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Advanced Therapy Medicinal Products in Israel:

Evolving Regulation

Dr. Ofra Axelrod

Director

The Institute for Standardization and Control of Pharmaceuticals

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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**

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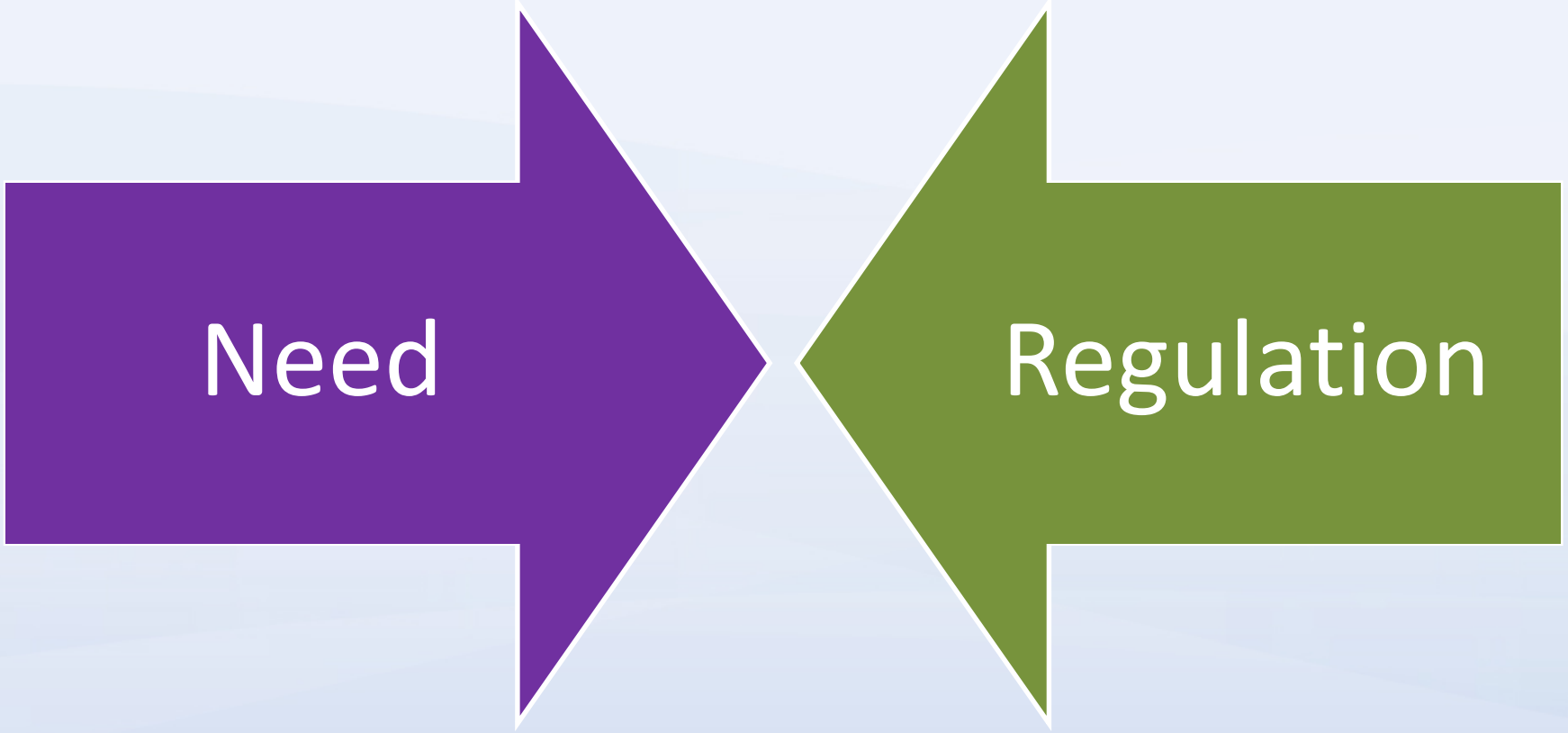

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What do we have?

• 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

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Clinical Trials Applications

Year	Cell based	Gene therapy	Hospital Exemption	Local Manufacturers
2015	9	3	-	7
2016	8	2	-	6
2017	10	4	-	7
2018 (Q1, Q2)	15	3	1 submitted	13

3 **GMP approved facilities**

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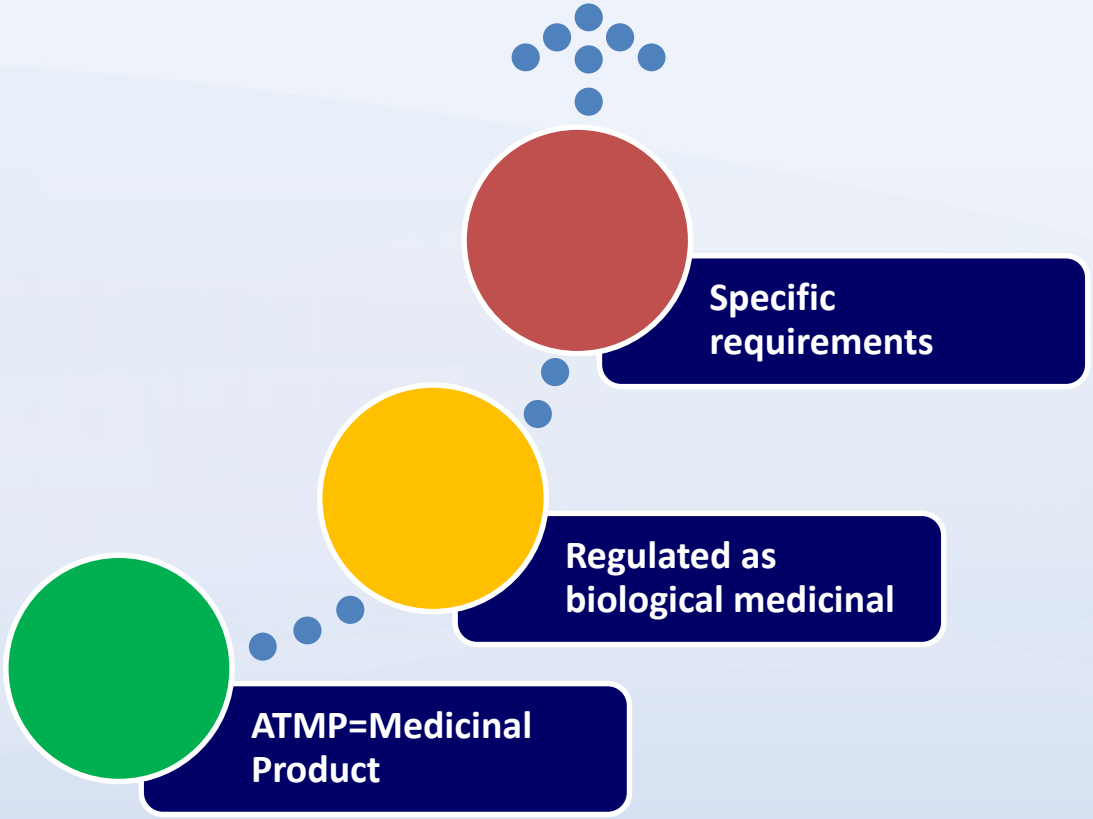
Marketing Authorizations

1 MA in 2017-Imlygic

4 MAA in 2018

Regulation


Specific requirements
Regulated as biological medicinal
ATMP=Medicinal Product

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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**
  - Regulation (EC) No1394/2007
  - Directive 2001/83
  - Commission Directive 2009/120 /EC(amending Directive 2001/83/EC)
  - 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
    - 5.1.12 - European Pharmacopoeia - raw Materials for the production of cell based and gene therapy medicinal product 9th Edition (July 2016, implementation 01.01.2017)

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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)

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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

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Approval Process

Evaluation of Quality, Safety and Efficacy

Advisory Committee

Marketing Authorization/Rejection

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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

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Clinical Trials Approval

Meetings with applicant- optional

Approval of Hospital Helsinki Committee

Evaluation of documents

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

Approval/Rejection

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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

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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

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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,
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Head of Biologicals Quality Assessment unit