Requirements for CAR-T cells to enter first-in-human studies: view from a consultant in regulatory affairs

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Agenda

- The Role of the Regulatory Consultant
- Scientific Advice
- Regulatory Context of CAR-T Cell Development
- Common Issues/Challenges
  - Pharmaceutical Quality/CMC.
  - Non-clinical
  - Clinical

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The Role of the Regulatory Consultant

- Generally understands and shares the view of the regulators.
- Receives all details on the project from the client.
- Performs in depth project/gap analysis.
- Tailors a product-specific development program, which takes into account:
  - The regulatory guidelines/requirements.
  - Knowledge from previous projects/regulatory interactions.
  - The client's specific needs.
- Organizes Scientific Advice with the client to ensure acceptance of the development program from regulators.

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Types of Scientific Advice

- **The Innovation Task Force provides a forum for informal dialogue between EMA and developers of ATMPs in the early stages of the medicine development process. Registered SMEs may approach the SME office to request a briefing meeting to discuss their planned regulatory strategy.**
  - **However, EMA is not involved in the approval of clinical trials.**
  - **Advice may be less tailored to Phase I requirements.**
  - **Only offered to Small or Medium-sized Enterprises (SMEs).**

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Types of Scientific Advice

- **Recommended format to support smooth CTA approval:**
- **National Scientific Advice**
  - **Discuss directly with regulators involved in the approval of your Clinical Trial Application (CTA), if conducted in the same country/ies.**
  - **Face to face meeting, lasting 1.5-2 hours.**
  - **Subjects to be discussed pre Phase I: CMC, non-clinical and/or clinical.**
  - **Obtain non-binding recommendations in writing (minutes).**
  - **Costs: usually < 5,000,- €.**
- **Granzer RC&S conducts approximately 200 such meetings per year.**

Important New Draft Guidance Document

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/CAT/852602/2018
Committee for Advanced Therapies (CAT)

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

Draft

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Important New Draft Guidance Document

- **Guideline is multidisciplinary and addresses CMC well as non-clinical and clinical development of ATIMPs.**
- **Relevant for clinical development of CAR-T cell products.**
- **Strong Differentiation between exploratory and confirmatory (=pivotal, MAA-supporting) clinical trials, especially regarding pharmaceutical quality/CMC.**
  - **CAVE: In very rare (Orphan) conditions, Phase I studies tend to evolve into 'Phase I/II/III' studies by cohort expansions etc. -> needs to be reflected in CMC**
  - **Pharmaceutical quality must be precisely documented from the beginning, to allow use of data from early trials**

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Challenges and potential pitfalls from a CMC perspective

- Definition of active substance and starting material
- Raw material
- Manufacturing process validation
- Specifications
- Analytics validation
- Comparability

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Definition of starting materials

- **Why is this important?**
  - The **same level of information** that is needed for active substance should be provided
  - The establishment of bacterial/cell/virus seed or bank(s) is expected for starting materials which are bankable.
  - GMP standards (as e.g. listed in the Guidelines for GMP for ATMP) should be applied *from the cell bank systems used to produce the starting materials*
- **Starting materials in typical CAR-T cell products:**
  - unmodified cells
  - the viral or non-viral vectors and any other nucleic acid and/or protein used in the genetic modification of the cells
  - viral vectors, plasmids, recombinant proteins and recombinant mRNA, the components to produce them (e.g. plasmids, cells)

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Example: SLAMF7 CAR-T cells

Active substance= gene modified autologous cells carrying a CAR (targeting SLAMF7 on MM cells)

Starting materials

- Autologous patient cells
- Minicircle DNA carrying the CAR construct
- mRNA coding for gene-modifying enzyme transposase
- and the components to produce them
  - For mRNA the template DNA (and the MCB to produce it)
  - For minicircle DNA the producing MCB

Following the wording of the EU GMP for ATMP guide, GMP would apply:

from the cell banks used to manufacture DNA (which would be the template for the mRNA)

as well as from the cell banks used for production of minicircle DNA.

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Raw materials

- The manufacturing process of Cell-based IMPs usually does not include terminal sterilisation, purification steps, viral removal and/or inactivation steps
- Therefore, stringent sourcing requirements and acceptance requirements
- Avoiding contamination, minimising variability of starting and raw materials
  - Reference to quality standards (e.g. compendial monographs or manufacturer's in-house specifications)
  - Information on the quality and control of non-compendial materials
  - Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) are suitable for their intended use
  - While raw materials should be of pharmaceutical grade, in some cases, only materials of research grade are available: risks should be understood

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Manufacturing validation

- The manufacturing process for ATIMPs is not expected to be validated for early clinical trials
- Prior to the FIH clinical
  - Process characterisation/ evaluation summaries
  - Validation of the aseptic process
  - Validation of the viral removal/inactivation steps
- For the confirmatory clinical trial
  - to be used in support of a marketing authorisation process
  - Validation is required to demonstrate that the manufacturing process of the ATIMP ensures consistent production.

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Specifications

- **Tests and defined acceptance criteria are expected for quantity, identity, purity, microbiological assays and biological activity (potency assay)**
- Can be acceptable to have reduced testing at one level provided an exhaustive control is performed at another
- Limited amount of final product might not allow for extensive release testing
  - In such circumstances it may be possible to rely on intermediate product release criteria
  - Provided these have been shown to be representative of the final product based on sufficient process evaluation/ validation data
- In some specific cases (for example due to the short shelf-life), it may be needed to release the drug product batch prior to all results of specification testing is available
  - Approach needs to be justified and supported by performed risk analysis
  - The procedure that is taken when out of specification test results are obtained after the release of the product need to be described.

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Validation of analytical methods

- For exploratory clinical trials, the **suitability** of the analytical methods used should be confirmed and preliminary acceptance limits defined
- Validations of sterility and microbial assays, as well as replication competent virus testing are required whatever the clinical trial phase
- For confirmatory clinical trials, the guidelines applicable to Marketing Authorisation Applications do apply. Validation of analytical methods for batch release and stability testing is expected

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Comparability

- Improvements and optimisations are considered as normal development work
- Complex and dynamic nature of AMTPs presents a challenge for the evaluation
- Biological characterisation and the potency assay(s) are the most important parameters to perform comparability on quality grounds
- During the confirmatory clinical studies
  - expected to conduct confirmatory clinical trials with a product based on a mature manufacturing process
  - introducing changes to the manufacturing process and the final product should be avoided
  - comparability issues may impact the acceptability of the data.

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Non-clinical Challenges

- **Target!!!**
  - **Very high potency of CAR-T cells requires detailed information on the nature and distribution of the target.**
  - **Sources of information (Reference products, literature, own data)**
  - **Transferability of information**
- **Relevant species and extent of in vivo characterization**
  - **Material used in non-clinical studies**
  - **Use of homologous models**
- **Environmental Risk Assessment**

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Clinical Challenges

- General trial design
- Definition of patient population
- Starting Dose and dose escalation steps

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Thank you!

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