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October 29-30 Zurich

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Building the Bridge from Pre-Clinical to Clinical Studies: an Overview of the Regulatory Landscape

Rocio Mugica Nava (PharmaD, BSc)

- 23+ years in clinical research
- 15+ of expertise in Regulatory Strategy/submissions and Start-up in countries all around the world, across all phases of clinical development, numerous compound type and therapeutic areas

Agenda

Building the Bridge from Pre-Clinical to Clinical Studies: an Overview of the Regulatory Landscape

Gaining a comprehensive overview of the regulatory landscape when transitioning from pre-clinical to clinical studies, focusing on the investigational medicinal product (IMP) nature and its implications for regulatory submissions

Key operational considerations, including navigating complex regulatory frameworks and meeting the requirements of the EU Clinical Trials Regulations,

Exploring how advanced therapies, such as gene, cell, and tissue therapies, are reshaping regulatory strategies and driving innovation in the clinical trial process

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Medicine & Science Integrated with Strong Operational Infrastructure

- Advancing Science
- Methodological Rigor
- Medical / Therapeutic Depth

Small/Midsize Pharma Biotech

- CNS / Neuroscience
- Oncology
- Rare Disease
- CVM / Inflammatory Diseases

Early Phase
- Bioa Lab
- CPU

Culture of Accessibility to Subject Matter Experts and Executives

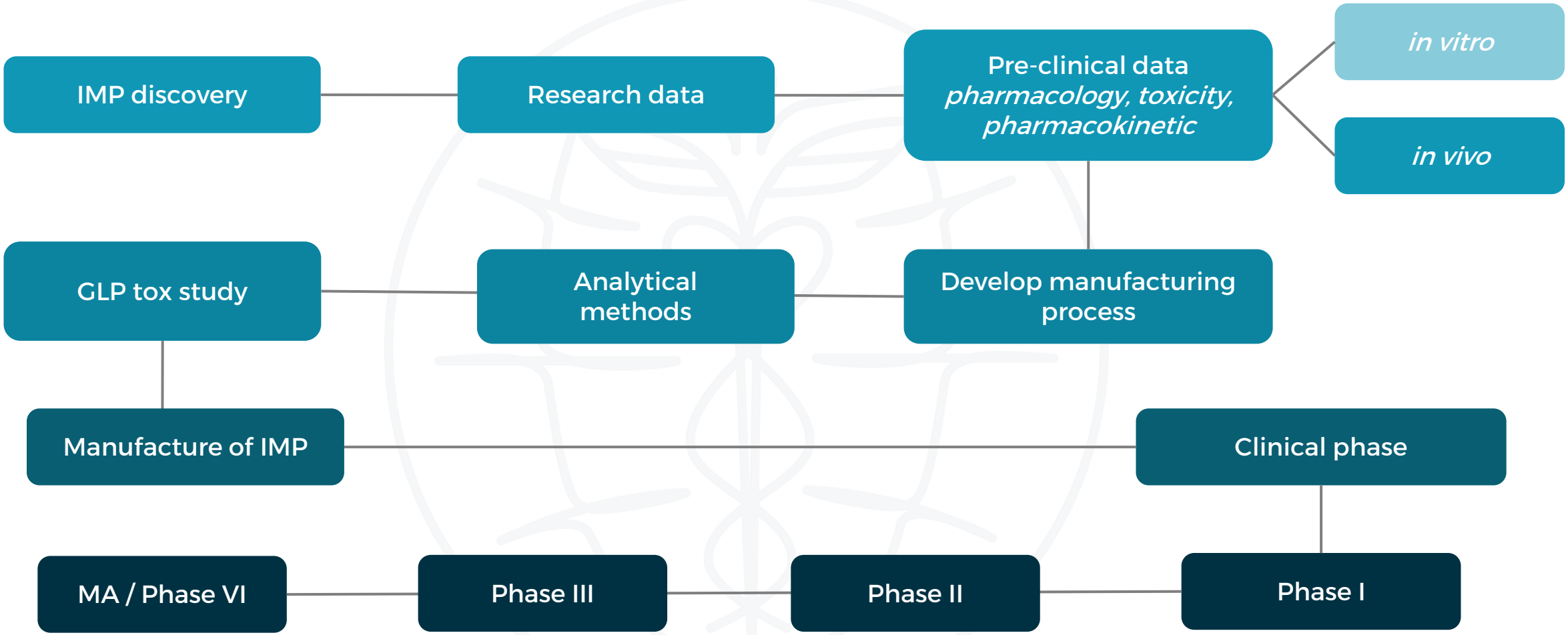
- Operational Acumen
- Reproduceable Delivery
- Partnership Mindset

Flexible Commercial Terms

- Over 3000 Local Experts
- 60 Countries; All Regions

Founded On Science, Focused On Patients And Fixated On Quality

Pre-clinical to Clinical pathway

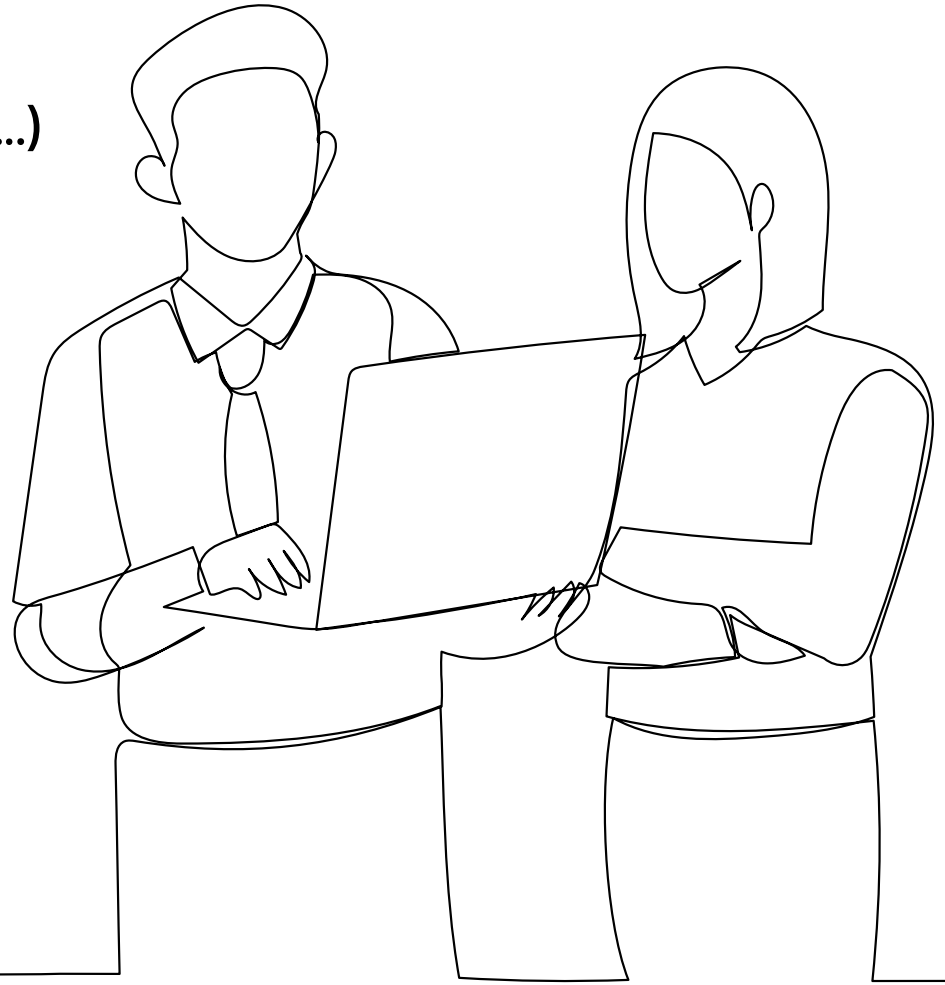


EMA: Non-clinical guidelines; EU Clinical Trials Regulation 536/2014

Scientific advice

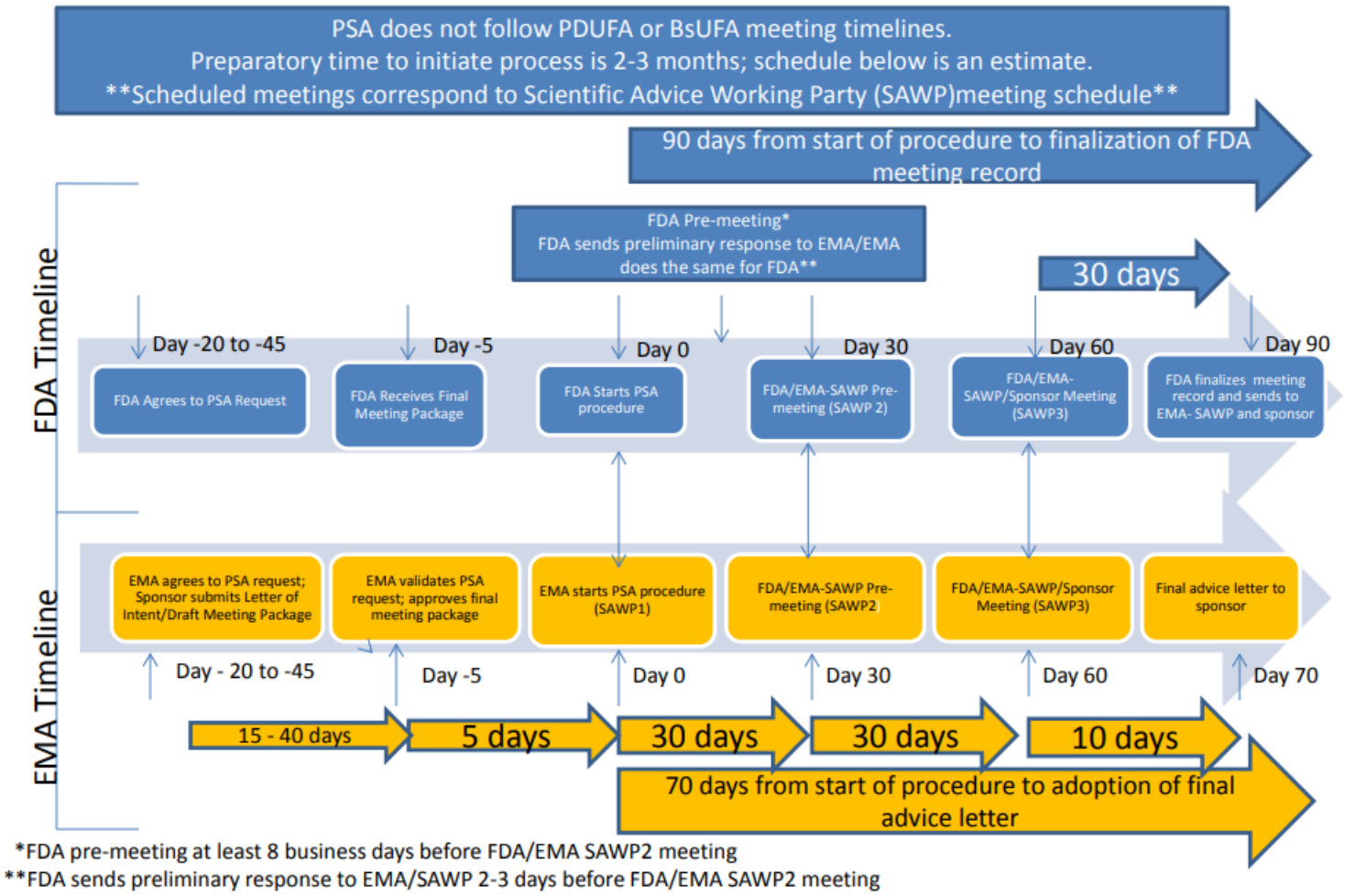
- EMA
- Parallel scientific advice FDA- EMA
- National Competent Authorities (BfArM, AEMPS, MHRA….)
  - Simultaneous national scientific advice (SNSA) pilot
- Pre-Clinical Trial Advice (pre-CTA) pilot

- Additional support from Regulators (EU)
  - PRIME
  - Orphan drug designation
  - CAT classification



Scientific advice – EMA-FDA

Parallel Scientific Advice (FDA-EMA)



*FDA pre-meeting at least 8 business days before FDA/EMA SAWP2 meeting

**FDA sends preliminary response to EMA/SAWP 2-3 days before FDA/EMA SAWP2 meeting

PSA Timeline Chart*

Day	FDA	EMA
Anytime	Sponsor submits informal request for Parallel Scientific Advice to FDA and EMA	
Day -20 to -45	FDA agrees to informal PSA request; Sponsor submits formal PSA request to FDA.	EMA agrees to informal PSA request; Sponsor submits letter of intent (formal PSA request) and draft package
Day 0 to -24		EMA reviews draft package; appoints Coordinator
Day -5	FDA receives final meeting package	EMA validates PSA request; approves final meeting package
Day 0	FDA PSA process starts	EMA PSA process starts (SAWPl)
Day 15-20	FDA pre-meeting	
Day 25-28	FDA sends preliminary responses to EMA	EMA sends preliminary responses to FDA
Day 30	Joint FDA/EMA meeting (SAWP2)**	Joint FDA/EMA meeting (SAWP2)
Day 60	Sponsor/FDA/EMA meeting (SAWP3)	Sponsor/FDA/EMA meeting (SAWP3)
Day 70 to 90	FDA issues final meeting record (day 90 for FDA)	EMA i.ssues final advice letter (day 70 for EMA)

- PSA does not follow PDUFA or BSuFA meeting tlmelines. Preparatory time to initiate process Is 2.3 months; schedule above Is an estimate. Scheduled meetings correspond to Scientific Advice Working Party {SAWP) meeting schedule.
- Best Practice: FDA and EMA develop a list of common issues/answers to questions. Both agencies send to sponsor preliminary common issues (EMA)/answers to questions (FDA). Sponsor sends in a revised proposal and meeting package prior to SAWP3.

Overview Regulatory Landscape

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Regulatory Processes

Risk Mitigation

IMP Nature

- ICH CTD M3 adaptation – IMPD: areas of focus FIH till Pivotal
  - Key: Tox & species significance, impurities, stability, manufacturing validation
  - ATMPs / GMOs / Combination products / delivery paths
- IMP – Import License depot & supply strategy
  - Auxiliary drugs/i.v. reactions control
- Stability stress – preservation conditions / vehicle /diluent/materials compatibility

Operational Considerations

- Countries participating
- Genome sequencing (DNA & RNA) – separate ICF
  - Genotyping – rule IVDR 3(i) class C
- Imaging – Methodologies (radiation/tracer/calibration)
- Pt consent/assent process – adaptation to specifics
- Pediatrics
  - Existing data
  - Juvenile tox studies / blood volume & frequency
  - PIP / ODD in EU status (SME)
- EU CTR 536/2014:
  - Strategic considerations/ Selection of RMS

EU Clinical Trials Regulation 536/2014

EU CTR went live on 31 Jan 2022

and mandatory after 31 Jan 2023

- Involves a single joint CA and EC submission for each participating country submitted via the EMA submissions portal (CTIS):
  - Single approval by each Member State covering both regulatory and ethical aspects
- EU CTR submission process consists of:
  - Part 1: Centralized submission of the study core documentation for approval and
  - Part 2: Individual country submission of all country specific documentation for the trial
- EU-wide approval of core docs package (Part 1): fewer country-specific versions
- Flexibility in submission procedures re Parts 1 and 2 parallel or in series (parallel recommended)
- 4 possible approval timelines: days 60, 75, 91, 106 or 156
- Whole process is coordinated by a Reference Member State (RMS)-sponsor requests
- Publication of some study docs mandated: data redaction/anonymization required
- Worldwide Pre-submission review of Protocol, IB and IMPD vs EU CTR Requirements

What we would need from Sponsors:

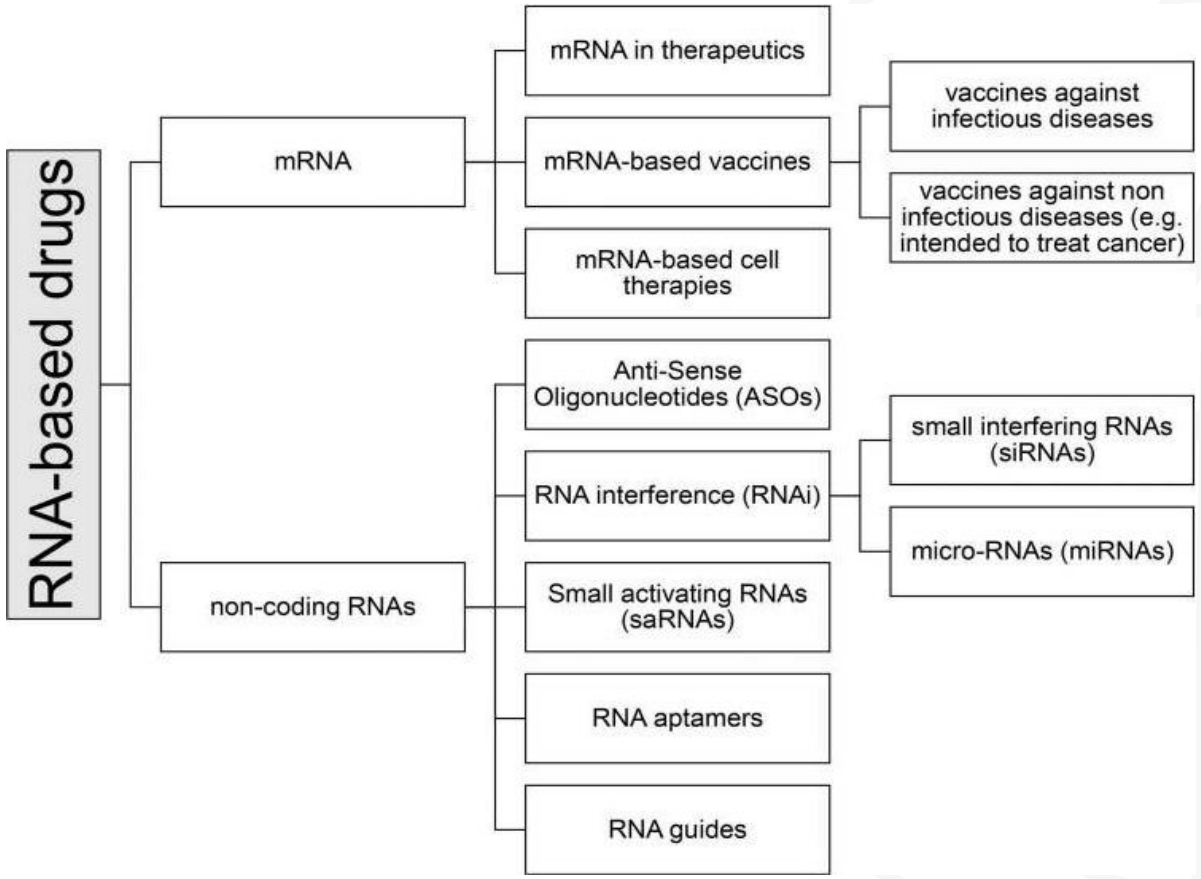
- Sponsor needs to register in CTIS (sponsor admin role) and then delegate to CRO additional users i.e., CT Admins/doc preparers etc. based on agreed SOW. WCT can assist.
- Sponsor to decide on organization-centric vs CT-centric approach
- All vendors and sites must be registered in OMS system
- Timely provision of all core docs i.e., protocol, IB, core ICF, IL docs etc.
- Close collaboration at the time RFIs have to be replied (12 calendar days as maximum)

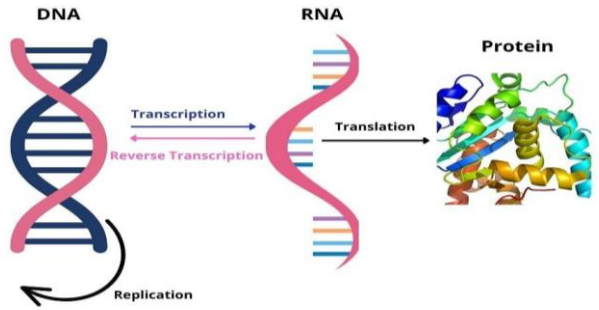
EU CTR submission - guidance

Allowed submission whilst ongoing evaluation of an application

Ongoing activity	Submission of an SM to Part I and Part II	Submission of an SM to Part I	Submission of an SM to Part II	Submission of a non-SM	Submission of an application for additional MSC
Initial application	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs	Not until a decision is issued by all MSCs
Evaluating Part I & Part II SM application	No	No	No	No	No
Evaluating Part I only SM application	No	No	No	No	No
Evaluating Part II only SM application	No	No	Only to MS who did not receive the Part II SM	No	Yes
Evaluating add additional member state	No	No	Only to MS not evaluating the application to add an additional MSC	No	Only to MS that is not an MSC or evaluating an assessment to become an MSC
Question in Q&A, as reference	*3.5*	*3.6*	*3.5*	*3.6*	*2.3*

Cutting edge – advanced therapies





What it is Gene editing:

- Method for introducing targeted genetic changes

  Somatic Cells: Non-reproductive cells
- Harness/Adapt bacterial defense against viral infection
- Nobel Prize 2020 (CRISPR-Cas9)

  Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

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thank you