Navigating early stage interactions with global regulatory authorities

Objectives

1. Cell and gene therapy product classification
2. Nonclinical considerations and when to engage?
3. How to gain early regulatory advice and address early engagement meetings: MHRA, EMA, and FDA
4. Engineering T cells to target the tumour vasculature: Case study
5. Q&A - with the MHRA

Cell and gene therapy product classification

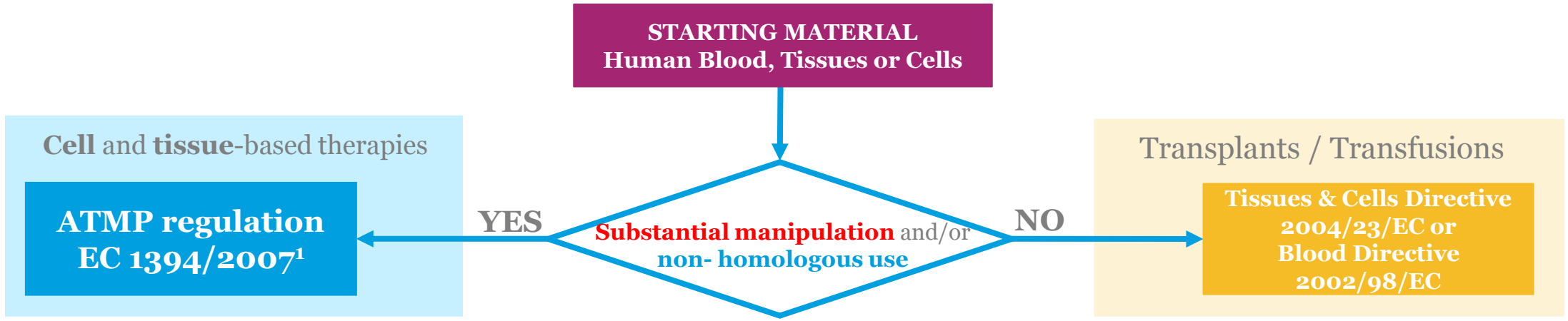
Dr Patrick Ginty

Classification:
Understanding your cell and gene therapy product

- In Europe, cell and gene therapies regulated as medicines are defined as Advanced Therapy Medicinal Products (ATMPs) as described in Regulation 1394/2007 and the revised Directive 2001/83/EC and are regulated at both national level and by the European Medicines Agency (EMA)
- In the US, cell and gene therapy products are biological products regulated within the FDA's Center for Biologics Evaluation and Research (CBER)
- The EMA provides a procedure for classification of ATMPs in Europe*
- The US FDA does not have an analogous classification procedure, but relies on the definitions of biological products (including cell and gene therapy products) within the Public Health Service Act (PHSA) and the Federal Food Drug and Cosmetic Act (FDCA) and relevant parts within title 21 of the code of federal regulations (CFR) e.g. Part 1271 covering cell and tissue based products

* Many national regulatory agencies in Europe will also provide classifications but the procedures may vary and diverge whereas the EMA provides a single classification that applies across Europe

When do cells and tissues become ATMPs



Substantial manipulation* (Manufacture)

Manipulated during manufacturing process so that biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function

Non-homologous Use[2] (Function)

Cells or tissues **not intended to be used for the same essential function(s) in the recipient and the donor** (may relate to function and/or location)

* Excludes: cutting, grinding, shaping, centrifugation, soaking in antibiotic/antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering…

1. Definition of ATMPs also includes gene therapies with or without cellular or tissue components
2. US FDA terminology from 21 CFR Part 1271 (significant overlap with EU definitions)

ATMP classification types (EU)

CATAPULT Cell and Gene Therapy

Gene Therapy Medicinal Product
Annex I, Part IV, 2.1 to Directive 2001/83/EC

Recombinant nucleic acid administered with a view to regulating, repairing, replacing, adding or deleting genetic sequence

Therapeutic, prophylactic or diagnostic **effect relates directly to the recombinant nucleic acid** sequence it contains

e.g. Glybera®

Somatic Cell Therapy Medicinal Product
Annex I, Part IV, 2.2 to Directive 2001/83/EC

Contains or consists of cells or tissues used **for prevention, diagnosis and/or treatment of diseases via pharmacological, immunological or metabolic** actions

e.g. Provenge®

Tissue Engineered Medicinal Product
Article 2.1.b in Regulation (EC) No. 1394/2007

Contains or consists of cells or tissues administered with a view to **regenerating, repairing or replacing** a human tissue

e.g. Holoclar®

Contain as an integral part of the product a **medical device**
e.g. MACI®

Combined ATMP
Article 2.1.d in Regulation (EC) No. 1394/2007

Advanced Therapy Classification at the EMA

- Process established in particular to clarify questions on borderline classification areas
- Conducted by the Committee for Advanced Therapies (CAT)
  - Not obligatory (but advisable) and free
  - Procedure = 60 days
- Developers can apply at any point during product development (even when you have no data) but the recommendation should be based on a defined product i.e. not on a scientific 'concept'
  - Can submit a follow-up request using the same procedure if new data comes to light.
- EMA publishes non-confidential summaries of previous ATMP classifications online

Benefits for early development:

- First opportunity to engage with regulators and provide product "visibility"
- Position the product in the ATMP category and clarify the applicable regulatory framework(s)
- Can help with clinical trial applications (national agencies will be made aware of classification so it will help them to identify most relevant criteria and procedure to apply)
- Opens the door to other incentives designed for ATMPs

How to apply

To **submit an application** for ATMP classification, complete:

- pre-submission request form (select 'ATMP-ATMP classification' in the drop-down menu);
- ATMP-classification request form and briefing information (including background information on scientific, legal, regulatory and medical aspects).

Return both forms to advancedtherapies@ema.europa.eu.

Further information can be found here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000296.jsp&mid=WC0b01ac058007f4bc

Summary of briefing information required

1. Description of active substance:
   - Starting materials
   - Additional substances such as scaffolds, matrices, biomaterials
   - Medical device or active implantable medical device
2. Finished Product:
   - Qualitative and quantitative composition, pharmaceutical form
   - Mode of Administration
3. Mechanism of Action
   - Claimed MoA (important if product has a combination of mechanisms)
   - Indication
4. Summary of development status
   - Key elements of manufacturing
   - Outline of clinical / non-clinical data to date relevant to the classification

Classification guidance

Challenges and points to consider when classifying your product:

- Product must contain an active substance of biological origin
- Where products meet the definition of a GTMP and a TEP or SCTMP, the product would be regulated as a GTMP
- GTMP definition does not include vaccines against infectious diseases
- Many borderline areas, especially for GTMPs and combined products – use the guidance and precedent

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

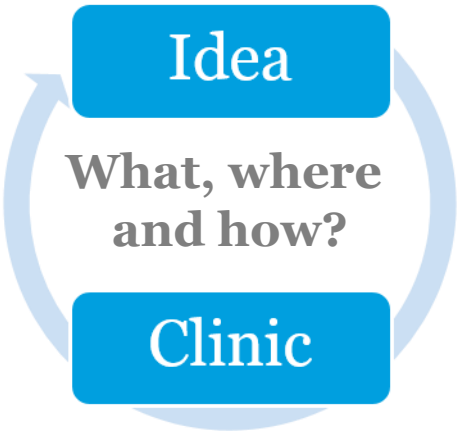
21 May 2015
EMA/CAT/600280/2010 rev.1
Committee for Advanced Therapies (CAT)

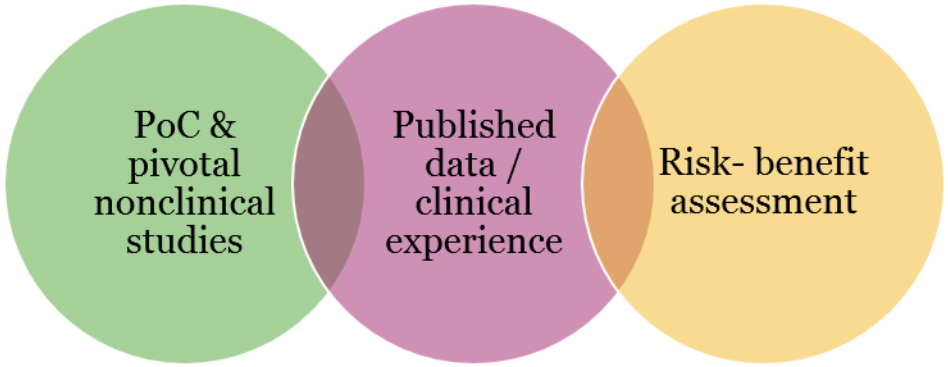
Reflection paper on classification of advanced therapy medicinal products

Nonclinical considerations and when to engage?

Dr Michaela Sharpe

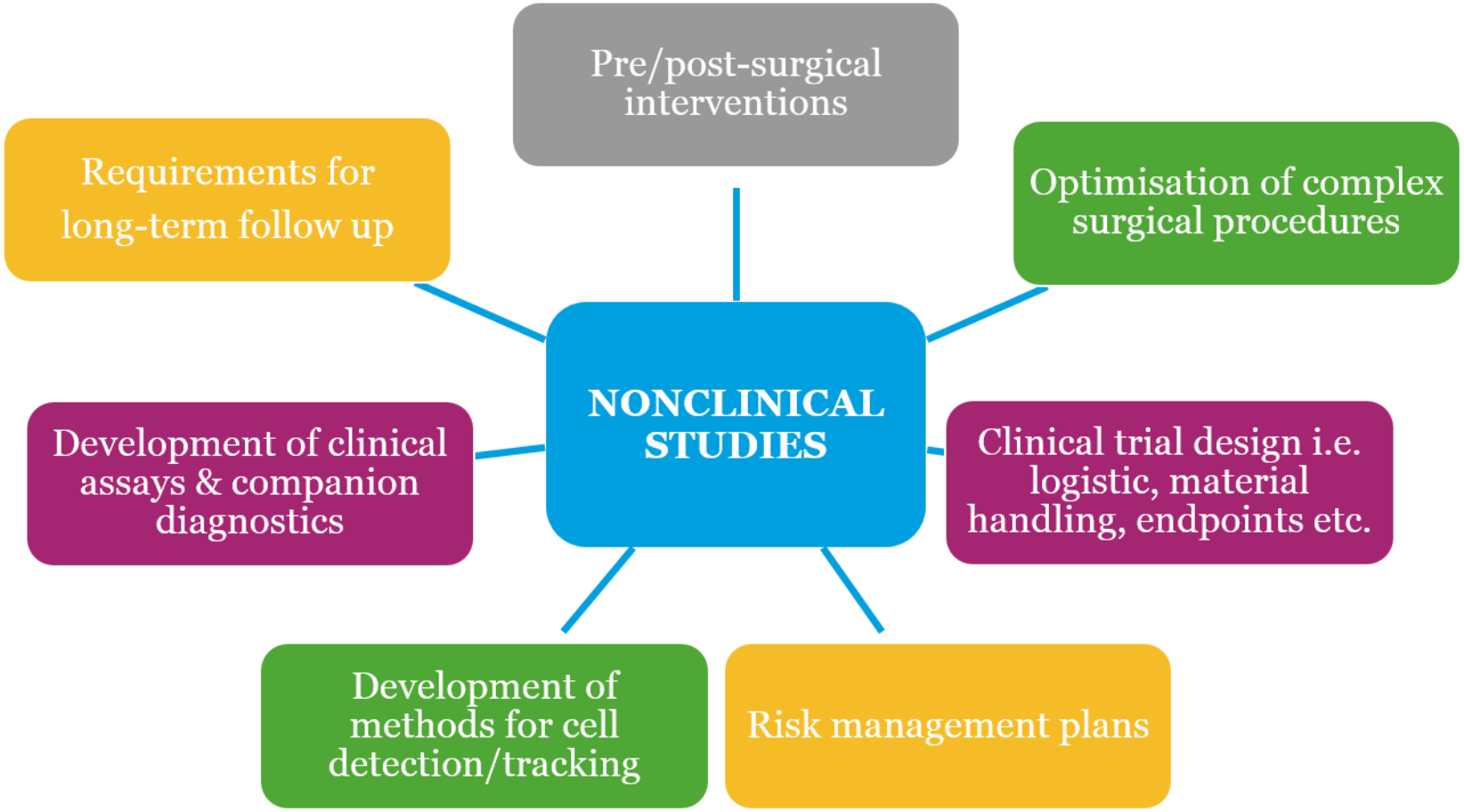
Goals of the preclinical programme





- Establishment of **biological plausibility**.
- Identification of biologically active **dose** levels (if feasible) and clinical dosing levels.
- Establishment of **feasibility** and reasonable **efficacy** of the investigational product.
- Identification of **physiologic parameters**/endpoints that can be used for clinical monitoring.
- Provide **safety** information to support translation into clinical trial

How nonclinical studies can inform plans for a FiH?



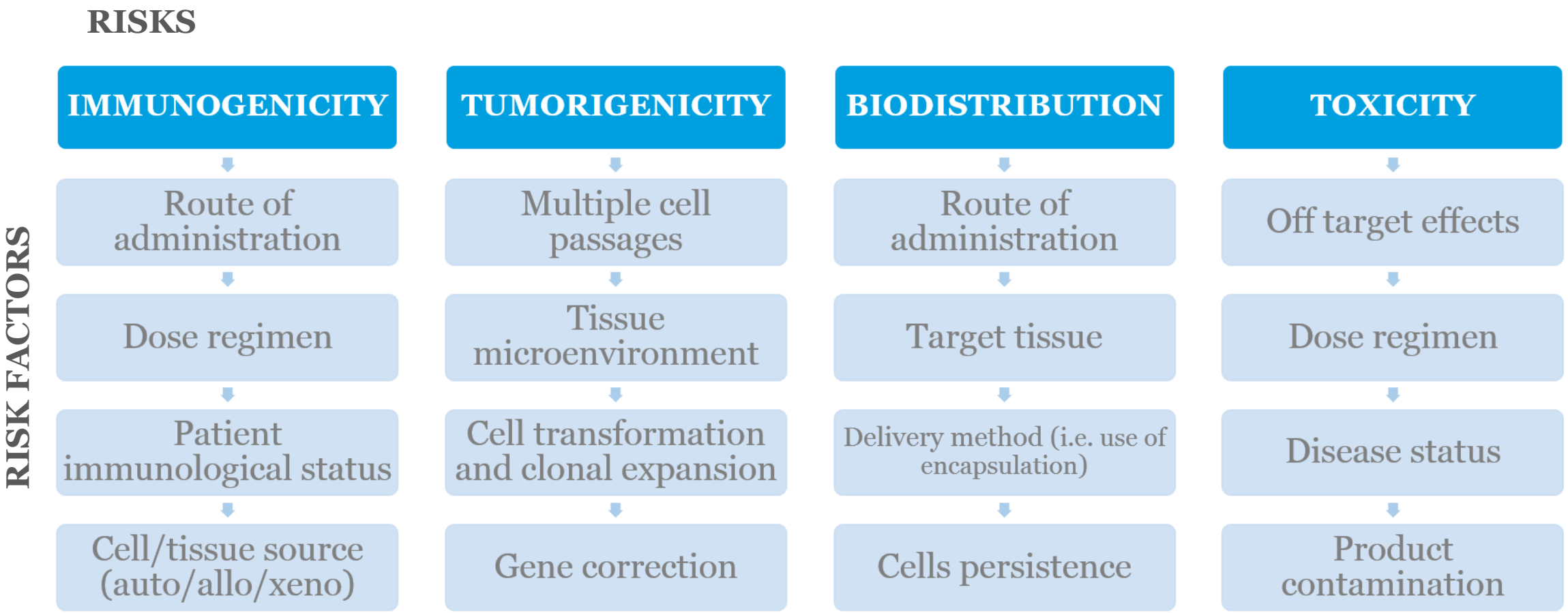
ATMP's: Common preclinical programme questions

- What are current regulatory expectations?
- What extent of preclinical evidence is required to support a FiH?
- What type of safety/toxicology studies shall be conducted?
- What animal/s model/s shall be used to support efficacy?
- Can we extrapolate a clinically relevant dose?

NO ONE SIZE-FITS-ALL STRATEGY

THE RISK-BASED APPROACH

ATMP potential risks



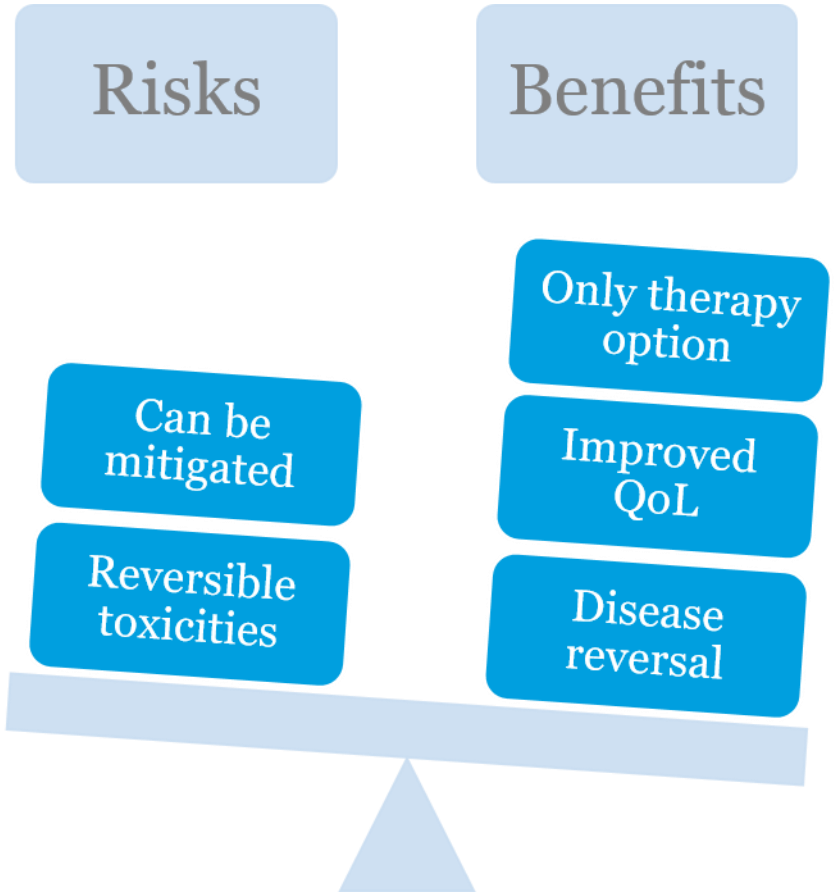
Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied for Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011).

Safety - The risk-based approach

- **Strategy** to determine the extent of preclinical data required to support product clinical translation
- Assess **potential risks** associated with the clinical use of an ATMP and **relative risk factors** with respect to quality, safety and efficacy
- Risk - “any potential unfavourable effect attributed to clinical use of the product”
- Risk factor - “a qualitative or quantitative characteristic related to the quality, biological activity, and clinical application of the cell therapy contributing to a specific risk ”
- **On-going process** starting at the beginning of development and that matures over time, as the knowledge of the product and its characteristics increases

Finding a balance

- Safety assessments are **not absolute**
- Preclinical studies will only ever be **predictive**
- Consider **early engagement** with **regulatory agencies**:
  - To understand their potential concerns and current expectations
  - To discuss potential, product-specific nonclinical challenges
  - To ensure appropriate design of nonclinical program to support FiH
  - To prevent unnecessary studies



How to gain early regulatory advice and address early engagement meetings

Dr Patrick Ginty

Early engagement with regulators

- Cell and gene therapy products are complex and provide unique regulatory challenges when compared to more conventional medicines
- Global regulatory authorities acknowledge that the legislation and guidance cannot keep pace with both the rapid development of the science and the innovative nature of these products
- This has been a key driver for the formation of a number of new early-stage development advice procedures
- Early Engagement creates an opportunity for:

  - **Developers** to engage with regulators at an early stage to gain feedback on major regulatory challenges for reaching the clinic / market and inform decision making on development plans

  - **Regulatory authorities** to gain access to new innovations and products at an early stage and provide advice that will help clarify the development pathway and / or assess the suitability of the planned approach

- Focus here is on three regulatory agencies: UK, EU and US

Medicines and Healthcare products Regulatory Agency (MHRA) Innovation Office

Medicines & Healthcare products Regulatory Agency

- The MHRA Innovation Office (IO) provides a single point of access to free and expert regulatory information, advice and guidance that helps organisations of all backgrounds and sizes, including SMEs and individuals to develop innovative medicines, medical devices or novel manufacturing processes
- The office is also the home to The **Regulatory Advice Service for Regenerative Medicine**, which responds to queries specifically about regenerative medicines
- RASRM provides access to experts from Health Research Authority (HRA) Human Fertilisation and Embryology Authority (HFEA), Human Tissue Authority (HTA) and the National Institute for Health and Care Excellence (NICE)
- The IO also provides access to expertise and experience from specialists; the Clinical Practice Research Datalink (CPRD) and the National Institute for Biological Standards and Controls (NIBSC)

MHRA IO – what to expect

Medicines & Healthcare products Regulatory Agency

- The IO provides regulatory advice, this is more general and at an earlier stage than scientific advice but MHRA will refer developers to the more formal scientific advice process if appropriate
- The advice service is intended for innovative medicines e.g. ATMPs, manufacturing processes, etc. and not established technologies
- Go early, but the key is to provide concise and informative content, conceptual is fine at an early stage but the more you put in, the more you get out!
- The office is more appropriate to developers of ATMPs in the pre-clinical phase as clinical stage development programmes are more likely to require scientific advice
- The approach is informal, so provides an easy environment in which to gain valuable regulatory advice for those with minimal experience when approaching regulatory agencies

MHRA IO – How to apply

Medicines & Healthcare products Regulatory Agency

- Complete the Innovation Office enquiry form or send an email to innovationoffice@mhra.gov.uk.
- After submitting your query, you will receive a single, consolidated, considered and confidential response
- This response (email) will contain regulatory information, advice and guidance, helping you to work to clear and predictable timelines
- Intended response time is 20 working days, depending on the complexity of the query and the availability of key experts and specialists
- In some cases a **regulatory advice meeting** may be proposed by the MHRA Innovation Office to discuss the details of the query

EMA's Innovation Task Force (ITF)

- The ITF is a multidisciplinary group that includes scientific, regulatory and legal competences.
- It was set up to ensure coordination across the Agency and to provide a forum for early dialogue with applicants on innovative aspects in medicines development
- Similar approach to the MHRA IO, targeting developers of early stage innovative medicines and technologies
- ITF briefing meetings provide a forum for early, informal dialogue on medicines innovation.
- They cover regulatory, technical and scientific issues arising from innovative medicines development, new technologies and borderline products – but ITF briefing meetings are intended to be much earlier than when one would normally seek scientific advice

EMA's Innovation Task Force (ITF) -what to expect

- The objectives of the ITF are two-fold:

1. for EMA to help clarify questions regarding the road to market of innovative medicines and,
2. to help ensure EMA awareness and preparedness for assessment of the most recent developments in innovative medicine

- The informal scientific discussions are led by experts from the Agency network, working parties and committees
- Meetings are free of charge and provide developers with a wide variety of expertise with experience in all aspects of centralised procedures for ATMPs

EMA's Innovation Task Force (ITF) – how to apply

- To apply for a briefing meeting, complete the application form https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines and e-mail it (Word format) to: **ITFsecretariat@ema.europa.eu**
- The EMA will then organise a brief telephone conversation to discuss your request before asking you to submit a **draft briefing document** to validate your request
- Prior to the meeting, send a final **briefing document** (max 30 pages) that could include the following information, as applicable (Annexes can be added as needed):
  - General background information.
  - Description of the technology or development method.
  - Composition of the product and description of the manufacturing process.
  - Description of the non-clinical and clinical development.
  - Presentation of the topics for discussion.

US FDA's INitial Targeted Engagement for Regulatory Advice on CBER ProducTs (INTERACT)

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- Previously known as pre-pre-IND meetings, an INTERACT meeting enables sponsors to obtain preliminary informal consultation with the Agency at an early stage of development prior to a pre-IND meeting
- Through an INTERACT meeting, sponsors can obtain initial, nonbinding advice from FDA regarding CMC, pharmacology/toxicology, and/or clinical aspects of the development program.
- The INTERACT program is also intended for such occasions when development of innovative investigational products introduces new safety concerns due to the unknown safety profiles resulting from the use of complex manufacturing technologies, innovative devices, or cutting-edge testing methodologies.

FDA INTERACT – what to expect

- INTERACT consists of one consultation on issues that a sponsor needs to address, often this is prior to moving forward with the submission of a pre-IND meeting request, such as choice of appropriate preclinical models or necessary toxicology studies
- An INTERACT meeting is not intended to take the place of a pre-IND meeting, which occurs prior to the submission of an IND to discuss the scope and design of planned initial studies, design of animal studies needed to support human clinical testing, and the format for the IND
- Prior to requesting an INTERACT meeting, a sponsor needs to have selected a specific investigational product or a product-derivation strategy to evaluate in a clinical study

FDA INTERACT – what to expect 2

- Timing is key with regard to gaining advice via INTERACT
- Questions regarding the adequacy and design of definitive toxicology studies and specific aspects of clinical study protocol design, such as inclusion and exclusion criteria = **out of scope**
- Advice related to the design of proof-of-concept or other pilot safety/biodistribution studies necessary to support administration of an investigational product in a FTIH clinical trial = **within scope**
- Further examples within the scope of INTERACT can be found at https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
- FDA recommend that sponsors review the following procedure: SOPP 8214, INTERACT Meetings with Sponsors for Drugs and Biological Products, which describes CBER's expectations for meeting requests and subsequent meeting packages

FDA INTERACT – how to apply

- INTERACT meetings requests should be forwarded to INTERACT-CBER@fda.hhs.gov
- Submission should include 1) a summary of the product and disease being treated, 2) information about the product development to date and future development plans, if appropriate and 3) questions the sponsor wishes to have addressed
- Sponsors will receive a response regarding the scheduling of their requested meeting from the responsible office within 21 calendar days of receipt
- Although CBER will do its best to hold INTERACT meetings within 90 calendar days of receiving requests, resource constraints may limit scheduling within this timeframe
- INTERACT meetings will generally be conducted via teleconference

Take home messages

- The approach of each agency is similar, but take note of subtle differences in scope and required content
- Consider the choice of agency in the context of scope e.g. national agencies in Europe may be better suited to non-clinical advice related to a FTIH trial, the EMA may be better for wide reaching development issues for ATMPs linked to centralised procedures
- Early interactions do not replace scientific advice and are not likely to be accepted for products close to or already, in clinical development
- Meetings are informal, but the manner in which they are conducted should be professional
- Meeting materials should be of high quality e.g. questions submitted should always be supported with a company position and suitable background information
- Keep the briefing materials concise; 25-30 pages is advisable

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