined the effort so that the Device team can produce both CDASH and SDTM domains which will meet the needs of the medical device and diagnostic industry. Since its inception, the team has expanded both in terms of scope and representation.

SCOPE

Originally, the Device team focused on SDTM. The scope has widened to include reviewing and modifying (as needed) the sixteen CDASH domains. Possible new CDASH and SDTM domains include device properties, tracking and malfunctions.

To facilitate the CDASH review, more than 170 Case Report Forms (CRFs) were collected from more than 40 device companies. A frequency analysis of these CRFs is being performed on the CRFs collected. The purpose of the frequency analysis is to find out where devices differ from the current CDASH domains and to modify the CRFs for devices where necessary. The goal is to incorporate these modifications for devices into CDASH version 1.1 in 2010. The new domains will also be incorporated into SDTM, marking the first time that new CDASH and SDTM domains have been developed at the same time.

REPRESENTATION

The Device team expanded its representation and now lists more than fifty members. Recruitment of new industry experts in 2009 was primarily accomplished through an organization called AdvaMed. Areas of industry expertise include diagnostics, imaging, implantable devices and orthopedics.

Initially, the FDA representatives on the Device sub-team were from CDRH (www.fda.gov/cdrh). In 2008, representative from CBER (Center for Biologics Evaluation and Research – www.fda.gov/cber) were added. CBER is involved in devices that pertain to blood screening and HIV testing.

CDISC representatives on the Device team include members from the SDS (Submission Data Standards) and CDASH teams.

TYPES OF STUDIES

The types of device which may be conducted in the device industry can be different than the types of studies conducted in pharmaceutical research. Phase I, II, III and IV, which are common in pharmaceutical research, do not apply to devices. Two types of studies are described here – reproducibility and clinical utility.

In addition to the difference in the types of studies in pharmaceutical and device research, the pace of the studies can be different. In particular, diagnostic studies can be much shorter in duration than pharmaceutical studies. Consequently, SAS® programmers may have a much shorter amount of time to program diagnostic studies (Smoak 2008a).

REPRODUCIBILITY

The purpose of a reproducibility study is to demonstrate the accuracy and precision of a device. For example, for a diagnostic assay, one might be interested in how well the assay performs at multiple testing sites, with multiple lab operators at each site and each operator testing multiple lots of the assay. For a qualitative diagnostic assay, hit rates are generally used to determine the reproducibility of the diagnostic assay. For a quantitative diagnostic assay, statistical measures such as coefficient of variation and precision analyses using PROC MIXED may be used to determine the reproducibility of the assay. In addition, the performance of device in terms of valid/invalid runs and valid/invalid test results is important in reproducibility studies on a diagnostic assay (both qualitative and quantitative).

CLINICAL UTILITY

The general purpose of a clinical utility study is to demonstrate the real-life use of device in clinical practice. For example, a diagnostic assay may be used to screen subjects for a certain condition in a clinical trial or used to monitor subjects given either a therapeutic or placebo in a clinical trial. Typical analyses in these types of diagnostic

clinical trial might include measures of sensitivity, specificity, positive predictive value and negative predictive value. Calculating these types of statistics using SAS has been demonstrated elsewhere (Mandrekar JN, Mandrekar SJ 2005).

CONCLUSION

The medical devices and diagnostic industry is becoming increasingly more and more important. The number of device approvals by the FDA has increased by 59% in the past decade. While devices are important by themselves, they are also increasingly used in pharmaceutical research including diagnostic imaging to monitor therapies, devices used to deliver drugs and diagnostic tests to determine if a patient will respond to a particular therapy. Devices are different than pharmaceutical products in terms of the FDA approval process, CDISC and types of studies.

REFERENCES

Campbell G. "The Role of Statistics in Medical Devices – The Contrast with Pharmaceuticals." *Biopharmaceutical Report 14:1-8, 2006.*

Mandrekar JN, Mandrekar SJ. "Statistical Methods in Diagnostic Medicine using SAS® Software." *Proceedings of the SAS® Users Group International,* April 2005. <http://www2.sas.com/proceedings/sugi30/211-30.pdf>

Smoak C. "CDISC for the Medical Device and Diagnostic Industry." *Proceedings of the Pharmaceutical Industry SAS® Users Group.* June 2007. <http://www.lexjansen.com/pharmasug/2007/fc/fc10.pdf>

Smoak C. "Empowering SAS® Programmers to Meet Deadlines." *Proceedings of the Pharmaceutical Industry SAS® Users Group.* June 2008a. <http://www.lexjansen.com/pharmasug/2008/ma/ma03.pdf>

Smoak CG. "A CDISC SDTM model for the medical device and diagnostic industry." *Pharmaceutical Programming 1:28-30,2008b.*

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

> Carey G. Smoak
> Manager, SAS Programming
> Roche Molecular Systems, Inc.
> 4300 Hacienda Drive
> Pleasanton, CA 94588
> Tel. 925-730-8033
> Fax 925-225-0195
> carey.smoak@roche.com