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CLINICAL REVIEW

Multiregional medical device development: regulatory perspective

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Abstract There are difficulties in conducting worldwide medical device development simultaneously because each country and/or region has their own medical device regulations. However, to aid globalization of the medical device market, and to quickly provide innovative medical devices to patients, attempts have been made to encourage harmonization and convergence of medical device regulations. 'Harmonization by doing' is a bilateral effort from the United States and Japan to develop global clinical trials and address regulatory barriers that may be impediments to timely device approval. The Global Harmonization Task Force (GHTF) was conceived in 1992 in an effort to achieve greater uniformity between national medical device regulatory systems. Since 2012, the GHTF has been replaced by the International Medical Device Regulators Forum.

Keywords Medical device · Global development · HBD · GHTF · IMDRF

Introduction

It might seem strange for clinicians that medical devices which are popularly used outside their countries are not available in their own country. It should be recognized that each country and/or region has their own regulation of medical devices. Basically, medical devices which are not registered or listed cannot be used.

The principal objective of medical device regulation is to protect the patients and medical care of the country. A medical device should provide effectiveness, safety and quality depending on the purpose of use. This means that the regulation of medical devices is not always convenient for manufacturers and users.

It might be assumed that the variety of medical device regulations is caused by differences in the thinking and range of responsibility of the user, manufacturer and country. However, approaches have been made to discuss the global convergence of medical device regulations despite these different situations.

Multiregional clinical trials

It is well-known that there are several steps in medical device development. For clinicians and patients, a clinical trial is the first exposure to devices in the development stage. Although not all medical devices require pre-market clinical trials to obtain market approval, clinical trials are the most important step to evaluate the safety and effectiveness, especially for novel devices. The safety, performance and effectiveness of medical devices are often evaluated by well-controlled clinical trials before marketing authorization. To obtain approval in various countries and regions at similar times, it is necessary to perform global clinical trials. A simultaneous global development approach is not limited to medical devices. Several articles have discussed the importance of multiregional clinical trials in the simultaneous worldwide clinical drug development [1–5]. However, global clinical trials are not easy

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to set up because many things have to be taken into account. Global development is more difficult than development in a single country for drugs as well as medical devices. Drugs have a long history of worldwide development and many things have to be considered in global development. For example, the International Conference on Harmonization (ICH) E5 guideline entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data," issued in 1998 [6], describes factors that could lead to different responses in different ethnic groups, including differences in pharmacokinetics, pharmacodynamics, and clinical properties. Furthermore, some organizations have established a center for multiregional clinical trials like Harvard MRCT center [7] and other organizations like APEC harmonization center provide training opportunities for multiregional clinical trials [8].

Because of the enormous variety of medical devices, development is usually based on an individual case-by-case basis rather than by following uniform guidance. Although many medical devices are not considered pharmacokinetic or pharmacodynamic, some developers have to consider evaluating product safety and effectiveness with non-negligible ethnic factors for certain types of devices.

Harmonization by doing

In order to overcome barriers against global medical device development, a unique program was started in 2003 called 'harmonization by doing' (HBD [9–11]. HBD is an international effort to develop global clinical trials and address regulatory barriers that may be impediments to timely device approval. The program has been operating using volunteers from industry, academia and government from both the USA and Japan.

The HBD had 4 working groups: (1) WG1— Global Cardiovascular Device Trials; (2) WG2—Post-market Registries (e.g., artificial heart); (3) WG3—Clinical Trials Infrastructure and Methodology; and (4) WG4—Regulatory Convergence and Communication (Fig. 1). The goal for each working group is the achievement of speedy and efficient medical device development in Japan and the USA (Table 1). Furthermore, the program has held multiple international meetings to deal with obstacles facing efficient medical device development and to share information and experiences with stakeholders [9, 12]. This process was a cooperative effort to move both Japan and the USA toward international regulatory harmonization. Participants in this process include the US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH), Japan's Pharmaceutical and Food Safety Bureau (PFSB) of the Ministry of Health, Labour, and Welfare (MHLW) and its review agency, the Pharmaceutical and Medical Devices Agency (PMDA), the Duke Clinical Research Institute (DCRI), the Japanese academic community, and the Japanese and US medical device industry.

Among these working groups, WG1 was commissioned by the HBD steering committee to promote the convergence of parallel clinical trials in Japan and the USA toward single clinical trial protocols that advance toward global device evaluation. Successful execution of single protocol clinical trials is intended to facilitate more rapid and cost-effective generation of more informative clinical data for pre-marketing, and potentially for post-marketing device evaluation in both the USA and Japan. Considering

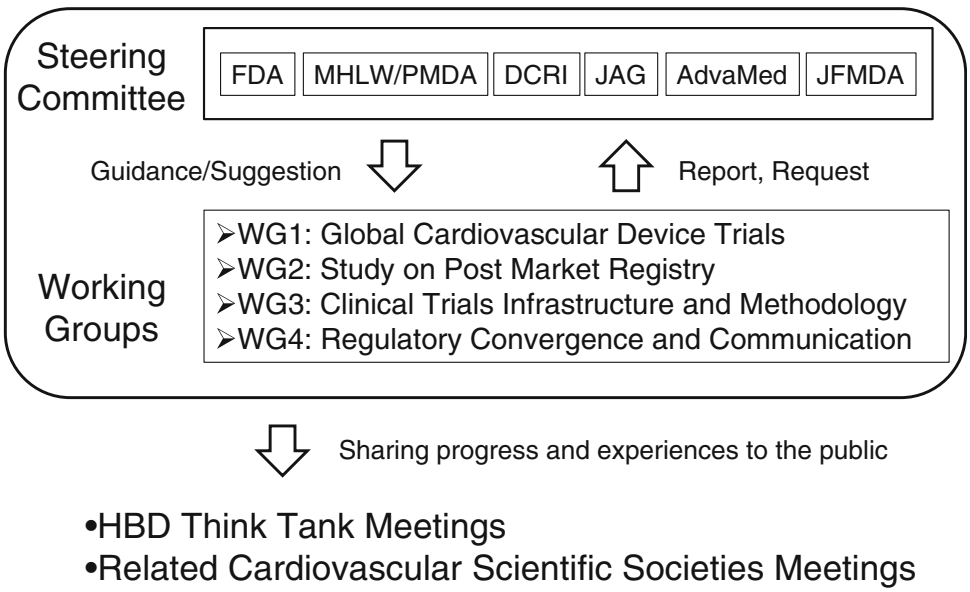

Fig. 1 Structure of harmonization by doing

the difficulty of worldwide medical device development, to understand each country's specific situation is an important first step in reducing the operational burden on clinical trials while maintaining the quality of the study.

As Uchida et al. reported, development of the drug eluting stent, which was a coronary stent placed into narrowed diseased coronary arteries in Japan, fell behind development in the USA when HBD started [13]. The HBD WG1 group discussed how to make the development speed of the two countries the same. The Japanese academia group decided to take a step-by-step approach. The first stage was to perform clinical trials in Japan following worldwide study protocols retrospectively to clarify and improve the problems that existed. The second stage involved Japanese sites joining a global drug eluting stent trial.

Good clinical practice

In order to conduct clinical trials, investigators have to follow a good clinical practice (GCP), which is an ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects [14, 15]. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical trial data are credible. However, since each country and region has their own GCP, discrepancies between GCPs makes the mutual use of results from a clinical trial difficult. Furthermore, it also appears to be a major barrier to conducting multiregional clinical trials.

In 2013, the HBD WG4 group compared the GCPs [16] that are most applicable to USA and Japanese marketing approval—US FDA regulation and guidance, Japanese GCP ordinances and notifications, ISO14155:2011 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice and ICH E6 (R1) Guideline for Good Clinical Practice [17]. While the ICH E6 guideline is specifically applicable to drug and biological products, it has been applied as a GCP reference standard for some device studies, and was therefore included in this analysis. They concluded that when a clinical investigation design is appropriate and acceptable to various regulatory authorities, non-substantive and administrative differences among GCPs can be addressed with supplemental information and should not be a barrier to transportability and acceptance of clinical investigation data from elsewhere. Historically GCPs have been revised repeatedly. In 2010, a previous study also performed a comparison of four well-known GCPs—The ICH Guideline for GCP E6 (R1), ISO14155:2003, Japanese regulations (JGCP) and US FDA regulations [18]. They reported no substantive differences with respect to the four fundamental criteria. Moreover, there were no contradictory requirements, i.e., no requirement that one GCP would necessarily cause noncompliance with one or more of the other GCPs studied.

Post-market phase data pooling

The medical device registry is one of the key issues for total product life cycle management [19]. The Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) is a post-market data-collection initiative for ventricular assist devices (VAD) in Japan [20]. This prospective, multisite, observational registry achieves a 100 % participation rate and is a collaborative effort that involves manufacturers of VADs, the Japanese government, and academia. The registry design of J-MACS is harmonized with that of INTERMACS [21], a North American registry established in 2005 for patients who have received mechanical circulatory support devices to treat advanced heart failure. J-MACS is therefore intended to design itself to future data pooling with INTERMACS as part of HBD WG2 activities [19].

Global harmonization activities

In the medical device field, simultaneous global development of medical devices has not been performed in the same positive way as pharmaceutical products. The reason for this is due to differences in thinking, history, and the framework regarding the regulation of pharmaceutical products and medical devices. Medical device regulations do not have a long history. For example, as foodstuffs, chemicals and pharmaceuticals were already regulated in the EU before 1985, a new legislative and technical frame was created in 1985 for other products circulating in EU countries [22]. This new approach concept is a legislative technical frame for harmonization in Europe. Elaboration of directives and technical standards leads to European conformity. In the United States, the US Federal Food, Drug and Cosmetic Act was enacted in 1938 and the Medical Device Amendments Act came into law in 1976 [23].

Global Harmonization Task Force [24]

The Global Harmonization Task Force (GHTF) was conceived in 1992 in an effort to achieve greater uniformity between national medical device regulatory systems. A partnership between regulatory authorities and regulated industry, the GHTF comprised five Founding Members—the European Union, United States, Canada, Australia and Japan. Since its inception, the GHTF now comprises of

Table 1 Goals of the HBD working groups [9]

	Specific aims	Deliverables	Possible regulatory target areas
WG1	Clearly define what constitutes a single prospective clinical plan Identify roadblocks to combined clinical plans, i.e., whether they constitute one single trial or parallel simultaneous studies Find solutions for the problems identified Identify proof-of-concept protocols and define how they are initiated and how they are earmarked Illustrate convergence goals through proof-of-concept projects and WG1 meetings Promote educational programs that supports the above	Definition of what constitutes a single clinical plan Summary of barriers that may be encountered when conducting a USA–Japan study, including regulatory, academic and industry perspectives Identify other unique risks for industry in conducting a USA–Japan endeavor Propose solutions (recommendations, suggestions, or points-to-consider) to the problems identified in (b) and (c) Reports (identification and summary of proof-of-concept studies) Follow-up on implementation of the proposed solutions Educational programs in support of these deliverables	USA–Japan clinical trials already conducted (for identification of differences or issues surrounding poolability of data) Devices for which prospective USA–Japan parallel or single-protocol clinical trials are planned Devices in the cardiovascular domain, but with potential to move outside of cardiovascular devices in future efforts
WG2	Identify key factors necessary to incorporate Japanese MCSD data into INTERMACS Identify how manufacturers can fulfill post-market requirements or reevaluation requirements in Japan and in the US through INTERMACS Identify mechanisms for the development of objective performance criteria or matched control datasets from registries	Provide adverse event definitions and data collection parameters to Japanese regulatory officials to determine if that information is acceptable Describe the similarities and differences in the regulatory practices involved in post-market re-examination or reevaluation of medical devices Identify problems that may arise in trying to incorporate Japanese MCSD data into INTERMACS	Type of information that is required in a post-marketing or re-examination report Others
WG3	Identify and share aspects of the clinical trial infrastructure in the US and Japan that will improve the timely introduction of safe and effective medical devices Identify or develop a forum to facilitate the public sharing of best practice solutions to these challenges for all stake holders Identify high-priority challenges for the clinical trial infrastructure that might be amenable to modification through proof-of-concept HBD projects Identify and share new best practice solutions to these challenges through proof-of-concept HBD projects	A summary document with an itemized, prioritized list of the aspects of the clinical trial infrastructure in the US and Japan that will improve the timely introduction of safety and effective medical devices into the USA and Japan (2007–2008) Identification and/or development of a public web-based forum to share best practices that address these challenges within the clinical trial infrastructure (2008–2009) Identify a limited number (2–3) of high priority, high potential impact challenges to the clinical trial infrastructure (2007–2008) Develop best practice solutions to these challenges and identify or develop potential proof-of-concept projects to test these solutions (2008–2009)	Site identification Site contracting Budgeting and clinical site finances Investigator training CRC identification and training Institutional review board processes Japanese academic involvement in study design Public perception of clinical trial participation Clinical trial metrics Roles and responsibilities Monitoring, auditing activities Data quality assurance Public forum for sharing of best practices and educational opportunities Public relations advertising to public of clinical trial studies Access to medical records (source documents) in clinical study

Table 1 continued

	Specific aims	Deliverables	Possible regulatory target areas
WG4	Share information on important similarities and differences in laws, regulations and regulatory practices related to medical devices in the US and Japan Find regulatory-related obstacles, experienced or envisaged, in conducting clinical trials, filing and reviewing applications for clinical trials and marketing approval of medical devices in the US and Japan, especially those resulting from the difference between the two countries' regulations, interpretations, and practices Formulate recommendations, suggestions, or points-to-consider intended for US FDA (Food and Drug Administration) and/or Japan MHLW/PMDA (Ministry of Health, Labour, and Welfare/Pharmaceutical and Medical Devices Agency) as well as those regulated (e.g., investigators conducting clinical trials, medical device manufacturers submitting applications ("sponsors"), to resolve the difficulties found	Summary of key similarities and differences between FDA and MHLW laws, regulations, and regulatory practices as related to medical devices Delineation of the problems related to current regulatory practice Prioritize identified problems that may significantly affect the progress of the HBD effort Identification, implementation and analysis of proof-of-concept projects Proposed solutions (recommendations, suggestions, or points-to-consider); and Follow-up on implementation of the proposed solutions	Regulations on clinical trials and medical device GCP (good clinical practices), including pre-authorization, medical device implementation issues, documentation requirements, comparison of standards, and agency recognition of medical device GCP standards and bioresearch inspection/audit practices Regulations on applications for marketing authorization/premarket approval/notification, including GHTF's STED (summary technical documentation) format and content differences between GHTF countries Consultation between the regulatory authority and the applicants, including timeliness, contents, adequacy, and cost Application review practices by FDA and MHLW/PMDA, including modes of review (modular approach and whole-dossier approach), ways to improve speed and quality of reviews; and Regulator/applicant and regulator/regulator communication

voluntary representatives from five founding members grouped into three geographical areas—Europe, Asia–Pacific and North America, each of which actively regulates medical devices using their own unique regulatory framework. The chairmanship is rotated among the founding members.

The purpose of the GHTF was to encourage convergence in regulatory practices related to ensuring the safety, effectiveness/performance and quality of medical devices, promoting technological innovation and facilitating international trade, and the primary way in which this was accomplished was via the publication and dissemination of harmonized guidance documents on basic regulatory practices. These documents, which were developed by five different GHTF Study Groups, can be adopted/implemented by member national regulatory authorities. The relationships between the works of each Study Group can be represented schematically.

The GHTF also serves as an information exchange forum through which countries with medical device regulatory systems under development can benefit from the experience of those with existing systems and/or pattern their practices upon those of GHTF founding members.

However, the GHTF terminated its activities at the end of 2012 by changing the situation surrounding medical devices; GHTF guidance documents (Table 2) can be seen on the website of the International Medical Device Regulators Forum (IMDRF), as described below.

International Medical Device Regulators Forum [25]

Representatives from the five founding members of the GHTF proposed participation from Brazil, Russia, China and India as management committee members of a new forum to discuss true globalization because of their population and economic influence. At the same time, the World Health Organization was also invited to be an observer. In 2012, a new forum was created (IMDRF) with Australia, Brazil, Canada, the European Union, Japan and the United States (in 2013, China officially joined the management committee member) [26]. The IMDRF is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundation work of the GHTF on medical devices and their aim is to accelerate international medical device regulatory harmonization and convergence.

Conclusion

Krucoff et al. [27] reported that professional societies were uniquely positioned to help facilitate such transformation

Table 2 GHTF major guidance documents [24]

	Main target	Document title (document number)
Study group 1	Premarket evaluation	Summary technical documentation for demonstrating conformity to the essential principles of safety and performance of medical devices (STED) (GHTF/SG1/N11:2008)
		Role of standards in the assessment of medical devices (GHTF/SG1/N44:2008)
		Principles of in vitro diagnostic (IVD) medical devices classification (GHTF/SG1/N45:2008)
		Principles of conformity assessment for in vitro diagnostic (IVD) medical devices (GHTF/SG1/N46:2008)
		Definitions of the terms manufacturer, authorised representative, distributor and importer (GHTF/SG1/N55:2009)
		Summary technical documentation (STED) for demonstrating conformity to the essential principles of safety and performance of in vitro diagnostic medical devices (GHTF/SG1/N63:2011)
		Registration of manufacturers and other parties and listing of medical devices (GHTF/SG1/N65:2011)
		Essential principles of safety and performance of medical devices (GHTF/SG1/N68:2012)
		Label and instructions for use for medical devices (GHTF/SG1/N70:2011)
		Definition of the terms 'medical device' and 'in vitro diagnostic (IVD) medical device' (GHTF/SG1/N71:2012)
		Principles of medical devices classification (GHTF/SG1/N77:2012)
		Principles of conformity assessment for medical devices (GHTF/SG1/N78:2012)
Study group 2	Post-market surveillance/ vigilance	Comparison of the device adverse reporting systems in USA, Europe, Canada, Australia and Japan (GHTF/SG2/N6R3:2002)
		Vigilance reporting guidance (GHTF/SG2/N08R4:1999)
		Global medical devices competent authority report (GHTF/SG2/N9R11:2003)
		Charge and mission statement (GHTF/SG2/N16R5:1999)
		Medical devices: post-market surveillance: national competent authority report exchange criteria (GHTF/SG2/N20R10:2002)
		Adverse event reporting guidance for the medical device manufacturer or its authorized representative (GHTF/SG2/N21R8:1999)
		Reporting errors medical devices by manufacturer (GHTF/SG2/N31R8:2003)
		Universal data set for manufacturer adverse event reports (GHTF/SG2/N32R5:2002)
		Medical device post-market vigilance and surveillance—timing of adverse event reports (GHTF/SG2/N33R11:2002)
		Manufacturer's trend reporting of adverse events (GHTF/SG2/N36R7:2003)
		National competent authority report exchange program (GHTF/SG2/N38R19:2009)
		Review of requirements on post-market surveillance (GHTF/SG2/N47R4:2005)
		Medical devices post-market surveillance: global guidance for adverse event reporting for medical devices (GHTF/SG2/N54R8:2006)
		Content of field safety notices (GHTF/SG2/N57R8:2006)
		PMS harmonization chart (GHTF/SG2/N61R4:2004)
		Where to send adverse event reports (GHTF/SG2/N68R3:2005)
		Medical devices post-market surveillance (GHTF/SG2/N79R11:2009)
		XML schema for electronic transfer of adverse event data (SG2 N87:2012)

Table 2 continued

	Main target	Document title (document number)
Study group 3	Quality systems	Risk management principles and activities within a QMS (GHTF.SG3.N15:2005)
		Guidance on quality management system (GHTF.SG3.N17:2008)
		Quality management system-medical devices-guidance on corrective action and preventive action and related QMS processes (GHTF.SG3.N18:2010)
		Quality management system—medical devices—nonconformity grading system for regulatory purposes and information exchange (GHTF/SG3/N19:2012)
		Guidance On quality systems for the design and manufacture of medical devices (GHTF.SG3.N99-8:1999)
		Design control guidance for medical device manufacturers (GHTF.SG3.N99-9:1999)
		QMS-process validation guidance (GHTF.SG3.N99-10:2004)
Study group 4	Auditing	Audit language requirements (GHTF/SG4/(99)14:1999)
		Guidelines for regulatory auditing of quality management systems of medical device manufacturers—part 1: general requirements (GHTF/SG4/N28R4:2008)
		Guidelines for regulatory auditing of quality management systems of medical device manufacturers—part 2: regulatory auditing strategy (GHTF/SG4/N30R20:2006)
		Guidelines for regulatory auditing of quality management systems of medical device manufacturers—part 3: regulatory audit reports (GHTF/SG4/N33R16:2007)
		Guidelines for regulatory auditing of quality management systems of medical device manufacturers—part 4: multiple site auditing (GHTF/SG4/N83R5:2010)
		Guidelines for regulatory auditing of quality management systems of medical device manufacturers part 5: audits of manufacturer control of suppliers (GHTF/SG4/N84R12:2010)
Study group 5	Clinical evaluation	Clinical evidence—key definitions and concepts (GHTF/SG5/N1R8:2006)
		Clinical evaluation (GHTF/SG5N2R8:2007)
		Clinical investigation (GHTF/SG5/N3:2010)
		Post-market clinical follow-up studies (GHTF/SG5/N4:2010)
		Reportable events during pre-market clinical investigations (GHTF/SG5/N5R13:2012)
		Clinical evidence for IVD medical devices—key definitions and concepts (GHTF/SG5/N6R4:2012)
		Clinical evidence for IVD medical devices—scientific validity determination and performance evaluation (SG5/N7R5:2012)
		Clinical evidence for IVD medical devices—clinical performance studies for in vitro diagnostic medical devices (SG5/N8R4:2012)

and revitalize the medical device innovation ecosystem based on their valuable experience on cardiovascular device innovation. Collaboration within one professional society is the first step. As the next stage, inter-society communication is important to create a dynamic, open-ended, transparent collaborative forum among stakeholders, whose objective is to develop consensus definitions and nomenclature and related processes, optimize applications in pivotal clinical trials of specific classes of new medical devices, and to disseminate such definitions and recommended processes into the public domain. The Academic Research Consortium (ARC) which was founded in 2006 invited the FDA to be an advisory participant [28]. Collaborative relationships between societies and countries are valuable. The HBD itself performs small activities only in the cardiovascular field by volunteers from industry, academia and governments of both the USA and Japan. However, they made remarkable progress in the cardiovascular field by having good communication with their stakeholders. It is also important for clinicians in the gastroenterology field to establish and maintain good communications with regulators, industry and other related participants. International medical device regulatory convergence has continued despite replacing the GHTF by the IMDRF. The simultaneous global development of medical devices is helped if the participants act in a positive way.

Disclosure

Conflict of Interest: Atsushi Tamura and Hiromu Kutsumi declare that they have no conflict of interest.

This review article does not have relevant issues of human/animal rights and informed consent disclosure to be reported.

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