Advanced Therapy Medicinal Products in Israel:
Evolving Regulation

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Advanced Therapy Medicinal Products (ATMPs)

Gene Therapy
Cell Based Therapy
Tissue Engineered

As Defined in:
- Directive 2001/83/EC Medicinal Products For Human Use
- Regulation (EC)1934/2007) on advanced therapy
Need  Regulation
What do we have?

- **R&D**
- **Private clinics (e.g. Plastic procedures)**
- **Procedures in Hospitals (cord blood transfusion for autism)**
- **Hospital Exemption**
- **Clinical trials**
- **Marketing Authorizations**

**Not regulated**

**Lack of information, lack of education**

**Regulated**
## Clinical Trials Applications

<table>
<thead>
<tr>
<th>Year</th>
<th>Cell based</th>
<th>Gene therapy</th>
<th>Hospital Exemption</th>
<th>Local Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>9</td>
<td>3</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>2016</td>
<td>8</td>
<td>2</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>2017</td>
<td>10</td>
<td>4</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>2018 (Q1, Q2)</td>
<td>15</td>
<td>3</td>
<td>1 submitted</td>
<td>13</td>
</tr>
</tbody>
</table>

3 GMP approved facilities
Marketing Authorizations

1 MA in 2017-Imlygic

4 MAA in 2018
Regulation

ATMP = Medicinal Product

Regulated as biological medicinal

Specific requirements
Israeli Legislation

• Legislation is covered by the general provisions of:
  
  – Pharmacists Ordinance [New Version], 1981
    • Definition of medicinal product to include ATMPs
  
  – The Pharmacists Regulations (Medicinal products) 1986
  
  – Pharmacist Regulations (Good Manufacturing Practice for Medicinal Products) 2008, in accordance with EU GMP legislation
  
  – Notice on the approval of general director according to pharmacist regulations (2016); Unlicensed medicines to include hospital exemption
  
  – Cord blood -law and regulations
  
  – Specific legislation in preparation
General Policy

• Basic principles of regulatory framework of the EU are followed
  – Directive 2001/83
  – EudraLex Vol 4 Good manufacturing practice Guidelines; Part IV-GMP Requirements for Advanced Therapy Medicinal Products

• Guidelines
  – ICH, EMA and FDA Scientific guidelines
  – Raw materials
    • USP 1043 - Ancillary Materials for Cell Gene, and Tissue Engineered Products
Israeli Guidelines

• **Tissues and cells based products (ISPC_2501206)**
  - Simple and advanced: basic safety requirements (Based on European Directives)
  - ATMPs - MAA requirements (based on relevant European Regulations and Directives)

• Regulatory requirements for importation of tissues and cells of human origin (ISPC_29042013)

• Clinical Trials in Humans (SOP 14 - November 2014)
  - Basic requirements for clinical trial applications

• Online submissions forms for import (June 2014)

• Simple Tissues and Cell - a detailed guidance is in preparation (based on EDQM guidance)
Marketing Authorization - Submission Requirements

• Demonstration of Quality, Safety and Efficacy
  • Israeli SOPs for registration (Registration department and Institute for standardization and Control of Pharmaceuticals)
    • Submission of MAA REG_08_2012
    • Application for quality certificate of new biological product (EX-013)
  • CTD according to EU Directive 2001/83 Part IV: Advanced therapy Medicinal products
• Approval in a recognized country
Approval Process

Evaluation of Quality, Safety and Efficacy

Advisory Committee

Marketing Authorization/Rejection
Clinical Trials - submission requirements

• Clinical trials in human (pharmaceutical division SOP No.14)
  – Protocol
  – Investigation Brochure
  – IMPD
  – Manufacturing compliance with GMP
    • Phase I and II - Declaration
    • Phase III - Inspection and certificate of the competent authority
Clinical Trials Approval

Approval of Hospital Helsinki Committee

Evaluation of documents

Dedicated Advisory Committee for gene and cell therapy (physicians, scientists, MOH regulators, ethics experts)

Approval/Rejection
Unlicensed medicines - Hospital Exemption (1)

- Manufacturing, distribution or usage of advanced therapy product which is not registered in the national medicinal product registry
- Manufacturing, distribution or usage of not registered product, on non-routine base, under specific quality standards, authorized by the general director, under the responsibility of the physician
- No import of such therapy is allowed
- The physician has supportive evidence for the efficacy of the therapy and it was approved by the Helsinki Committee of the Hospital
Unlicensed medicines - Hospital Exemption (2)

• Conventional requirements for clinical trial can not be fulfilled
• The ATMP will be used in hospitals only
• Manufacturing complies with GMP
• Manufacturer should have traceability and vigilance systems
• The physician has to submit an annual report, presenting No. of patients treated, No. of batches produced, adverse events and data related to efficacy
Some examples of unresolved issues

- Small country with a lot of small local facilities, creativity, Public pressure
- Lack of understanding by Stakeholders (e.g. physicians, manufacturers, public)
- Extent of quality data for clinical trial applications
- Animal models
- No. of patients for clinical trials, gradual approval
  - Phase of clinical trial
- Placebo
- Distribution (directly to the hospital)
- Hospital exemption- No. of treatments, tourism medicine, payments
- Ethical issues
Thank you for your attention

Thanks to my colleagues

Dr. Catherine Ela,
Head of Clinical Trials Department

Dr. Vered Ben Naim,
Head of Biologicals Quality Assessment unit