Executive Summary of WHO Implementation Workshop on
‘WHO Considerations in Developing a Regulatory Framework for Human Cells and Tissues and for Advanced Therapy Medicinal Products’

14-16 May 2024
Muscat, Oman

The implementation workshop on WHO considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products was held in Muscat, Oman from 14-16 May 2024 and was attended by 68 participants from 31 countries across 6 WHO regions, including regulators, members of the Expert Advisory Panel on Biological Standardization, manufacturers and WHO staff from HQ, EMRO, AFRO, and Oman country office.

![Fig 1. Participants from 31 countries across six WHO regions.](image)

![Fig 2. (a) The number of participating regulators/experts, manufacturers and WHO staff (total 68). (b) Breakdown by region of participating regulators/other experts.](image)
During the three-day workshop, key issues outlined in the recently published document entitled “Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products” were presented and discussed in seven open sessions. The agenda for the workshop has been included at the end of this document.

Cells, tissues, and gene therapy products (CGTPs) represent biological products across a spectrum of complexity from those that require minimal oversight (such as a simple allogeneic skin graft) to those (such as chimeric antigen receptor T-cells) which require significant regulatory evaluation to demonstrate product safety and efficacy before marketing authorization. The spectrum of biological products and the key risk considerations were discussed at the workshop.

A risk-based approach for regulation of CGTPs, classification, terminology for CGTPs and the importance of global harmonization especially on terminology were discussed. The sessions included discussion of the approach to regulation of CGTPs, considerations for classification and terminology, as well as perspectives from national regulatory authority (NRA) representatives on the regulatory landscape in their countries. Manufacturers’ perspectives on the current state for development of CGTPs also were discussed in a session, as well as the role of WHO in supporting countries to strengthen their regulatory systems and build technical capacity to regulate CGTPs. The workshop concluded with a summation of recommended next steps.

Group activities included discussion of three case studies: 1) Minimally manufactured tissue used for same function in recipient as in donor: Irradiated, sterile human skin allograft, 2) Biological products requiring full premarket authorization with a demonstration of safety and efficacy: Autologous CAR T cell product targeting CD19, and 3) Manufactured tissue used for same function in recipient as in donor: Allogeneic pancreatic islet cells and Mesenchymal stem cells (MSCs). Overall, review of the case-based studies reiterated a pressing need for a risk-based approach to classification for cell and gene therapy products and the need for increasing stringency in manufacturing compliance (GTP vs GMP) with higher risk products. Participants highlighted that there was an urgent need for harmonized definitions of minimal manipulation and of homologous use to prevent misinterpretation as different interpretations of the regulatory frameworks (or lack of a regulatory framework) could make it more attractive for “bad players” to enter the cell and gene therapy market, and that can have harmful consequences for patients. The crucial point was also raised that the implementation of such regulatory frameworks needs to be done in parallel with education and the provision of sufficient information.

Table 1. Case studies on CGTPs for risk-based regulatory approach

<table>
<thead>
<tr>
<th>Case</th>
<th>Products</th>
<th>Description of product classes</th>
<th>Risk considerations</th>
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</table>
| 1    | Irradiated, sterile human skin allograft | • Minimally manufactured tissue used for same function in recipient as in donor | • No manipulation or minimal manipulation  
• Same intended use in donor and recipient |
| 2    | Autologous CAR T cell product targeting CD19 | • Biological products requiring full premarket authorization with a demonstration of safety and efficacy | • Substantial manipulation or non-homologous use in the recipient |
| 3    | Allogeneic pancreatic islet cells and Mesenchymal stem cells (MSCs) | • Manufactured tissue used for same function in recipient as in donor | • More than minimal manufacturing or non-homologous use in the recipient |
There were common themes in the feedback from NRAs participating in the workshop. There was strong support for the WHO CGTP document. Some regulators noted they are utilizing the concepts outlined in the document to develop a regulatory framework in their country for CGTPs. Countries indicated need for technical assistance for review of CGTP applications from clinical trials through marketing authorization and post-licensure monitoring (including long-term follow up). Regulatory capacity building for both the regulatory system as well as regulatory staff was noted as a need by many countries, and role of WHO in providing training and other means of support was highlighted. Joint reviews involving multiple WHO were proposed to increase efficiency and build capacity.

Medical tourism was highlighted as a global challenge. In countries that have little or no regulation of CGTPs, unauthorized products are used (with no regulatory oversight), which can harm patients. Countries that have regulations for CGTPs are impacted by lack of regulation in neighboring countries. If there are adverse events in response to treatment received in another country, the healthcare system of the home country must bear the cost of treating the patient. Medical tourism is a global problem.

Most countries noted they have not received any or received only very few clinical trial applications for CGTPs. There was speculation that lack of capacity and lack of regulatory guidelines may be the reason why manufacturers are not conducting clinical trials for advanced therapies in some countries. There was broad request for development of international, regional, and local (country level) guidelines on regulation of CGTPs on a range of topics. Increasing knowledge of CGTPs and strengthening regulatory capacity were highlighted as necessary actions to increase patient access to CGTPs in LMICs.

Countries highlighted the value of and need for mechanism(s) to practice regulatory reliance on decisions of more advanced NRAs and/or the WHO. The role of WHO programs such as the Collaborative Registration Process (CRP) or prequalification could be means to facilitate marketing authorization and patient access to advanced therapies in LMICs.

Another challenge highlighted by multiple regulators was how to control products made in hospitals. In some countries, therapies for individual patient can be used without regulation (like European hospital exemption). Additionally, many of the advanced therapy products start from organs, tissues, or cells which may be under a different authority like a transplantation authority or an inspectorate (it may not be the regulator). This was cited as another factor to consider when establishing a regulatory framework.

The workshop concluded with chair, rapporteurs, and participants requesting that WHO assists countries to facilitate:

- Regulatory capacity building including the provision of training and any other means of support to LMICs. This was noted as a need both for (1) establishing/strengthening regulatory systems as well as; (2) strengthening the knowledge and capacity of regulatory staff.
- Development of international, regional, and national guidelines on regulation of CGTPs for a range of topics including good tissue practices; good manufacturing practices; tissue traceability; and adverse event reporting and long-term follow up for products where that is needed (e.g., some gene therapies).
- Technical assistance for review of CGTP applications through the product lifecycle from clinical trials through marketing authorization, post-licensure monitoring and long-term follow up.
- Practice of regulatory reliance on decisions of more advanced NRAs and/or the WHO.
- Development of WHO international standards for CGTPs and;
- Recommendations and guidelines for implementing pharmacovigilance, especially in the case of gene therapies that require long term follow-up (e.g., 15 years or more).
# WHO Implementation Workshop:
WHO Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products

**14-16 May 2024**
Grand Millennium Hotel, Muscat, Oman

## AGENDA

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Details</th>
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<tbody>
<tr>
<td>9:00 – 11:00</td>
<td>Pre-meeting only for the WHO staff and facilitators</td>
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<tr>
<td>11:00 – 12:00</td>
<td>Registration</td>
<td>All participants</td>
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<tr>
<td><strong>12:00 – 13:00</strong></td>
<td>Lunch</td>
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<tr>
<td><strong>Session 1</strong></td>
<td>Welcome and introduction</td>
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<td>13:00 – 14:00</td>
<td>Opening remarks and welcome speech</td>
<td>Dr Siham Salim Al Sinani, University Medical City, Oman</td>
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<td>Dr Jean Jabbour, WR Oman</td>
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<td>Dr Ivana Knezevic, WHO</td>
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<td>Group photo</td>
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<td>Self-introduction</td>
<td>Participants</td>
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<td></td>
<td>Statement on DoI assessment</td>
<td>Dr Eunyung Kim, WHO</td>
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<td>Housekeeping information</td>
<td>Ms Lamiaa Shoman, WHO</td>
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<tr>
<td><strong>Session 2</strong></td>
<td>Background and objectives</td>
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<td>14:00 – 14:30</td>
<td>Background and history of activities</td>
<td>Dr Peter Marks, US FDA</td>
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<td>14:30 – 14:50</td>
<td>Update on WHO biological standardization</td>
<td>Dr Ivana Knezevic, WHO</td>
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<td>14:50 – 15:00</td>
<td>Objectives and expected outcomes of the workshop</td>
<td>Dr Eunkyung Kim, WHO</td>
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<td><strong>15:00 – 15:30</strong></td>
<td>Coffee break</td>
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Session 3  Evaluation of CGTPs: Current practices & NRA perspective on regulatory landscape in their countries

15:30 – 15:50  Feedback from countries                              Dr Eunkyung Kim, WHO
15:50 – 17:20  Round table discussion by NRAs                   NRAs & Chair
17:20 – 17:40  Measurement standards for cell and gene therapy products Dr Chris Burns, MHRA
17:40 – 18:00  Discussion                                       
18:00 – 18:10  Wrap-up of Day 1                                 Chair
18:30 – 20:00  Welcome reception                                All participants

Day 2: 15 May 2024, Wednesday

Session 4  WHO Considerations on cell and gene therapy products (CGTPs)

Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products (Annex 3, WHO TRS 1048, 2023)

09:00 – 09:30  Risk-based regulatory approach                    Dr Peter Marks, US FDA
09:30 – 10:00  Classification and terminology                    Dr Ilona Reischl, AGES-MEA
10:00 – 10:30  Discussion                                       

10:30 – 11:00  Coffee break

Session 5  Case studies on CGTPs

11:00 – 11:30  Brief explanation of case study 1 & 2:            Dr Peter Marks, US FDA

1) Minimally manufactured tissue used for same function in recipient as in donor: Irradiated, sterile human skin allograft

2) Biological products requiring full premarket authorization with a demonstration of safety and efficacy: Autologous CAR T cell product targeting CD19

11:30 – 13:00  Group work: case study 1 & 2                     All participants

13:00 – 14:00  Lunch break
14:00 - 15:00  Reporting of the outcomes (*10 min for each group*)  Each Group
15:00 – 15:30  Brief explanation of case study 3:  Dr Mickey Koh
*Manufactured tissue used for same function in recipient as in donor: Allogeneic pancreatic islet cells and Mesenchymal stem cells (MSCs)*

**15:30 – 16:00  Coffee break**

16:00 – 17:00  Group work: case study 3  All participants
17:00 – 18:00  Reporting of the outcomes (*10 min for each group*)  Each Group
18:00 – 18:10  Wrap-up of day 2  Chair

**Day 3: 16 May 2024, Thursday**

**Session 6  Implementations of WHO considerations: Manufacturers’ perspectives on regulatory issues**

09:00 – 09:15  IFPMA’s view on development of CGTPs and challenges  Dr Srinivasan Nadathur Kellathur, Roche, IFPMA
09:15 – 09:30  DCVMN’s view on development of CGTPs and challenges  Dr Antonio C. Campos de Carvalho, Fiocruz, DCVMN
09:30 – 09:45  Development of CGTPs and challenges in EM region  Dr Savash Erdem, OPAL Bio Pharma
09:45 – 10:00  Development of CGTPs and challenges in EM region  Dr Samira Ahmadi, Caryakhhte Tajhiz Azma
10:00 – 10:30  Discussion: How to implement WHO considerations,  *e.g. implementation plan, tools to facilitate, support needed from WHO*  All participants

**10:30 – 11:00  Coffee break**

**Session 7  Conclusions and way forward**

11:00 – 11:45  Summary report of points raised during the workshop  Chair & Rapporteur
11:45 – 12:00  Conclusions and next steps  Chair & Rapporteur
12:00 – 12:15  Evaluation form – feedback from participants  Dr Houda Langar, WHO
12:15 – 12:30  Closing remarks  Dr Ivana Knezevic, WHO
12:30  Close of the open meeting  Chair
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<th>Time</th>
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<tr>
<td>12:30 – 13:30</td>
<td><strong>Lunch break</strong></td>
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<td>13:30 – 15:00</td>
<td>Closed session (regulators and participants without conflict of interest)</td>
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<tr>
<td>15:00 – 16:00</td>
<td>Feedback from workshop participants</td>
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<td>15:00 – 16:00</td>
<td>Discussion</td>
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<td>16:00</td>
<td>Close of meeting</td>
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All NRAs
Chair & WHO