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REVIEW

US Food and Drug Administration international collaborations for cellular therapy product regulation

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Abstract

Cellular therapy products are an emerging medical product class undergoing rapid scientific and clinical innovation worldwide. These products pose unique regulatory challenges both for countries with existing regulatory frameworks and for countries where regulatory frameworks for cellular therapy products are under development. The United States Food and Drug Administration (US FDA) has a history of productive working relationships with international regulatory authorities, and seeks to extend this to the cellular therapy field. The US FDA and its global regulatory counterparts are engaged in collaborations focused on the convergence of scientific and regulatory approaches, and the education of scientists, clinicians, regulators, and the public at large on the development of cellular therapies.

Introduction

The field of cellular therapies is undergoing rapid scientific and clinical innovation, and product development and clinical investigations are frequently conducted internationally. Regulatory authorities must confront the scientific and medical complexities of these products in order to protect the public health and promote effective product development. Regulatory frameworks for cellular therapies are in different states of maturity internationally; some are only now being established, and others are in a more mature state. The development of cellular therapies would benefit from a maturation and evolution of regulatory frameworks. This may be aided, in part, by information exchange between international regulatory authorities. Information and experiences shared by regulatory authorities with established regulatory frameworks for cellular therapy products can be considered and potentially incorporated by countries that have yet to fully design and implement their regulations and policies for cellular therapies. US FDA welcomes interactions with international regulatory authorities to work towards prospective regulatory harmonization and convergence.

The term 'harmonization' is typically interpreted as the production of consensus guidelines, such as the guidelines produced by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 'Harmonization' can also refer to a convergence of regulatory perspectives that informs the independent development of national guidelines and regulations. For the purposes of this document, we will use 'regulatory convergence' to describe interactions that generate a shared regulatory perspective but do not have the explicit goal of production of a consensus guideline.

The purpose of this article is to provide an overview of US FDA's participation in regulatory convergence activities with international regulatory authorities on regulation of cellular therapies, including stem cells. In the US, cellular therapy products are regulated by the US FDA, Center for Biologics Evaluation and Research (CBER, Office of Cellular, Tissue, and Gene Therapies (OCTGT); the FDA Office of International Programs coordinates activities between the US FDA and international regulatory authorities). For information on the regulatory process for cell therapy products and biologics, please see the US FDA website [1-3].

US FDA's global strategy for regulatory harmonization and convergence

US FDA has a history of productive working relationships with regulatory authorities around the globe, as well as international organizations such as the World Health Organization (WHO). Activities have included informational exchanges, support for establishment of

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international standards, and harmonization of regulatory requirements.

Regulatory convergence and leveraging of regulatory effort have emerged as shared goals of the global regulatory community [4]. Like other regulatory authorities, US FDA's global efforts aim to pool regulators' resources for public health protection and facilitate the marketing of safe and effective treatments to consumers and patients. Regulatory convergence can contribute to these goals by supporting best regulatory practices, assuring that the global regulatory community is well-informed of current scientific and regulatory issues, and establishing regulatory pathways for industry that are predictable and that share a foundation of common, internationally recognized requirements. And while such collaborative activities can benefit global public health in general, they also hold direct benefit for US FDA and the US public health by helping to ensure that medical products imported into the US are subject to more effective regulatory oversight to assure their quality, safety, and effectiveness.

Regulatory convergence for cellular therapy products

Cellular therapy is an emerging product class that poses unique regulatory challenges. Only a few cell-based medical products have been authorized for marketing in one or more countries; therefore, most regulatory bodies have minimal experience with cellular products in the marketplace. The lack of regulatory oversight in some nations is a widely recognized risk to public health. To address the limited experience and the recognized risks, it is important for regulatory authorities to share information and experiences and to develop common regulatory approaches for these products.

At the Regulators Forum (RF) held in November 2010 (Fukuoka, Japan) in association with the ICH, US FDA proposed that the RF consider undertaking a preliminary assessment of potential topics of regulatory importance for cellular therapy products. The intent of these efforts is to provide a forum for discussions among international regulatory authorities on the convergence of regulatory perspectives.

The goal of US FDA's global efforts in the cell therapy product area is to support the independent development of national/regional guidelines and regulations that reflect a shared regulatory experience. Information exchanges regarding regulations, policy, and experience between US FDA and our international counterparts are essential for achieving these goals. US FDA participates in various activities that support this effort. For example, regulatory staff from US FDA and representatives from other international regulatory authorities have participated in an exchange program whereby staff members visit their counterpart organization to observe regulatory practices. Other activities include the Regulators Forum Cellular Therapy Group mentioned above; standing interactions with the European Medicines Agency (EMA) Committee for Advanced Therapies (CAT) and Health Canada; and *ad hoc* interactions with EMA, Japan Ministry of Health, Labour and Welfare (MHLW) and Pharmaceutical and Medical Device Agency (PMDA), Health Canada, Singapore Health Sciences Authority, and others. US FDA actively engages with international organizations, including the Pan-American Health Organization (PAHO), WHO, ICH, and Asia-Pacific Economic Cooperation (APEC). It is important to note that the information exchanged during US FDA's engagements with international regulatory counterparts may be limited by whether or not Confidentiality Commitments and Memorandums of Understanding are in effect. These arrangements allow for the discussion of non-public regulatory information, and protect against the disclosure of such information. In the absence of such arrangements with regulatory counterparts, US FDA's activities are limited to information that is in the public domain.

Below is a description of some of US FDA's regulatory convergence activities in the cellular therapy area.

US FDA-EMA-Health Canada Advanced Therapy Medicinal Products Cluster

In 2008, US FDA and EMA established the Advanced Therapy Medicinal Products (ATMP) Cluster. ATMPs are medicines for human use that are based on gene therapy, somatic cell therapy, or tissue engineering [5]. The purpose of the ATMP cluster is to provide a forum for US FDA and EMA to share thinking on regulatory approaches, both in general and on specific issues, to share information on draft documents, and to discuss participation in workshops, advisory committees, and working parties. The ATMP cluster teleconferences take place five to six times per year. Health Canada joined the ATMP cluster in June 2012.

EMA-US FDA Parallel Scientific Advice

In 2004, EMA and US FDA began a program known as Parallel Scientific Advice (PSA), in which US FDA and the EMA Scientific Advice Working Party (SAWP) exchange views on scientific issues during the development phase of a medical product. For the US FDA, this program most closely aligns with pre-investigational new drug application or end-of-phase 2 meetings. PSA meetings are voluntary and usually occur at the request of the sponsor. The goal of a PSA procedure is to increase dialogue between the agencies (US FDA and EMA) and the sponsor and to avoid duplication of efforts in the evaluation and conduct of a proposed clinical trial. During the PSA procedure, each agency provides

independent advice to the sponsor on the questions presented. The expectation is that the PSA procedure will result in a sponsor having a greater understanding of the respective requirements of the US FDA and EMA. It is important to note, however, that the US FDA and EMA may provide different advice or have different regulatory requirements.

Cellular Therapy Convergence Efforts by the Regulators Forum (ICH)

The Regulators Forum is composed of: ICH members (US FDA, EMA, and Japan PMDA/MHLW); ICH observers (Canada, European Free Trade Association (EFTA), WHO); regional harmonization initiatives (APEC, Association of the Southeast Asian Nations (ASEAN), Southern African Development Community (SADC), Gulf Cooperation Council (GCC), Pan-American Network for Drug Regulatory Harmonization (PANDRH)); individual drug regulatory authorities from Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia, and Singapore.

The purpose of the RF is to provide an environment in which regulatory and scientific expertise can be shared among regulatory authorities in order to enhance the availability of safe and effective products in the global market. Meetings of the RF are held in association with ICH biannual meetings.

Regulators Forum Cell Therapy Group

In March 2011, members of the RF formed a brainstorming group with the goal of identifying potential areas for convergence in the regulation of cellular therapy products. This Cell Therapy Group agreed that an understanding of the similarities and differences in the global regulations and policies applicable to cellular therapy products would be essential to identify common ground for future regulatory convergence activities. Therefore, this Cell Therapy Group initially focused on understanding the regulatory landscapes in different regions. This included identifying existing regulations and guidelines/guidance documents, and identifying the types of cell-based products that are under clinical investigation and those that have received marketing authorization. Taking the responses of this initial landscaping exercise into consideration, the group decided to next focus on terminology for cellular therapy products, in order to facilitate mutual understanding during our discussions. This terminology project is ongoing. The RF is considering potential mechanisms to publicly disseminate the information we have gathered and exchanged.

Asia-Pacific Economic Cooperation (APEC)

APEC was established in 1989 to promote and facilitate trade among the Asian Pacific countries and beyond. APEC members include Australia, Brunei, Darussalam, Canada, Chile, China, Chinese Taipei, Indonesia, Japan, Republic of Korea, Malaysia, Mexico, New Zealand, Papua New Guinea, Peru, Philippines, Russia, Singapore, Thailand, United States, and Vietnam. In 2002, APEC established the Life Sciences Innovation Forum (LSIF), a tripartite forum of government, industry, and academia whose purpose is to create a policy environment for life sciences innovation. LSIF operates under the guiding principles of transparency and meaningful dialogue with stakeholders and due process for successful implementation of policies. Efforts by APEC LSIF are supported by the APEC LSIF Regulatory Harmonization Steering Committee (RHSC). The primary objectives of RHSC are to identify international standards and guidelines to propose to APEC economies and to facilitate implementation of standards and guidelines through education and workshop support.

APEC Cell and Tissue Roadmap

APEC LSIF RHSC recently accepted a new Priority Work Area to 'promote regulatory convergence for the regulation of cell and tissue-based therapies'. The short-term goals of this Priority Work Area are to establish a harmonized understanding of cell and tissue-based therapies and to establish training programs. The long-term goal is to stimulate prospective convergence of technical requirements. The next step will be the development of a strategic roadmap by a team of interested regulators with Singapore Health Sciences Authority (HSA) as the project lead. The roadmap will outline the project scope, roles and responsibilities, and expected milestones and deliverables.

APEC Workshop on Stem Cell Product QA/QC

In July 2011, the APEC LSIF Workshop on Stem Cell Product QA/QC (Quality Assurance/Quality Control) took place in Bangkok, Thailand, hosted by the Thai Ministry of Health. Participants in this workshop included representatives from 13 countries or regions, including Australia, Canada, China (Hong Kong), Chinese Taipei the European Union, Indonesia, Japan, Pan American Health Organization (PAHO) representing the WHO, Saudi Arabia, Singapore, Republic of Korea, Switzerland, Thailand, and the United States. The US was represented by FDA/CBER/OCTGT. The goal of the workshop was to discuss QA/QC aspects for stem cell therapy products. The workshop also provided an ideal opportunity to gather information on the regulatory landscape for cellular therapy products.

Workshop sessions consisted of presentations on stem cell banking, perspectives on the promise of stem cell therapies in Thailand, presentations of international regulatory frameworks or proposed frameworks for

cellular therapy products by national authorities, a session on considerations for manufacturing QA/QC, pre-clinical studies, and pre-marketing clinical trials. The workshop concluded with a roundtable discussion on regulatory issues for cellular therapy products. The workshop is summarized below.

Presentations of international regulatory frameworks or proposed frameworks for cellular therapy products were provided by US FDA, EMA, Health Canada, Japan MHLW, Swissmedic, Thai FDA, Republic of Korea FDA (KFDA), Singapore HSA, Saudi Arabia FDA (SFDA), Chinese Taipei (Taiwan FDA), and Australia Therapeutic Goods Administration (TGA). It was noted that there are no specific legislative distinctions between stem cell products and other cellular therapy products. Common considerations for the determination of the regulatory pathway for cellular therapy products included the amount of manipulation and the clinical use.

Presentations on considerations for manufacturing QA/QC, pre-clinical studies, and pre-marketing clinical trials for cell-derived products were presented by US FDA, EMA, Japan PMDA, KFDA, Thai FDA, and HSA. The presentations highlighted unique safety concerns posed by cellular therapy products, including stem cells. Considerations for QA/QC focused on identity, purity (including testing for undifferentiated cell populations and for cells that are lineage-committed), tumorigenicity (especially for human embryonic stem cells and induced-pluripotent stem cells), and potency testing. A major challenge in assuring the safety of a stem cell product is the development of assays that can detect cells with undesired characteristics and identify characteristics that are predictive for safety and clinical effectiveness. The presenters recommended *in vitro* assays for karyotyping, proliferation capacity, and senescence assays. IPS cells may present risks associated with the method of re-programming, such as insertional mutagenesis from a viral vector, or genetic instability. EMA pointed to their 'Guideline on Human Cell-Based Medicinal Products' [6], 'Reflection Paper on Stem Cell-Based Medicinal Products' [7], and 'Draft Guideline on the Risk-Based Approach defined in Annex 1, Part IV of Directive 2011/83/EC applied to Advanced Therapy Medicinal Products (ATMP)' [8]. The key recommendations from the US FDA 'Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products' (January, 2011) [9] were also highlighted.

Pre-clinical testing for stem cell products is challenging in that non-clinical findings are difficult to extrapolate to the human population. The pre-clinical data needed to support a clinical trial and subsequent licensing depend on the nature of the stem cell product. For clinical trials with stem cells, a specific surveillance plan for the assessment of long-term safety was recommended. It was also suggested that post-authorization safety and efficacy follow-up should be required for high-risk stem cell products.

During the roundtable discussions, a preliminary effort was made to identify technical requirements for stem cell products for clinical use. The group acknowledged that the level of regulatory oversight depends on the type of stem cell product. Substantially manipulated cells are considered to be higher risk than minimally manipulated cells, and therefore more extensive QA/QC testing is expected for substantially manipulated cells. Some participants suggested that development of a minimum set of quality/manufacturing requirements for minimally manipulated stem cell therapy products is important, and could be used as a guide in regions where regulatory oversight is limited.

Major outcomes of this workshop included the identification of regulatory gaps for cell therapy products among international regulatory authorities, and recognition that QA/QC requirements for stem cells depend on the type of stem cell product. The group also concluded that in order to provide safe and effective stem cell products to patients, it is important to educate patients on the current limitations of stem cell therapy, as well as to educate physicians and scientists on the conduct of appropriate clinical trials for such products. The final report of the workshop will be presented to APEC, ICH, and the RF.

Conclusion

The US FDA is committed to active participation in international regulatory convergence efforts for cellular therapy products, as part of our mission to facilitate the development of safe and effective medical products in the US and worldwide. These efforts are currently in early stages, with an initial focus on development of a common understanding of the similarities and differences in regulations and policies for cellular therapy products in different countries/regions.

This article is part of a thematic series on *Clinical applications of stem cells* edited by Mahendra Rao. Other articles in the series can be found online at http://stemcellres.com/series/clinical

Abbreviations

APEC, Asia-Pacific Economic Cooperation; ATMP, Advanced Therapy Medicinal Product; CBER, Center for Biologics Evaluation and Research; EMA, European Medicines Agency; HSA, Singapore Health Sciences Authority; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; KFDA, South Korean Food and Drug Administration; LSIF, APEC Life Sciences Innovation Forum; MHLW, Japan Ministry of Health, Labour, and Welfare; OCTGT, Office of Cellular, Tissue, and Gene Therapies; PAHO, Pan-American Health Organization; PMDA, Japan Pharmaceutical and Medical Devices Agency; PSA, Parallel Scientific Advice; QA, quality assurance; QC, quality control; RF, Regulators Forum; RHSC, APEC LISF Regulatory Harmonization Steering Committee; US FDA, United States Food and Drug Administration; WHO, World Health Organization.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
JA, JB, and KB have contributed to the writing and final approval of this manuscript.

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References

1. FDA Vaccines, Blood & Biologics: Cellular & Gene Therapy Products [http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm]
2. FDA Vaccines, Blood & Biologics: OCTGT Learn [http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm]
3. FDA Vaccines, Blood & Biologics: CBER Foreign Regulatory Seminar [http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm272086.htm]
4. 14th International Conference of Drug Regulatory Authorities: Singapore, 30 November to 3 December 2010 [http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/14-ICDRA_recommendations.pdf]
5. EC Regulation No 1394/2007 [http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf]
6. Guideline on Human Cell-Based Medicinal Products [http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003894.pdf]
7. EMA Reflection Paper on Stem Cell-Based Medicinal Products [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf]
8. Draft Guideline on the Risk-Based Approach According to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/01/WC500120989.pdf]
9. FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products [http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf]

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