Advanced Therapy Medicinal Product – a prospective view

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Agenzia Italiana del Farmaco

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Public Declaration of transparency/interests*

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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N.B. I am not receiving any compensation

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They are not intended to be an official and/or binding regulatory position.

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Let me introduce ourselves!....

Multi-professional

One of a kind

Keep evolving

The driving principles

Affiliation

Integrity

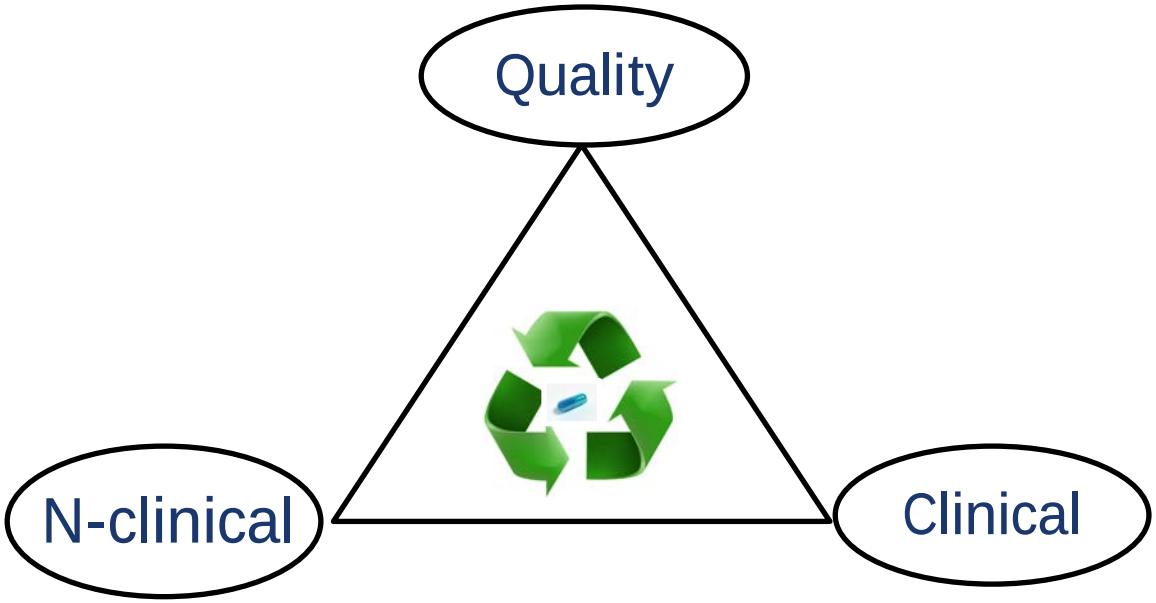
Responsibility

Technical Innovation

Transparency

Participation

Our mission/vision



Safeguard public health through regulation and evaluation of medicinal products and treatment safety also via stringent post-marketing controls

Regulatory framework

PhVig legislation

Blood
2002/98/EC

Tissues / Cells
2004/23/EC

ATMPs
1394/2007CE

Clinical Trials
2001/20/EC

Other starting materials

Paediatrics
1901/2006

Medical Devices
93/42/EC

GMP
2003/94/EC

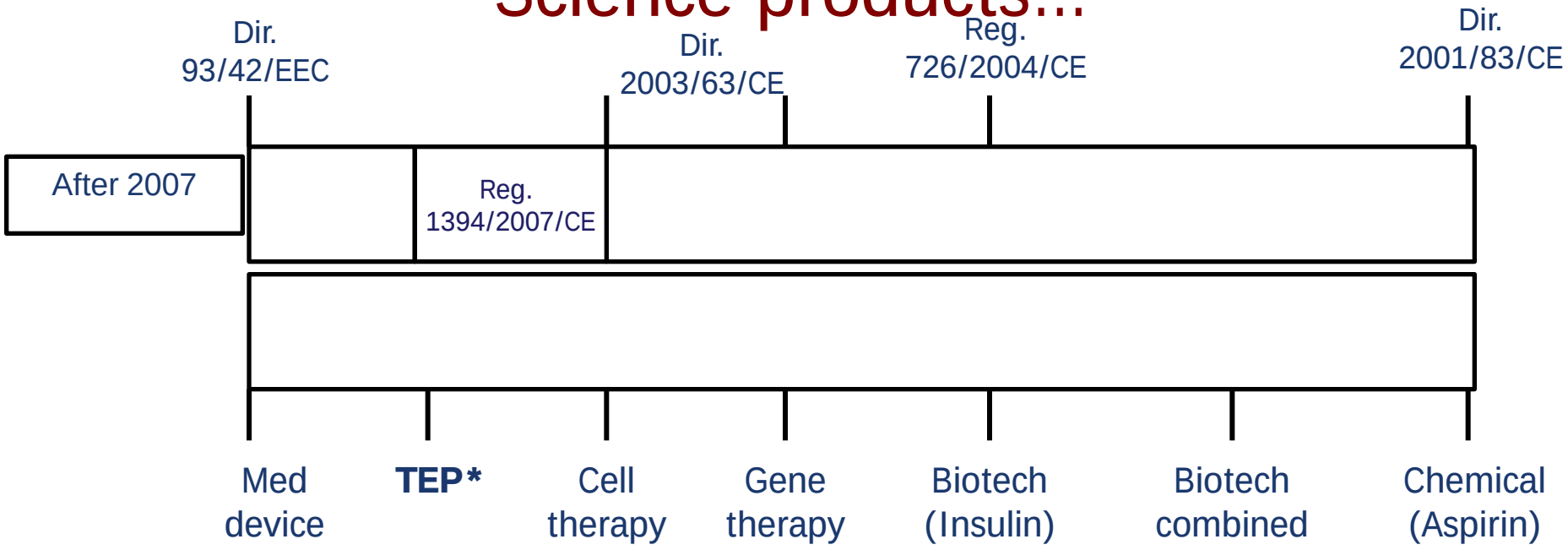
'Annex I'
2003/63/EC
2009/120/EC

Falsified Med.
Dir. 2011/62/EU

Variations
1084(5)/2003
1234/2008

Orphans
141/2000

Science products...



It is key to know in which regulatory framework a given product falls:

- who and with which competences is responsible for evaluation and approval?
- who suggests development strategies for Q, NC e C?

**Tissue engineering products*

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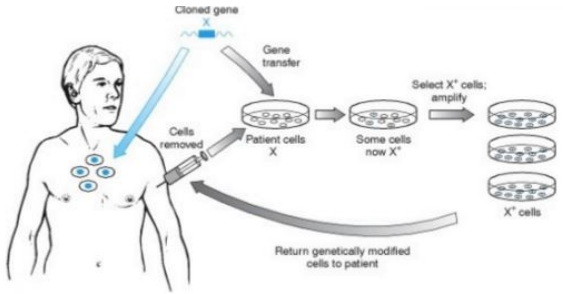
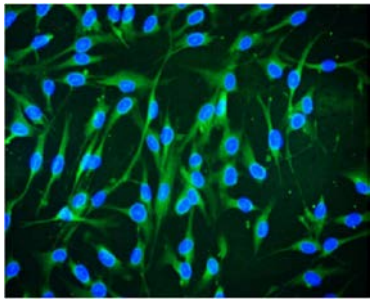
ATMPs

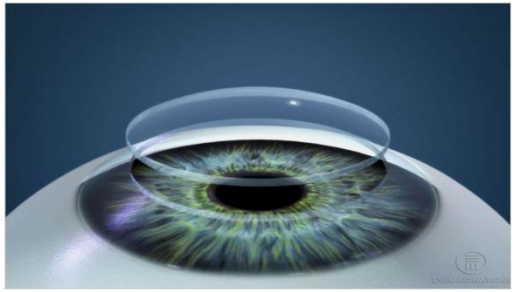
Gene therapy medicinal product



Somatic cell therapy medicinal product

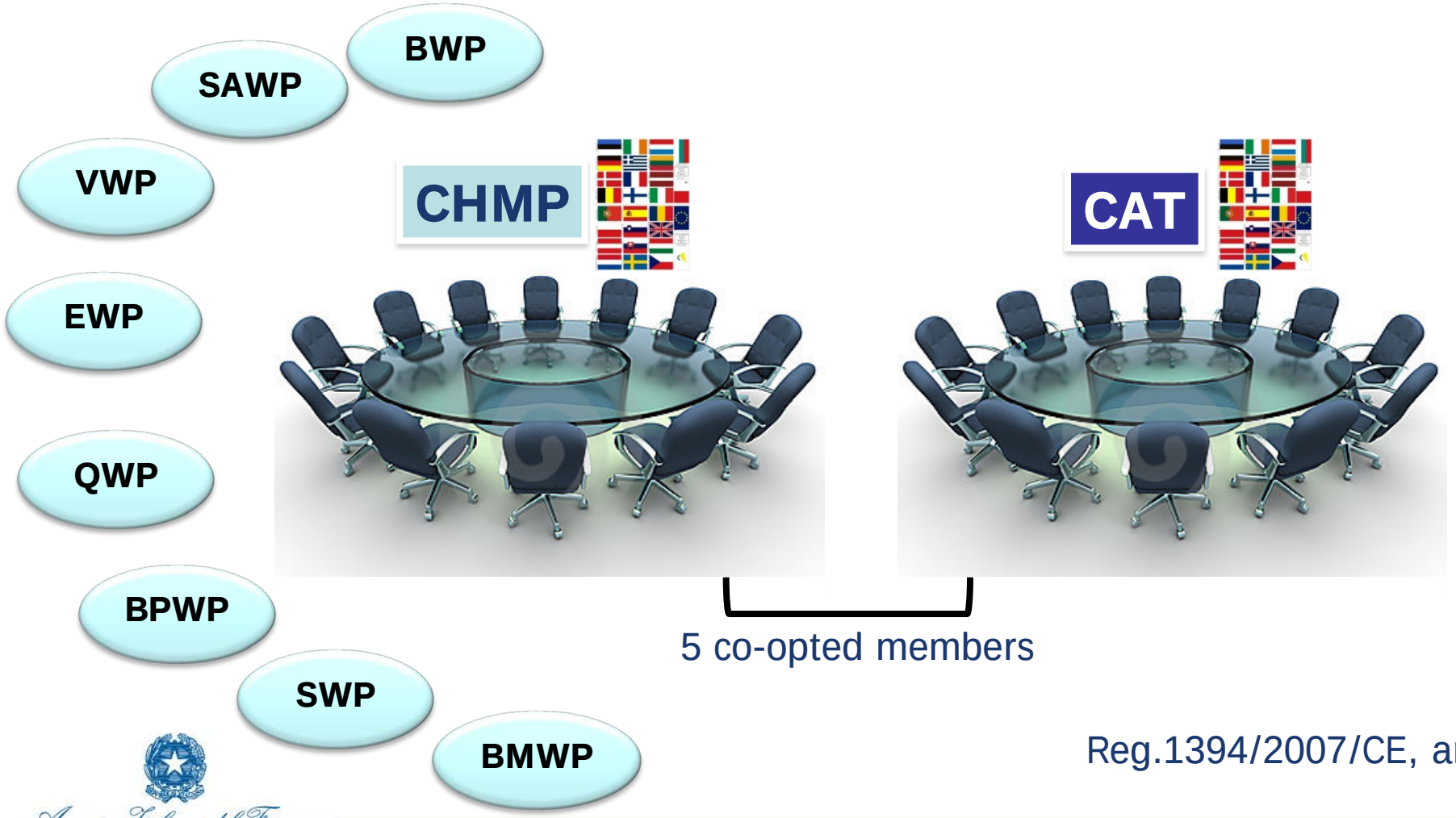


Tissue engeneering product



ATMP + medical device = combined ATMP

CAT interactions



Reg.1394/2007/CE, art.8

...since 2009....

- ChondroCelect for cartilage repair (2009)
- MACI for cartilage repair (2012) – closure of EU manufacturing site in 2014
- Glybera for tretment of LPL deficiency (2013)
- Provenge for treatment of advanced prostate cancer 2013 – withdrawn in 2015

Where's the issue??....

- Quality issues?

  Not really, even if quality can impact safety and efficacy profile

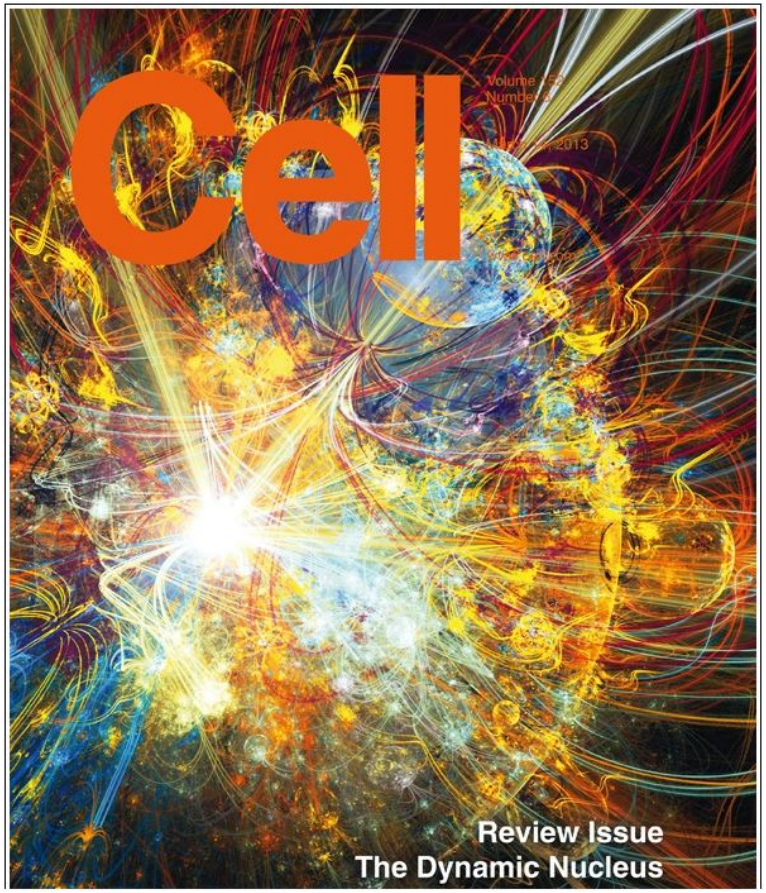
- Non-clinical issues?

  No, screening at clinical trial level

- Clinical issues?

  YES! Efficacy!

Cells are complex!



- Respond to signals and extracellular stimuli
- Activate enzymes, gene expression, secondary messangers
- Secrete bioactive molecules
- Cell motility
- Apoptosis
- Secondary messangers
- Proliferate, differentiate
- ....

ATMPs are special and complex medicinals

- Gene therapy: transgene, type of vector, genetically modified cells, comparability

- Cell therapy: autologous, allogenic, complex manufacturing, combined, starting material

- Development requires high-specialization and know-how

- Product safety and efficacy profile must be carefully prospectively planned in order to produce robust and reliable data

ATMPs risks and limitation

•contamination (microbial contamination of starting materials or during manufacturing)

•tumourigenicity (cell transformation, insertional mutagenesis)

•de-differentation / cells loss of function

•immunogenicity, rejection

•ectopic engraftment of cells to non-target tissues

•shedding (germ line, environment)

•small sample sizes, short shelf-lives, availability of proper animal models, applicability of analytical methods etc.

Regulatory flexibility

•The risk-based approach for all ATMPs has been included into the legislation (revised Annex I, Part IV, Dir. 2001/83/EC), aim to provide regulatory flexibility

•Risk analysis should comprehend the whole development in order to determine the amount of data needed for MAA

•Existing guideline for the Risk based approach

ATMPs – specific major development

• Targeted stakeholder consultation on the development of GMPs for ATMPs

• Revised reflection paper on the classification of ATMPs (June 2015)

• Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

• Italian decree dated 16 January 2015 on ATMPs prepared on a non-routine basis

Targeted stakeholder consultation on the development of GMPs for ATMPs

- Article 5 of Regulation 1394/2007:

  The Commission shall, after consulting the Agency, draw up detailed guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

Targeted stakeholder consultation on the development of GMPs for ATMPs (cont.)

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

GMPs are very general concept to apply and interprete where the main concept...is to comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy...To achieve this quality objective reliably there must be ...a Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management.

Targeted stakeholder consultation on the development of GMPs for ATMPs – (cont.)

- The consultation paper has been published the 27 Jul 2015 on EC web-site

- Target: all stakeholders involved in the development, manufacture and/or commercialisation of ATMPS. Comments from small and medium-sized enterprises (SMEs) are particularly welcome.

- Period of consultation: from 23 July 2015 to 12 November 2015

Targeted stakeholder consultation on the development of GMPs for ATMPs – (cont.)

- Adaptation of GMP to specific characteristics of ATMPs
- Reduction of burdens without compromising public health
- Making GMP requirements more understandable and accessible
- Single document with all requirements relevant to ATMPs
- Requirements not relevant to ATMPs will be removed
- Text drafted with specific focus on ATMPs
- Evaluation of comments from stakeholder consultation

Revised reflection paper on the classification of ATMPs (June 2015)

•The classification procedure has been introduced by the Reg. 1394/2007 and is a responsibility of the CAT

•The procedure allows developers to receive confirmation that a medicine, which is based on genes, cells or tissues, meets the scientific criteria for defining an ATMP

• Public consultation on the revision of reflection paper closed and it has been adopted on June 2015

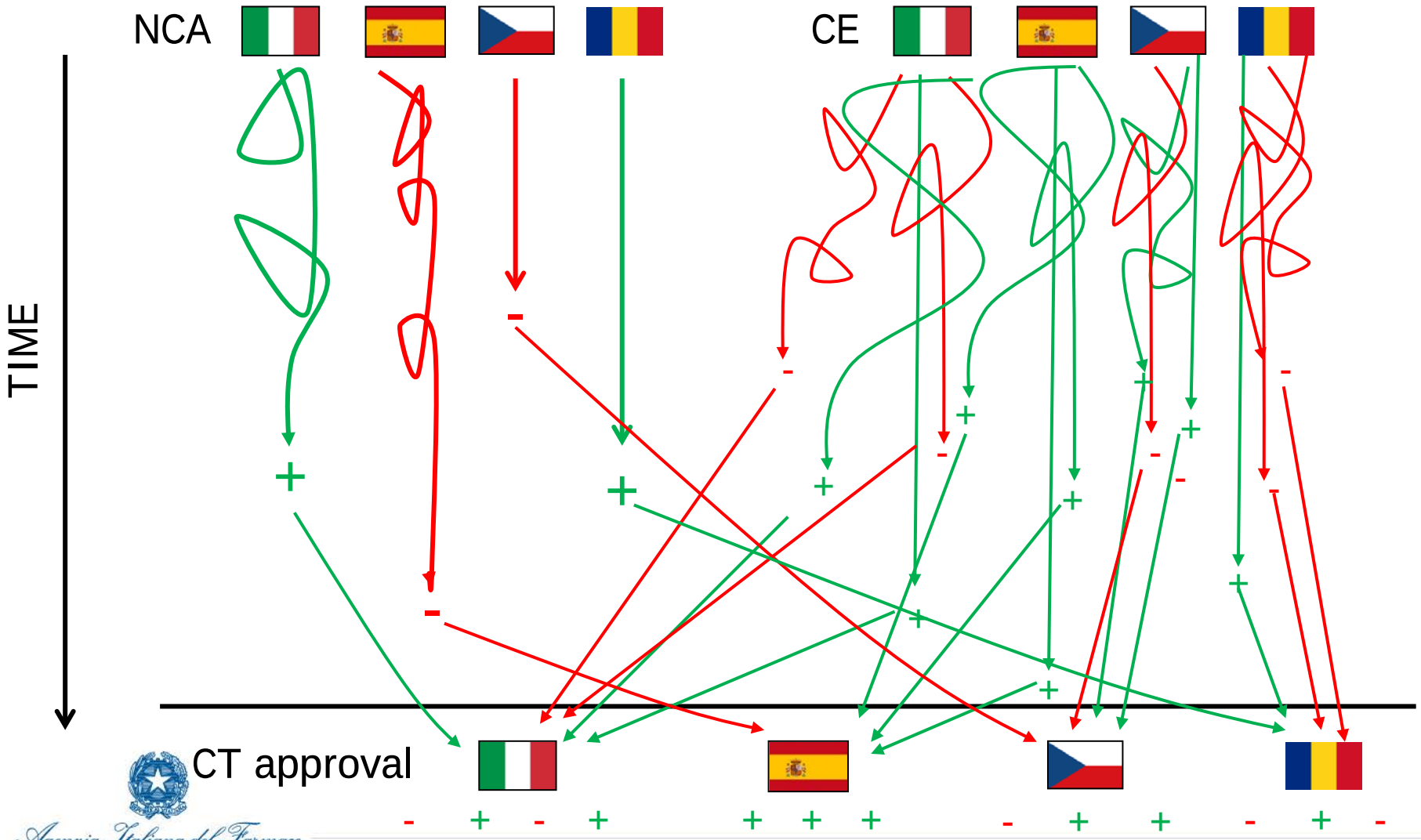
• Clarify the concepts of ATMPs' definition and in particular clarify "substantial manipulation and non-homologous use" concept

Revised reflection paper on ATMP classification

- Substantial manipulation:
  - Cell culture
  - Enzymatic digestion of a tissue to release cells (different from release of intact functional units –i.e. pancreatic islets)

- Different essential function (non-homologous use) - In case no substantial manipulation, the classification is based on the essential function of the cells/tissues.
  - The cells are used to maintain the original function(s) in the same anatomical or histological environment
  - bone marrow cells or peripheral blood cells used for haematopoietic or immune reconstitution (homologous) otherwise non-homologous
  - adipose cells transplanted to other than fat tissue (non homologous)

Clinical trial – Present scenario



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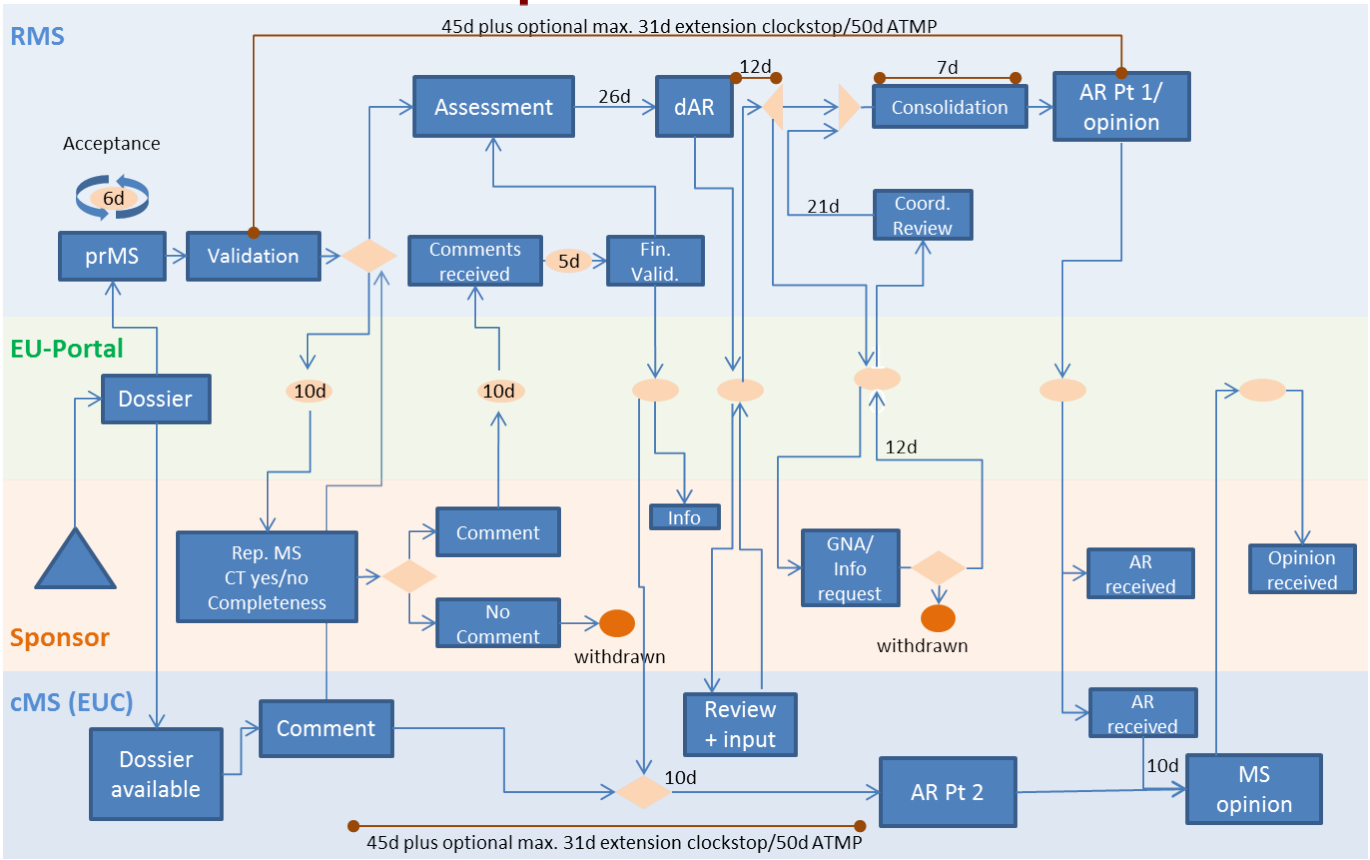
New Clinical Trial Regulation (N. 536/2014) – Assessment part I – future scenario



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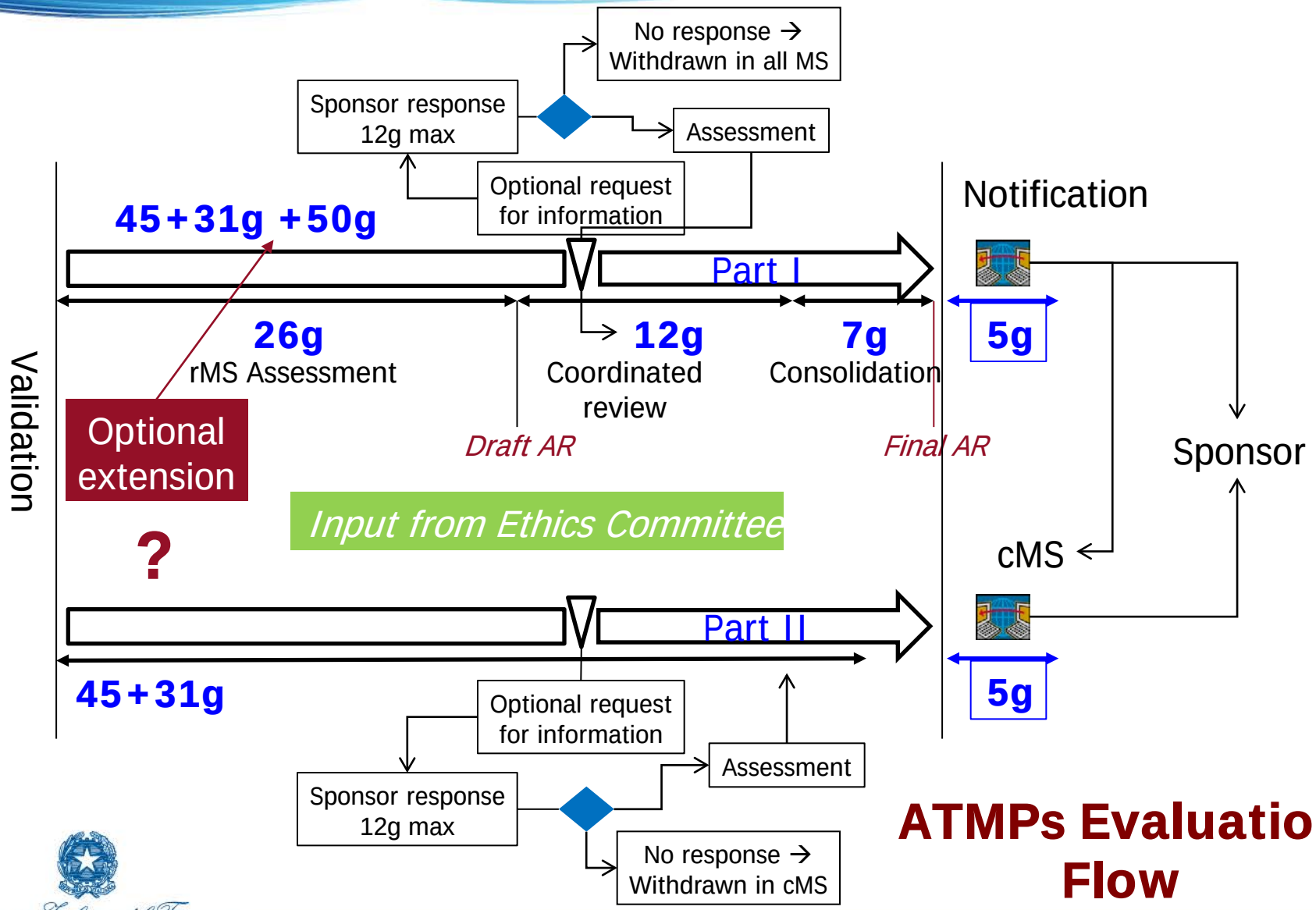

ATMPs Evaluation Flow

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Patients needs for ATMPs: Reg.1394/2007 art.28

Several ATMPs are not used under compassionate use (no PhII/III CT results), nor off-label (not approved), ATMPs used before regulation entering into force:

Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

D. 16 Jan 2015 regulates ATMPs prepared on a non-routine basis (H/E)

- Regulates production and use of ATMP prepared on a non-routine basis

- Definition of ATMPs according to Reg.1394/2007CE; Annex1, part IV of D.Lgs. 219/2006 (Dir.2001/83CE) and subsequent amendments

- AT-IMPs are excluded

- Compassionate use for ATMP still valid (PhII and PhIII data)

D. 16 Jan 2015 Production and use (H/E)

Production:

Authorization released by AIFA (cGMP) in 60 days

Use:

Authorization released in 30 days by AIFA with technical assessment by a NIH commission

D. 16 Jan 2015 Manufacturer authorization

Is released following AIFA inspection and it is based on:

- Type of ATMP to be produced based on a “IMPD-like” dossier
- Previous production authorization, if any, and premises details
- Equipment
- QP and PhV responsible person identification and personnel
- Manufacturing process and IPC
- QC equipment
- QA, SOP and analytical methods

D. 16 Jan 2015 authorization for use

- Only for single patients AND without therapeutic option AND in urgency/emergency situation AND in life-threatening conditions

- Based on rationale for use, previous clinical experience, quality, NC and clinical existing data and ultimately on risk/benefit profile

- In case of different indication, new authorization is required

D. 16 Jan 2015 producer / treating physician obligation (H/E)

- The production must comply with authorization and current applicable requirements
- Traceability of product and patients
- Pharmacovigilance (including lack of efficacy)
- To communicate yearly the n. of produced lots
- According to cGCP principles

D. 16 Jan 2015 data monitoring (H/E)

- AIFA and NIH collect and evaluate safety clinical data
- Every 30 days from treatment, clinical data and records for efficacy evaluation should be transmitted to AIFA
- AIFA can suspend/retire the authorization

Conclusions I

- ATMPs are regulated as medicinal products: demonstration of quality, safety, efficacy and positive benefit/risk

- Mandatory centralised procedure for MA and CA evaluation for CTs

- ATMPs are complex medicinal and some pitfalls still exists

- Regulatory flexibility to cover the pitfalls is in place (as risk based approach)

Conclusions II

- Several regulatory development are in place to solve different issues
  - adaptation of GMP requirements to specific characteristics of ATMPs.
  - new reflection paper on classification
  - new clinical trial regulation
  - national decree to fill the gaps of EU legislation

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