Medical Device Review Processes of U.S. Food and Drug Administration

Takahiro Uchida, M.D., M.Sc., Ph.D.¹⁾

Center for Devices and Radiological Health, one of the 8 Offices of the Food and Drug Administration under Department of Health and Human Services, is in charge of U. S. medical device regulations.

In the U.S., medical devices are classified into 3 classes based on its risk. A review pathway, 510(k), is applicable for some Class I devices and most Class II devices. The 510(k) pathway is considered to be flexible and under discussion to introduce in the Japanese regulatory process. The highest risk medical devices classified into Class III are approved through the Premarket Approval (PMA) pathway. Investigational Device Exemption (IDE) is necessary for clinical trials with high-risk medical devices in the U.S. A system of Pre-IDE meeting is very useful for sponsors.

FDA may require a Panel Meeting that is similar to the Japanese Senmon Kyogi for a medical device approval. FDA's Panel Meetings are very transparent. The Panel conclusion facilitates FDA's final decision, but not always followed by FDA.

Immunity from lawsuits among FDA reviewers is legitimate, although that among Japanese medical device reviewer is not.

Keywords : FDA, Medical device regulations, Medical device review, Panel Meeting, Immunity from lawsuits

1. U.S. FDA Medical Device Review Processes

1) U.S. FDA

The U.S. Food and Drug Administration (FDA) (Rockville, MD, USA) is one of the 12 federal offices that comprise the Department of Health and Human Services (DHHS). Although it is just one institution of the DHHS, the FDA has approximately 10,000 employees, and covers a wide range of issues. The FDA regulates and controls approximately 1 trillion-U.S. dollar-worth of products, which account for 25 cents of every dollar of consumption in the United States.

The history of the FDA begins with the enactment of the Federal Food and Drugs Act of 1906, which gave the federal government power to control and regulate inadequate foods and drugs that were being distributed without regulation at the time. Jurisdiction for this law was given to the Department of Agriculture's Bureau of Chemistry, which could be called the antecedent of the FDA, but later in 1927 this bureau's status rose, and its name was changed to the Food, Drug, and Insecticide Administration that was then changed to the current name in 1930. After the 1937 sulfanilamide elixir incident (FDA, 1981), the Federal Food and Drugs Act was amended to become the Federal Food, Drug, and Cosmetic Act in 1938. This Act required companies to conduct pre-approval clinical testing of all drugs, and expanded the scope

¹⁾ Boston Scientific Corporation, Former Medical Officer /Reviewer of U.S. Food and Drug Administration

of coverage to cosmetics and medical equipment while clarifying the responsibility of manufacturers and establishing the perspective of consumer protection. In 1940, the FDA was transferred from the Department of Agriculture to the newly created Federal Security Agency. Various changes were made afterwards, and the Public Health Service Act was passed in 1944. The Food Additives Amendment was enacted in 1958. The Kefauver-Harris Drug Amendments (1-Establishment of Good Manufacturing Practices (GMP); 2-Requirement of informed consent through clinical evaluation; 3-Requirement of a prompt report for side effects of medical devices) were passed in 1962. The Medical Device Amendments to the Federal Food, Drug, and Cosmetic (FFD&C) Act were enacted in 1976 in order to establish basic framework governing the regulation of medical devices. The greatest change in recent history was the enactment of the FDA Modernization Act in 1997, in which most of the current structure of the FDA was created.

2) Center for Devices and Radiological Health

One of five FDA Centers, Center for Devices and Radiological Health (CDRH), is responsible for regulating medical devices and radiation emitting electronic products such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions (medical and non-medical). In 1976, Medical Device Amendments was implemented because medical device related adverse events and device malfunctions became a social problem. After that, CDRH resulted from the merger of the Bureau of Medical Devices and the Bureau of Radiological Health in 1982.

As of December, 2008, CDRH has 8 offices, Office of the Center Director, Office of Compliance, Office of Device Evaluation (ODE), Office of Management Operations, Office of Science and Engineering Laboratories, Office of Communication, Education, and Radiological Programs, Office of Surveillance and Biometrics, and Office of In vitro Diagnostic Devices Evaluation and Safety. Among them, the ODE is primarily in charge of medical device reviews. The ODE has five device divisions and three administrative divisions. As of February, 2006, there were 332 employees in the Office of Device Evaluation,

including 82 staff members (mostly reviewer) in Division of Cardiovascular Devices, 69 staff members in the Division of General, Restorative, and Neurological Devices, 61 staff members in the Division of Reproductive, Abdominal, and Radiological Devices, 42 staff members in Division of Ophthalmic and Ear, Nose, and Throat Devices, and 41 staff members in Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (Uchida, 2006). Since reviewers review not only for clinical study results but also for preclinical tests results, they have a background in various fields, medicine, pharmacology, veterinarian medicine, dental medicine, biostatistics, biology, biomedical engineering, etc. Among reviewers, there were 49 physicians (Medical Officer) at ODE (as of February, 2006).

Giving this number of ODE reviewers, the number of medical device reviewers at the Pharmaceuticals and Medical Devices Agency (PMDA, Tokyo, Japan) seems to be very small. For a total of 35 positions are currently available for medical device reviewer at PMDA. However, PMDA has been trying to hire 30% more medical device reviewers by the end of 2009.

3) Overview of FDA Medical Device Regulations

In the U.S., medical devices are classified into three categories, Class I, II, and III. Regulatory control increases from Class I to Class III, as risk of the device increases in general. The device classification defines the regulatory requirements for a typical device in a class. Most Class I devices are exempt from Premarket Notification-510(k); most Class II devices require Premarket Notification-510(k); and most Class III devices require Premarket Approval (PMA).

All clinical trials with significant risk devices under a 510(k) or a PMA pathway have to be approved by both Institutional Review Board (IRB) and FDA. To get approval of the trial by the agency, applicants have to submit an Investigational Device Exemption (IDE) application. Until the IDE is approved, applicants should not start enrolling patients. Since the study design of a clinical trial is crucial, FDA offers Pre-IDE submissions to discuss study protocol from

the early phase of its development. With using this fee-free consultation system, sponsors are able to discuss the investigational plan with FDA reviewers with ease. Once FDA and sponsors reached an agreement during the pre-IDE meeting processes, the terms of the agreement are put in writing and made part of the administrative record by FDA. The accessibility for a pre-IDE meeting is very high. Also, the content of the consultation is quite consistent across the entire review process.

(1) **Premarket Notification (510(k))**

For some Class I devices and most Class II devices, a 510(k) submission must be submitted to the FDA at least 90 days prior to marketing the device in the U.S. There is no formal 510(k) form; however, information regarding the content is given in 21 CFR Part 807.87. The 510(k) is a submission for clearance to market medical devices that can be considered “substantially equivalent” to a predicate device(s) already approved in the U.S. “Substantially equivalent” means that its intended use and technological characteristics are the same as the predicate devices, or the differences are not considered to cause any new issues in effectiveness or safety compared to the existing devices if the technological characteristics are different. Approximately 5 to 10% of 510(k) medical devices need clinical trials for market approval. Over 90% of all devices sold in the U.S. were approved through 510(k).

A 510(k) is required not only when a device is first marketed, but also if the device is newly marketed with a different indication for use from that given in the original 510(k), or if a change in specifications or performance could significantly affect its safety or effectiveness. Whether or not there is a change in safety or effectiveness is technically determined by the applicant, although FDA informally reviews the judgment call. In Class II devices, there are some medical devices which do not require a 510(k), e.g. pediatric hospital beds. In brief, those are Class II devices for which there are relatively few safety concerns; however, with issues that are subject to Special Controls or Guidance Documents.

The New 510(k) Paradigm is a program created in accordance with the 1997 FDA

Modernization Act (FDAMA) in order to streamline the 510(k) review process. It was implemented by CDRH on March 20, 1998 as a Guidance Document. The new paradigm adds two new options to the existing 510(k): the Special 510(k) and the Abbreviated 510(k). The Special 510(k) is a simplified 510(k) which can be used in cases where a manufacturer makes a modification to their own devices, where the indications and fundamental scientific technologies of devices approved in the past according to 510(k) have not changed, but only the device specifications have been modified. This change in the 510(k) process made a problem from the Safe Medical Devices Act of 1990 (SMDA) (Pub. L. 101-629) amended section 520(f) of the Act, which provides FDA with the authority to issue regulations requiring pre-production design controls (For details of Design Controls, please refer to 21CFR 820.30 or the CDRH web site). Under the scope of SMDA, companies had to submit separate responses for quality assurance of their device in order to follow the Design Controls requirements. Apparently, it was considered inefficient to also require an application to the FDA for quality assurance approval as per the traditional 510(k) submission. However, the Special 510(k) was designed for companies that have met the Design Controls requirements to simplify content of the 510(k) application.

When predicate devices were marketed under FDA Special Controls or Guidance Documents, the Abbreviated 510(k) submission was available as premarket review of medical devices should be simpler. Figure 1 shows a flow-chart of the new 510(k) paradigm.

The 510(k) review process is considered to be somewhat flexible. The similar regulatory pathway for medical device approval has been being considered by both the Japanese government and the medical device manufacturers.

(2) **PMA (Premarket Approval)**

The PMA is the approval process for high-risk medical devices, categorized into Class III, and more stringent than 510(k). The decision for a typical PMA application is basically made within 180 days. An original PMA may require a panel meeting that is equivalent for the Senmon-Kyogi at the PMDA.

Source: Modified from the original chart on the FDA's website.

Figure 1. Flowchart of the New 510(k) Paradigm

① Traditional PMA

In the traditional PMA pathway, the complete PMA application is submitted to FDA at once. The volumes include device description and intended use, nonclinical and clinical studies, case report forms, manufacturing methods, labeling, etc.

② Modular PMA

In a Modular PMA, complete contents of a PMA are broken down into well-delineated components (or module) and each component is submitted to FDA separately when the applicant has completed the module, compiling a complete PMA over time. The PMA is reviewed as a compilation of sections or “modules,” such as preclinical, clinical, or manufacturing module that together become a complete application.

③ Product Development Protocol (21 CFR § 814.19)

In the Product Development Protocol (PDP) process for market approval, non-clinical and clinical evaluations of a device are merged into one review process. Ideal candidates for the PDP process are those devices in which the technology is well established in industry. The PDP process provides the manufacturer with the advantage of predictability once the agreement has been reached with FDA. However, the acceptance criteria for the clinical trial are pre-specified. Therefore, sponsors must take a risk of failing the criteria and disapproval.

④ Humanitarian Device Exemption (21 CFR § 814 Subpart H)

As Japan has as for “Orphan Devices”, there is a similar review/approval process called HDE (Humanitarian Device Exemption) within the FDA. In the U.S., those devices are called Humanitarian Use Device (HUD). An HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. To obtain approval for an HUD, first an HUD application should be approved by the FDA Office of Orphan Products Development. Then, an HDE application is to be submitted to FDA. An HDE is similar in both form and content to a

premarket approval (PMA) application, but is exempt from the effectiveness requirements unlike PMA. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, a sponsor must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market. An approved HDE authorizes marketing of the HUD, but an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

In CDRH, reviews for a PMA application are performed by a team. In a team, a medical officer(s) is in charge of clinical part, engineers are in charge of the part in which each has back ground or relevant part.

The content of a PMA application is well addressed on the FDA website.

Labeling is also subject to review in a PMA application. Labeling review is important because the information on the labeling is what practitioners and patients will care after marketing. Labeling is broadly interpreted and sometimes includes content of advertisements and brochures.

⑤ Postapproval Requirements

a. General Requirements (21 CFR § 814.82, § 814.80)

FDA may impose postapproval requirements in a PMA approval order, as a condition of PMA approval at the time of approval of the PMA or by regulation subsequent to approval. Postapproval requirements may include as a condition of approval of the device:

(i) restriction of the sale, distribution or use of the device, (ii) continuing evaluation and

periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such a requirement and the number of patients to be evaluated and the reports required to be submitted, (iii) prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards or precautions important for the device's safe and effective use, (iv) in the case of an implant device, on cards given to patients, (v) device tracking requirements under § 821, Medical Device Tracking, (vi) at specified intervals, submission of periodic reports containing the information required by § 814.84 (1) Identification of changes described in § 814.39 and changes required to be reported to FDA under § 814.39, (2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant, (3) Adverse Reaction and Device Defect)

b. Postmarket Surveillance Studies

FDA may order postmarket surveillance studies to be conducted as a condition of PMA approval. The FDA can order postmarket surveillance for any Class II or Class III device: (i) the failure of which would be reasonably likely to have serious adverse health consequences; or (ii) which is intended to be implanted in the human body for more than one year; or (iii) which is intended to be a life sustaining or life supporting device used outside a device user facility.

Sponsors must submit a plan for approval within 30 days of receiving an order to conduct a postmarket study from FDA

⑥ Adverse Reaction and Device Defect Reporting [814.82(a)(9)]

The sponsor is required Adverse Reaction and Device Reporting stated in 21 CFR 814.82(a)(9).

⑦ Medical Device Reporting (MDR)

The Medical Device Reporting (MDR) Regulation (21 CFR 803) requires that all manufacturers report to FDA whenever a device: (i) may have caused or contributed to a death or serious injury or (ii) has malfunctioned and would be likely to cause or

contribute to a death or serious injury if the malfunction were to recur. The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for the PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Adverse Reaction Report" or "Device Defect Report" condition of approval for the PMA, the applicant must submit the report on the MedWatch form as required by the MDR Regulation with the PMA reference number. Reports made under the MDR Regulation must be identified as MDR reported events if included in the periodic (annual) report to the PMA to prevent duplicative entry into FDA information systems.

⑧ Premarket Approval Application (PMA) Supplement.

Before making any change affecting the safety or effectiveness of the device, a PMA supplement for review and approval by FDA must be submitted unless the change is of a type for which is permitted under § 814.39(d) or an alternate submission is permitted in accordance with § 814.39(e). A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification. In addition, a PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

(3) FDA Panel Meeting and PMDA Senmon Kyogi Meeting

As described above, FDA may call for a Panel Meeting for an original PMA submission if FDA thinks adequate. FDA's panel meetings are noticed to public and open to public. As potentially any body can attend the meeting, a panel meeting excuses ordinary people for a while in the meeting when it handles intellectual properties of the sponsor. Apparently, the panel member list is available on the FDA website. The FDA panel meeting system is

very much transparent. A panel meeting conclusion facilitates FDA's final decision for the medical device. However, FDA makes a decision opposed to the panel's decision from time to time when FDA has a rationale.

On the other hand, the PMDA's Senmon Kyogi is somewhat exclusive. Although the policy of conflict of interest among the Senmon Kyogi members was released (PMDA, 2007), its meetings and meeting members are not officially disclosed at this point.

2. Medical Device Review, and Immunity from Lawsuits

1) Reviewers for new drugs/medical devices and immunity from lawsuits

In the U.S., reviewers' regulatory judgments at the FDA are essentially immune from lawsuits as long as the decisions were made in accordance with adequate laws/regulations¹. On the other hand, in Japan which is the second biggest drug/medical device market, regulatory judgments of drug/medical device reviewers at the PMDA have never been immune to detective lawsuit. It could be that a judgment of Japanese government officials can be a subject to be dealt at a court in Japan. No PMDA reviewers have been held legally liable on the basis of his/her regulatory judgment so far. However, there is a case that an MHLW official was sued due to his administrative negligence (omission to act). Dr. Akihito Matsumura, who was serving as Director of the Biologics Division of the old Health and Welfare Ministry, received a one-year suspended sentence at the Supreme Court of Japan after being accused and found guilty of administrative negligence in March, 2008.

Drug/medical device approval process in Japan requires more data and takes a longer time period than that in the United States or Europe due to the increased regulatory requirements. Drug and medical device lag, the delayed availability of new drugs/medical devices in the Japanese clinical community, is considered to be a problem in Japan (Narukawa, 2005; Rajan,; Aritake, 2008). The lag is caused by multiple factors including the PMDA's prolonged review time. Without immunity from a lawsuit, it may be that the PMDA reviewers

cannot help being more conservative, asking for considerable more data, than reviewers at the U.S. FDA or EU notified bodies. This may result in long and meticulous review process.

Transparency of the review process of a new drug/medical device is important. The review process ultimately requires a judgment that the reviewer make a decision based on his/her evaluation of the available data. If reviewers at regulatory bodies are at risk of being accused of and held legally liable for an inadequate regulatory judgment, the judgment will necessarily be more conservative and may delay or even prevent the approval of new drugs and medical devices. As long as the regulatory judgment is made based on the best available scientific, technical, and clinical knowledge, regulatory agency reviewers should be protected from legal liability for exercising their reasonable judgment in Japan.

Disclaimer

The content of this article are based on the views and judgments of the author, and does not represent those of neither the Boston Scientific Corporation nor U.S. Food and Drug Administration.

References

- Aritake T (2008) "Japan Stimulus Program Focuses On Device Approval Lag, R&D Cooperation with Asia," < <http://www.medicaldevicestoday.com/2008/07/japan-stimulus.html> > Accessed December 24, 2008.
- FDA (1981) "Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident," *FDA Consumer Magazine*. June 1981 Issue. < <http://www.fda.gov/oc/history/elixir.html> > Accessed December 24, 2008.
- Narukawa M (2005) "Early Approval and Launch of New Drugs: Dissolution of Drug Lag," presented at The 6th Kitasato University-Harvard School of Public Health Symposium. October 26, 2005. < http://www.pharm.kitasato-u.ac.jp/biostat/presentation2005/26/Session6/05Mr_Narukawa_draft.pdf > Accessed December 24, 2008.
- PMDA "Policy of Conflict of Interest among the Senmon Kyogi Members," < <http://www.pmda.go.jp/guide/hyougikai/19/h190622gijishidai/file/h190622siryoo6.pdf> > Accessed December 24, 2008. (in Japanese)
- Rajan S "Drug Lags in Japan- Are the Steps Focused?,"

¹⁾ 28 CFR Part IV C, Sec. 1346., 28 CFR Part VI C, Sec. 2680 (a).

< http://pharmalicensing.com/public/articles/view/1194605405_47343b5d9ec4b > Accessed December 24, 2008.

Uchida T (2006) "From an Office of US FDA," *Medical Tribune*. 2006 (February).

Correspondence : Takahiro Uchida
tuchidahsph@gmail.com

米国 FDA における医療機器審査概要と実際

内田 毅彦¹⁾

米国で医療機器規制を司る Center for Devices and Radiological HealthはFood and Drug Administration (FDA) の8つのセンターの一つであるが、FDA 自体も日本の厚生労働省にあたる Department of Health and Human Services 傘下にある。

米国では医療機器はそのリスクに応じて3つのクラスに分類され、相応の規制がなされている。一部の Class I と殆どの Class II 医療機器は510(k)と呼ばれる様式で審査され、最もリスクの高い Class III 医療機器は PMA (Premarket Approval) と呼ばれる様式で審査がなされる。510(k)に相当する審査体系は現在日本に無く、その柔軟性のために、日本でも導入が検討されている。米国における治験には日本の治験届に該当する IDE (Investigational Device Exemption) の承認が必須であり、ICH-GCP 準拠をはじめとするシステムは共通点が多い、しかし、FDA の Pre-IDE というシステムは無料でアクセスがよく、実際の審査との一貫性も高いことから有用である。

米国と日本での相違のもう一つは審査の判断を手助けする外部の専門協議の在り方である。FDA でのパネル会議は日本の専門協議とは異なり原則的に一般に開放され透明性が高い。会議の結論は FDA 審査の参考となるが、FDA がパネルの判断を覆すこともある。

また、審査官の免責も FDA では明確にされており、不作為で訴訟のリスクを抱える日本の審査官とはこの点で大きく異なる。

キーワード：FDA, 医療機器規制, 医療機器審査, 専門協議, 審査官の免責

¹⁾ ボストン・サイエンティフィック／元食品医薬品局審査官