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Title:

Roadmap to Promote Prospective Regulatory Convergence for Advanced Therapy Products

Lead Economy: Singapore Health Sciences Authority

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Goal of Topic: The goal of the roadmap is to stimulate and promote prospective regulatory convergence for advanced therapy (cell, tissue and gene therapy) products. The roadmap's short- and long-terms goals are listed below:

Short-Term Goals:

- To establish a mutual and common understanding of advanced therapy products
- To identify opportunities, develop relevant materials, and establish a training programme such as conferences/workshops on advanced therapy products for collaborative actions and information exchange

Mid- to Long-Term Goal:

- To facilitate and implement strategies to stimulate and promote prospective regulatory convergence and application of scientific principles and best practices to ensure and enhance the safety, quality and efficacy of advanced therapy product development throughout the product life cycle

Background and Challenges

Advanced therapies hold the promise to treat medical conditions and diseases that currently have limited or no effective therapeutic options. According to Business Communications Company's market research, the global market for stem cell products was $3.8 billion in 2011[1]. This market is expected to reach nearly $4.3

[1] Paul Evers (2012), Global markets for stem cells (http://www.bccresearch.com/report/stem-cells-global-markets-bio035d.html).

billion in 2012 and $6.6 billion by 2016, increasing at a compound annual growth rate of 11.7% from 2011 to 2016. With the rapidly expanding role of advanced therapy products as an emerging group of health products that is setting a new paradigm in medical science and therapy for diseases and conditions where currently limited or no effective therapeutic options exist and extensive cross-boundary transportation of human cells and tissues across different regions and continents, different economies have begun to look into the development of an appropriate regulatory framework, which might not fit into the conventional drug regulatory paradigm. We stand at the dawn of a new therapeutic era, with great opportunity for prospective convergence, such as development of a common regulatory understanding on terminology, regulatory approaches and requirements at this initial stage before significant divergence happens.

For the purpose of this roadmap, advanced therapy products would mean viable autologous or allogeneic human cells or tissues, viable xenogeneic cells and tissues and gene therapy products. The roadmap scope will exclude non-viable human and xenogeneic cells and tissues, and other biotherapeutic products such as prophylactic vaccines, recombinant proteins, plasma derivatives and monoclonal antibodies.

The proposal for placement of advanced therapies as a priority work area within the scope of Life Science Innovation Forum (LSIF), in addition to the current Pharmaceuticals and Medical Devices, was put forward and endorsed at the Regulatory Harmonization Steering Committee (RHSC) meeting in September 2011. The initial work focus that was accepted within the advanced therapy category was cell, tissue and gene therapy products. It was also endorsed that Health Sciences Authority (HSA), Singapore would lead the initiative and work with other interested regulators to develop the roadmap that outlines the strategic approach to this priority work area. The concept note outlining the regulatory convergence approaches was presented at the RHSC meeting in March 2012 and was subsequently endorsed by the steering committee at the 2013 Senior Officials Meeting 3.

From a regulatory perspective, advanced therapy products must be safe, efficacious and produced with high quality standards as for any small molecule pharmaceutics or biologics. Some of the advanced therapy products are associated with complex manufacturing process with a long *ex vivo* expansion or culturing running few weeks, product characterisation and potency assays, long term safety and efficacy follow-up and environmental risk assessment, thus raising potential safety concerns and impact to public health. Further, some cell-based therapies are considered standard medical practice in some economies/regions and hence these products may not be subject to pre-market approvals. Hence, a common platform involving regulators, scientists, healthcare practitioners, and other interested parties for sharing and exchange of knowledge, ideas, experiences and best practices are important for regulators to work towards the goal of prospective convergence. Even though rapid advances are being made in this area, regulatory frameworks

for advanced therapies are in a nascent stage in many regions across the globe, which in-deed may be a great advantage to our efforts in regulatory convergence of standards, best practices and technical requirements. In order to achieve the goal of prospective regulatory convergence, significant efforts are necessary to understand the international regulatory landscape for advanced therapy products.

A number of joint efforts have been formed in various international organizations working towards the goal of regulatory harmonization for advanced therapies, including

- The International Pharmaceutical Regulators Programme, IPRP Cell Therapy Working Group (CTWG) and Gene Therapy Working Group (GTWG (formerly known as the International Pharmaceutical Regulators Forum, IPRF).
    - IPRP is a network of regulators from about 12 agencies working in the field of cell therapy and gene therapy product regulations. The group interacts on a routine basis via teleconference to discuss, share and exchange various issues and challenges in the regulation of cell therapy and gene therapy products in their respective jurisdictions. IPRP's outcomes include guidelines and guiding principles, reflection papers, white papers, and recommendations for potential ICH harmonization topics. Part of the IPRP's mandate is to explore information sharing with regional bodies including APEC. As such, APEC, IPRP CTWG and GTWG collaborate on activities that are complementary to the advanced therapy roadmap such as workshops or stakeholder training to maximize synergies and avoid duplication of efforts.
- Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S)
    - PIC/S expert circle on human blood, tissues and cells enable specialised inspectors to discuss and exchange information in the area of cell and tissue therapies. The aim of this expert circle is to develop guidance documents (e.g. recommendations or *aide-memoires*) or to draft / revise Annexes to the GMP Guide that are specific to advanced therapy products.

APEC economies are also members in these joint efforts that encompass various aspects of regulatory convergence. Taking advantage of the APEC LSIF unique role as an 'enabler of regulatory convergence' in promoting the use of international standards, guidance and best practices while at the same time serving as a vehicle to promote prospective regulatory convergence, we put forward the roadmap for this priority work area on human cell- and tissue-based therapies.

The roadmap contributes to achieving the strategic plan adopted in 2010 by APEC's RHSC and the LSIF's mission to promote market access for new and innovative medical products and regional regulatory convergence for medical products by 2020.

The work plan would also explore possible synergies with the following other relevant roadmaps that were developed or being developed within APEC LSIF:

- Good Clinical Practices and Multiregional Clinical Trials
- Biotherapeutic Products
- Pharmacovigilance
- Good Registration Management
- Global Medical Product Quality and Supply Chain Integrity
- Medical Devices

Specific activities and time frames:

This roadmap intends to identify the current regulatory status and to propose a tailored pathway towards prospective convergence of best practices and technical requirements which is necessary to ensure mutual and harmonized understanding within APEC economies and other regions in the area of advanced therapy products. The work plan will also explore mechanisms to help fill the identified gaps through development of an appropriate training programme such as seminars, symposia and workshops, and recommendations for consideration that fall within the APEC LSIF strategic scope. The roadmap will also provide a feedback loop for modification of the plan based on outcome and assessments. The timeframe for implementation of various activities described in the roadmap will be determined following consultation and comments by the RHSC.

Step 1: Initial Assessment (2012-2014)

A Steering Committee has been established with Health Sciences Authority (HSA), Singapore, as the project lead, with other interested RHSC members and other non-members. HSA is responsible for overseeing the development and progress of the road map. Different regulatory frameworks exist in the different economies / regions and also, the definition / classification of an advanced therapy product differ among different jurisdictions, e.g., a product might be considered a medical device in one economy, a medicinal product in another, and a transplant product in a third economy. Hence, the initial focus of the roadmap is to understand the current practices and gaps in the regulatory oversight of advanced therapy products in different jurisdictions. The work plan will take into consideration the outcome and recommendations of the workshop on QA/QC for stem cell products that was held in Bangkok, Thailand on 5-7 July 2011 (the workshop was organised under the umbrella of the APEC/LSIF), and the international workshop on cell and tissue therapy: converging science and regulations organised by HSA (March 22-24, 2012). Overview of recommendations

gathered at the two workshops is summarized below, some of which could be beyond the scope of this roadmap:

- Minimum set of quality/manufacturing requirements for minimally manipulated advanced therapy products to be defined
- Harmonisation of donor eligibility and screening test requirements for cells and tissues
- Reagent qualifications – majority of reagents are not GMP/clinical grade
- Education of the sponsors and product developers on scientific rationale for regulatory requirements – majority of sponsors or applicants are from either academics or small- or medium-sized enterprises
- Education of consumers/patients to raise awareness of the potentials and limitations of therapeutic application of such novel and complex advanced therapy products

The roadmap will identify a path forward for areas that may be ready for the development of relevant points-to-consider recommendations, and for areas that will require specific emphasis, e.g., in the form of targeted focus group discussions on the potential for regulatory convergence or better interpretation of regulatory expectations for a prospective convergence initiative. The plan will take into consideration existing relevant frameworks and will also include recommendations from the above training workshops and activities of the IPRP, and provide recommendations for next steps, such as training methods (meetings, seminars, symposiums, workshops, etc.), including recommendations for assessing outcomes and success towards achieving the goal of the topic. The roadmap will also be a vehicle to feedback the lessons learned and provide recommendations to IPRP for consideration, including the need for consensus guidance document if applicable.

The roadmap will identify how each of elements in the plan will be addressed, including identification of leads for the issues(s), timeline, and what is needed to complete that element of the plan. Further actions (including personnel training) proposed to reach the desired regulatory convergence status will be listed according to priority setting.

The champion economy with inputs from supporting economies will provide reports/updates periodically to the RHSC for comments.

Step 2: Training (24-36 months)

Step 1 outcome will be analysed for the current gaps and challenges in regulation of advanced therapy products, and key areas will be prioritized for the development of training programmes. As determined in

Step 1, relevant training materials and modules, including best practices and standards that currently exist or are being developed, will be consolidated. We also intend to engage members of the IPRF (cell therapy and gene therapy) for inputs and feedback. Training activities will focus on increasing the awareness of regulators and industry stakeholders of regulatory best practices, in efforts to promote the use of regulatory guidance for greater regulatory cooperation, and implementing a science- and risk-based approach for prospective convergence. The roadmap is intended to provide targeted training relevant to the respective stakeholders; regulatory agencies starting to develop advanced therapy frameworks, clinicians, academics and industries, both large players and small- and medium-sized enterprises.

Specific action plans and timelines will be further refined by the lead for that document or project and will be reported back to the governance team and ultimately to RHSC.

Step 3: Assessment of training (2018-2020)

The outcome of Step 2 training/workshop that include the status of implementing international guidelines as well as other learning points and recommendations in achieving the roadmap goal of regulatory convergence for advanced therapy products will be assessed and reviewed. A training curriculum will be developed based on the roadmap goal and key areas identified from Step 2 training/workshop and other efforts that align with RHSCs strategic plan of regulatory convergence such as recommendations from other international efforts, international guidelines and best practices. Training materials developed in Step 2 will be used to conduct follow-up targeted training workshops and seminars for APEC economies and relevant stakeholders, such as industry, drug regulatory authorities, and health care professionals. The goal of the exercise is towards convergence of scientific principles and technical requirements in the regulation of advanced therapy products among the APEC economies.

Step 4: Training to reach the goal and further recommendations for regulatory convergence (2020)

The purpose of training is to provide a platform for information sharing and to ensure consistent implementation of standards/ guidelines. Hence the assessment should provide measures of the overall regulatory convergence level within APEC economies. Assessments shall be performed to evaluate the effectiveness of training programs and determine modifications, if any, that are needed for the program. Training would be updated/ revised and conducted with assistance from other APEC economies and/or the RHSC. Use of case studies based on actual implementation of the topic under consideration will be considered.

The team will compile and consolidate all of the assessment results and provide them to the RHSC. Identified best practices and improvement recommendations will also be included in the report. The team will also evaluate the implementation and progress of the strategic plan and will make course adjustments, as needed. Any changes in the strategic plan will be discussed with the RHSC.

Performance Indicators

- Completion of respective steps to meet the target timeline and to provide periodic progress updates at RHSC meetings. Step 1 diagnostic workshop(s) to be completed in the first two years following endorsement of the roadmap
- Identification of challenge areas and development of training programs and targeted workshops which is key for prospective convergence
- Identification of key lessons learned at every stage and to amend or fine tune approaches or training programme to meet the ultimate goal of prospective regulatory convergence. RHSC will be kept informed of all changes made to the roadmap during the entire process of achieving the goal in stimulating and promoting prospective regulatory convergence for advanced therapy products
- Submission of final assessment report to LSIF RHSC for endorsement

Relevant Guidelines

- US Food and Drug Administration – cell therapy and tissue products
    - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm
    - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/default.htm
- European Medicines Agency – advanced therapy medicinal products (ATMPs) and human tissues (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&mid=WC0b01ac05800862bd)
- Health Canada – human cells, tissues and organ regulations (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/index-eng.php)
- TGA Australia – Biologicals framework (http://www.tga.gov.au/industry/biologicals.htm)
- European Commission's GMP guidelines, revised Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use (http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm)
- PIC/S GMP guidelines - http://www.picscheme.org/publication.php?id=4

- WHO guidelines on INN nomenclature scheme for Cell Therapy Products - http://www.who.int/medicines/services/inn/inn_bio_ct/en/
- International Pharmaceutical Regulators Programme (cell and gene therapy working groups) - https://www.i-p-r-f.org/index.php/en/