משרד הבריאות

לחיים בריאים יותר

דרישות איכות ורגולציה בשלבים הראשונים של תרפיה תאית

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המכון לביקורת ותקנים של חומרי רפואה
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Advanced Therapy Medicinal Products – ATMPs - European Term

- Gene Therapy
- Somatic Cell Therapy
- Tissue Engineered
- Combination Products

cell based products

Somatic Cell-Based Therapy-Definition

- **Somatic cell therapy medicinal products**:
  - **Substantially manipulated cell/tissue-** to treat, prevent or diagnose a disease (through pharmacological, immunological, or metabolic action)

  or

  - **Cell/tissue not intended to be used for the same essential function(s)** in the recipient and the donor

Non-substantial Manipulation - minim

Everything else is considered as substantial

- **cutting**
- **grinding**
- **shaping**
- **centrifugation**
- **soaking in antibiotic or antimicrobial solutions**
- **sterilization**
- **irradiation**
- **cell separation, concentration or purification**
- **filtering**
- **lyophilization**
- **freezing**
- **cryopreservation**
- **vitrification**

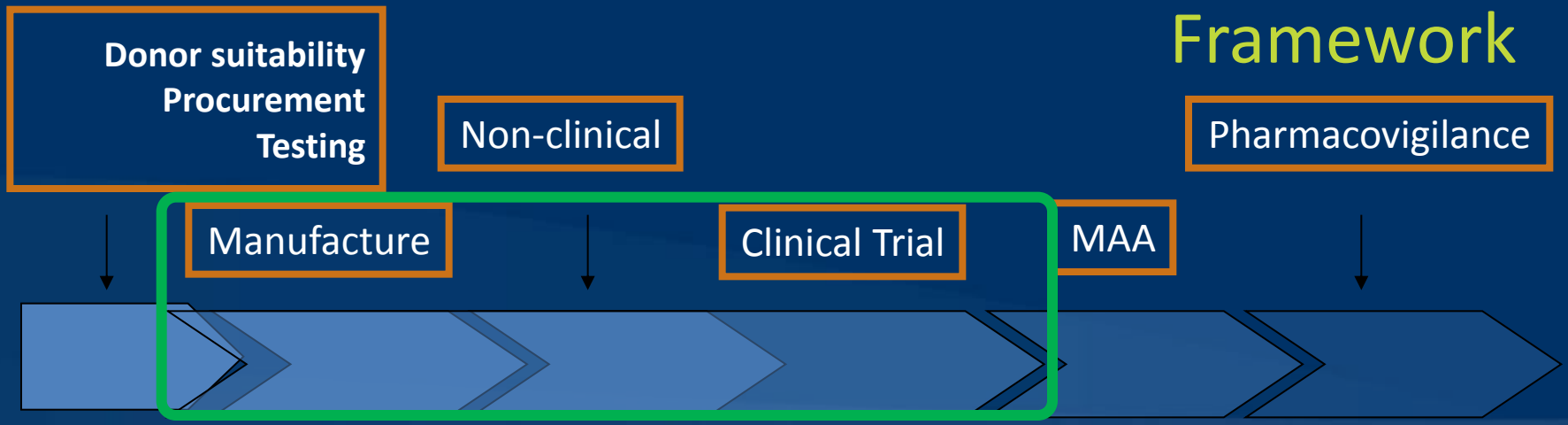
General Comments

- Regulation according to EU regulation
  - **Reg/1394/2007/EC on Advanced therapy medicinal products**
- Because of the huge potential variation in product type, “one size fits all” is not applicable.
  - The amount of data required to proceed FIM will vary according to product type, extent of processing, anticipated MoA and the benefit –risk balance for the intended indication.
- Risk based approach is recommended
  - GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS (EMEA/CHMP/410869/2006)
  - Draft guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products(EMA/CAT/CPWP/686637/2011)

Regulation

- Human Medicinal product
  - Biological product
    - Advanced Therapy Medicinal products -**Somatic cell therapy medicinal products**

Framework



Tissues and Cells
Dir/2004/23/EC
Dir/2006/17/EC
Dir/2006/86/EC

Medicinal Product
Dir/2001/83/EC
Dir/2009/120
Dir/2001/20/EC
Reg/1394/2007/EC **on Advanced therapy medicinal products**
Dir/2003/94/EC

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Clinical studies - Quality

- **Starting point**
  - Guideline on the requirements for Quality documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (*EMA/CHMP/BWP/534898/2008)*
    - Although ATMPs are not in scope , the guideline represents the expectation of the regulators regarding biotechnology products
- Guideline on cell based medicinal products (EMEA/CHMP/410869/2006)
- Guidance for FDA Reviewers and Sponers: Content and Review of Chemistry, Manufacturing, and Control Information for Human Somatic Cell Therapy Investigational New Drug Applications, April 2008

Main topics

- IMPD (Investigational Medicinal Product Dossier)

  or Equivalent IND
- GMP
- Issues of concern

Quality Issues

- IMPD (Investigational Medicinal Product Dossier)

  or Equivalent IND
- GMP
- Issues of concern

IMPD

- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004)
- ATMPS - Drug Substance vs. Drug Product: The distinction is not always clear.
  - **It is important to set out in the IMPD how this distinction is made.**

Quality Aspects

- IMPD (Investigational Medicinal Product Dossier)

  or Equivalent IND
- GMP
- Issues of concern

GMP

- Manufacturer(s)must comply with the principles of GMP
  - Inspection - Phase III
  - Declaration of compliance –Phase I + II
- Directive 2003/94/EC- laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

  - Annex 13 to volume 4 Eudralex - Investigational Medicinal Products
  - Annex II to volume 4 Eudralex - Manufacture of Biological Active Substances and Medicinal Products for Human use
  - Annex I to volume 4 Eudralex Annex 1-Manufacture of Sterile Medicinal Products

  - **תקנות הרוקחים (תנאי ייצור נאותים לתכשירים) תשס"ט-2008**
  - **נוהל יצור וייבוא תכשיר ניסיוניים במדינת ישראל (EX-012/01)**

Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2.

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, ATMPs immunosera,	Collection of plant, organ, tissue or fluid[9]	Cutting, mixing, and / or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB[10], WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotech-nology - fermentation/ cell culture	Recombinant. products, MAb, allergens, vaccines Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and / or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins, ATMPs	Master and working transgenic bank	Collection, cutting, mixing, and / or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting[11]	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid[12]	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human and / or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells[14]	Manufacture vector[13] and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or cell stock	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells[14]	Establish MCB, WCB or cell stock	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells[14]	Initial processing, isolation and purification, establish MCB, WCB, primary cell stock	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill

Increasing GMP requirements

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Increasing GMP requirements

annex II

Intersection Blood/Tissues/Cells and GMP

Tissues and Cells

- Donation
- Procurement
- Testing

- Processing
- Storage

→ **ATMPs GMP**

- Manufacture

Responsible person

Qualified person

Heterologous use and GMP

- **Scenario**: ATMP definition applies - heterologous use of a non-substantially manipulated product

The GMP aspects:

- Product definition (specifications)
- Release testing
- Release by Qualified Person
- Stability
- QC including sterility and environmental control

Unique Features

- Sterilization of the finished product can not be achieved
- Temperature sensitive
- Release testing - sometimes limited
  - **Limited sample sizes**
  - **Short life time**
  - **Availability of potency test**
  - **Microbial purity**

Tight Control strategy and tests throughout manufacture at early stages of development

⇒ Safety, Consistency

Quality Issues

- IMPD (Investigational Medicinal Product Dossier)

  or Equivalent IND
- GMP
- Issues of Concern

Issues of Concern

- Manufacturing Process
- Starting Materials
- Raw materials / excipients
- Process Validation
- SpecificationStability
- Tumorigenicity
- Traceability

Manufacturing Process (1)

- Definition of batch and scale
- Flowchart of all successive steps
- IPC
  - the results may be reported as action limits or preliminary acceptance criteria (should be reviewed when more knowledge is gained)

Manufacturing Process (2)

- **Potential risk of contamination**
  - Manufacturing steps should be conducted aseptically
  - segregation of autologous materials obtained from infected donors
    - the robustness of the control and test measures put in place for these source materials should be ensured.

Starting Materials (1)

- Variability in quality and/or composition may be unavoidable and this should be explained in the context of being “fit for purpose”.

Starting Materials (2)

- Donations
  - All human cells and tissues must be donated, procured and donor tested in accordance with EU Directives of quality and safety of human cells and tissues(Dir/2004/23/EC, Dir/2006/17/EC, Dir/2006/86/EC)
  - Where relevant, a rational programme for extended viral safety testing based on relevant factors (location, history of foreign travel) should be established.
    - For autologous therapies, the directive does not exclude the use of cells of virus positive individual. Information is important for: risks to employees, facility, cross contamination, increased expression of virus as a result of extended processing.

Starting Materials (3)

- Cell Banks
  - MCB - should be established prior to the initiation of phase I trials.
  - WCB - may not always be established prior to the initiation of phase I
  - The generation and characterization of the cell banks should be performed in accordance with principles of ICH guideline **Q5D** (Derivation and Characterization of Cell substrate used for Biotechnological/Biological products)
    - Adventitious agents
    - Cell substrate stability (including PDL)
    - Tumorigenicity
  - The principle of **ICH Q5A** (Viral safety evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin) should be applied, but it should be kept in mind that **cells tissues become the IMP**.

Raw Materials

- The sourcing of a Pharmaceutical grade material for ATMPs manufacturing is not always possible and therefore challenging
  - Usage of non pharmaceutical grade (research grade) should be justified
  - Description of their quality control should be provided
  - Information demonstrating that materials meet standards applicable for their intended use should be provided.
  - Summaries of adventitious agents safety information for biologically-sourced materials should be provided.
- Collaborating CAT/BWP/EDQM on standardization of raw materials for production of ATMPs

Excipients

- Animal/Human Origin
  - Information regarding adventitious agents safety evaluation (e.g. sources, specifications, description of the testing performed) and viral safety data should be provided.
  - Compliance with the TSE guideline (EMA/410/01, current version) should be documented.
  - If human albumin or any other plasma derived medicinal product is used as an excipient, information regarding adventitious agents safety evaluation should follow the relevant chapters of the Guideline on Plasma-Derived Medicinal Products (CPMP/BWP/269/95). If the plasma derived component has already been used in a product with MA then reference to this can be made.
- Specifications
  - For non-compendial excipients, the in-house specifications should be justified.

Process validation (1)

- Process validation/evaluation data should be collected throughout the developement
- Process establishment and validation can be done using cells from healthy donors.

- BUT verify sufficiently with patient material PRIOR to initiation of clinical trials, because
  - The characteristics of Patients‘ cells might differ → i.e. degree of adherence, expression of markers
  - Impact on critical product parameters
  - Impact on dose

Process validation (2)

- Validation of aseptic process (Simulation of aseptic manufacturing)
  - validation of sterilizing processes should be of the same standards as for products authorized for marketing.

Specifications (1)

- The following tests are mandatory:
  - **Identity** } Clear evidence of identity and purity of cell population
  - **Purity** } should be available before FIM
  - **Potency** **(Biological activity)**
    - Some evidence of relevant biological functionality
    - Marker based assays + functional assays
    - Should be related to clinical response
    - In place As Soon As Possible and as a must before phase III (usually required before)
    - To improve the ability of linking the functional quality of cells from each study and maximizing the relevance of the information gained.

Specifications (2)

- **Sterility**
  - IMP may be released before final sterility testing result
  - May be released on the basis of rapid methods (validated)
  - Parallel pharmacopoeial testing is expected for post release confirmation of product microbiological quality
    - PhEur 2.6.27. MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS2.6.27. MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS
  - An action plane/procedure should be developed in conjunction with clinical investigator(s) in the event that positive results are received after the product has been administrated to a patient
- **Endotoxins**

Specifications (3)

- Impurities - upper limits
- Product characteristics:
  - that are not completely defined at a certain stage of development,
  - or for which the available data is too limited to establish acceptance criteria

such product characteristics could be included in the specifications, without pre-defined acceptance.

Impurities

- Process related impurities and product related impurities should be addressed.
- Quantitative information on impurities should be provided including maximum amount for the highest clinical dose.
  - For certain process-related impurities estimation of clearance may be justified.
  - In case only qualitative data are provided for certain impurities, this should be justified.

Analytical procedures

- The analytical methods should be described for all tests included in the specifications.
- Validation
  - **phase I**
    - **suitability of the analytical methods used should be confirmed. The acceptance limits and the parameters for performing validation should be presented in a tabulated form.**
  - **Phase II/III**
    - **A tabulated summary of the results of the validation carried out should be provided. It is not necessary to provide a full validation report.**

Tumorigenicity

- Tumorigenicity assessment
  - **Must be investigated prior to FIM**
  - **Must be performed with cells at the limit of routine cell culturing or beyond.**

Stability

- Stability studies should provide sufficient assurance that the IMP will be stable during its intended storage period.
- Hold times and storage conditions for process intermediates should be justified and supported by data.
- Shipping conditions
  - It is advisable, prior to starting of FIM study, to conduct some studies confirming the ability of proposed transport containers to maintain critical conditions.

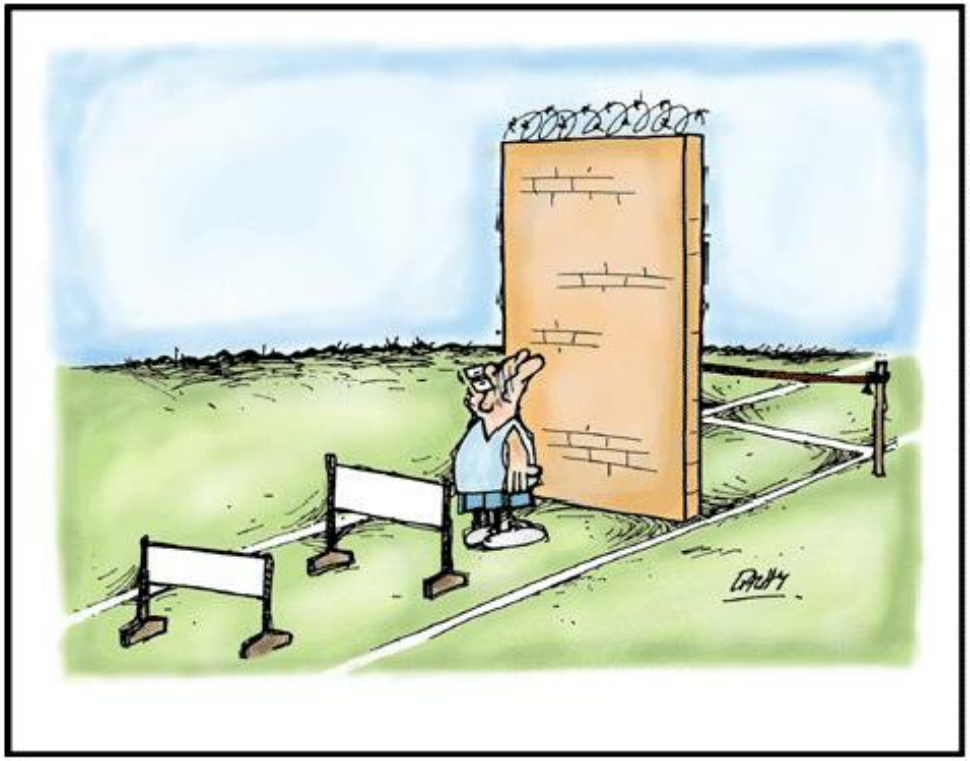
Product Traceability – Coding System

- A system connecting the required traceability from cell donation and procurement to the manufacturer and user .
  - At the tissue establishment: link between donor and donation
  - At the manufacturing site: link between donation and product.
  - Hospital/practice: link between product and recipient .
  - The systems should allow full traceability from donor to recipient through **anonymous coding** systems.

Final Remarks

- No compromise on safety issues
  - Sterility, viral safety, impurities, certain characteristics
- Quality attributes to control the IMP are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes, while process validation is incomplete.
- Upcoming guideline
  - **Reflection Paper on Investigational CBMP**
    - **Quality and non-clinical issues at various stages of development**
    - **Minimal Quality requirements for FIM clinical studies**

Challenge: Balanced view



תודה על ההקשבה

Hurdles should neither be too high…

…nor too low.