Registration of innovative medicinal products in Europe

Anna Hanzlikova, M.D.

About A-REG

- Established in 03/2025 based on previous extensive global regulatory experience of both co-founders
- Focused on end-to-end regulatory affairs consultation services (and beyond) with global coverage and expert team located in Europe, US and Asia
- Supporting mainly biotech clients

- Find out more: www.a-reg.com and/or on our LinkedIn profile

Agenda

1

- **Determining Regulatory Pathway & Strategy**

Product types & prior knowledge, TPP

Geographical scope, competition and others

Regulatory pathways

2

- **Pre-submission Activities**

Scientific Advice

PIP

Orphan Designation, NRG interaction & others

3

- **Preparing the Marketing Authorisation Application**

CTD vs. information pyramid

Content consistency, gaps, risks & mitigations

4

- **Submission & Validation phase**

Data package completeness and correctness

Validation questions understanding

5

- **Scientific Evaluation and Review Process**

Initial assessment

List of questions & applicant responses

Final assessment

6

- **Final Opinion, Decision & Post-Approval Obligations**

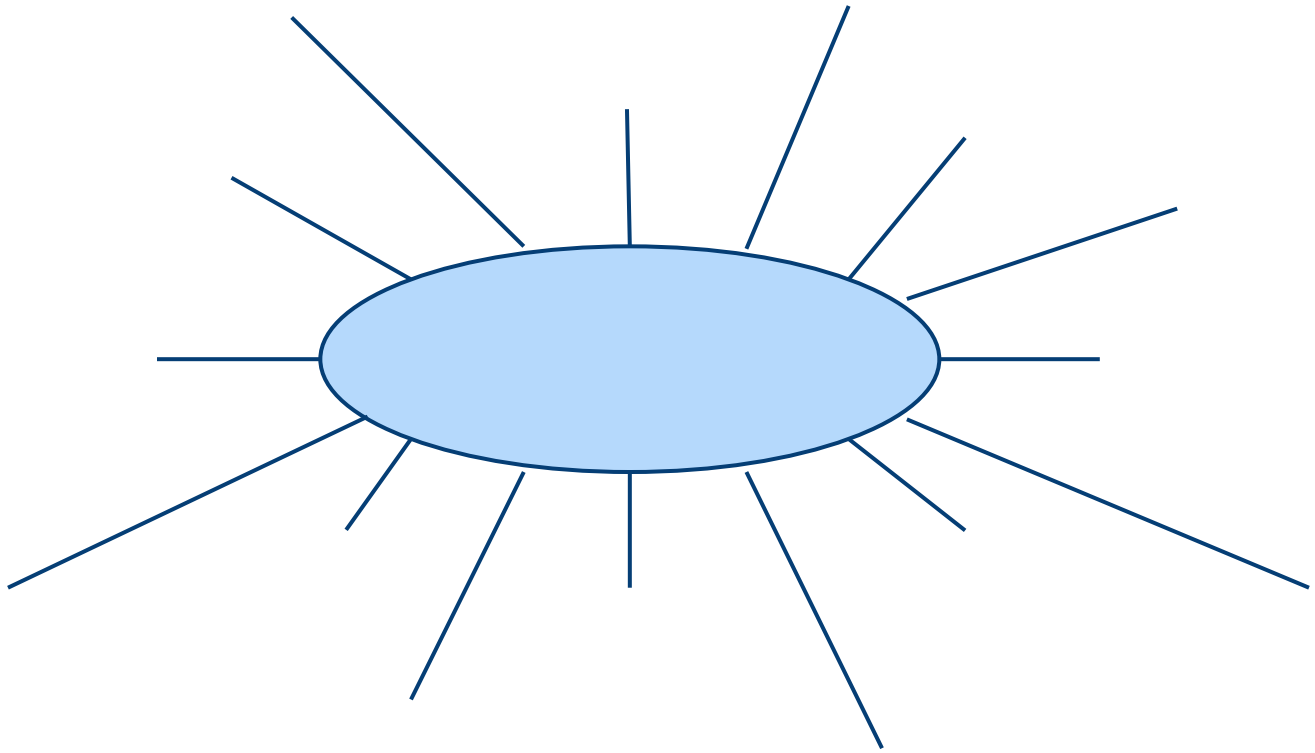
Final opinion & decision

Post-Approval obligations and measures

Determining Regulatory Pathway & Strategy

What everything may influence regulatory strategy?

What may belong to the regulatory strategy?



Product types

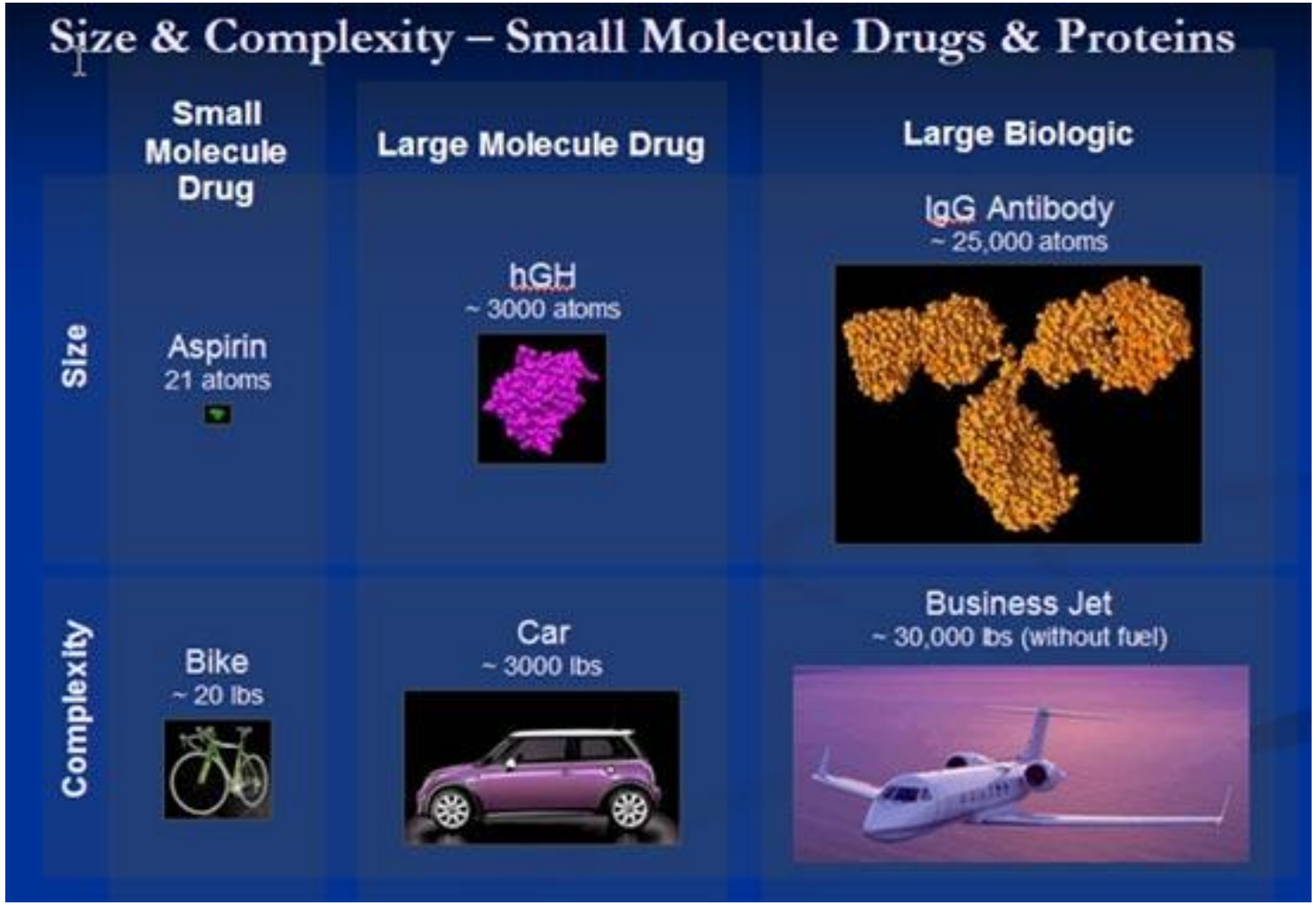
Small molecules

- Chemically synthetized
- Simpler structure

Large molecules

- Derived from living organisms
- More complex

Why does the size matter?



Picture credit: https://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate

Product types

Innovative products → Generics

New active substance included or mechanism of action

Bioequivalent to existing approved medicinal products

Innovative biological products → Biosimilars

Picture credit: https://blog.elixirsolutions.com/healthandwellness/facts-about-generic-drugs-0

Product types

- **Orphans:** designed for rare diseases
- **ATMPs:** include gene therapies, somatic cell therapies, tissue-engineered products
- **Vaccines:** biologically derived product designed to stimulate the immune system to recognize and defend against specific pathogens
- **Drug-Device combinations:** integrate a medicinal substance with a device
- **Personalized medicines:** tailored treatments based on genetic, biomarker or patient-specific data
- …
- …

Picture credit: https://specialistlanguagecourses.com/lesson-plan-types-of-medications/

Prior knowledge

- Platform approach
- Product group(s)
- Immunobridging possibility?
- Animal models and translational science

- Similar type of the products developed in the past?
- Well described in literature?

Target Product Profile (TPP)

What do you want your product to be?

Clinical:

- Indication
- Patient group

CMC

- Shelf life
- Pharmaceutical form
- Presentation

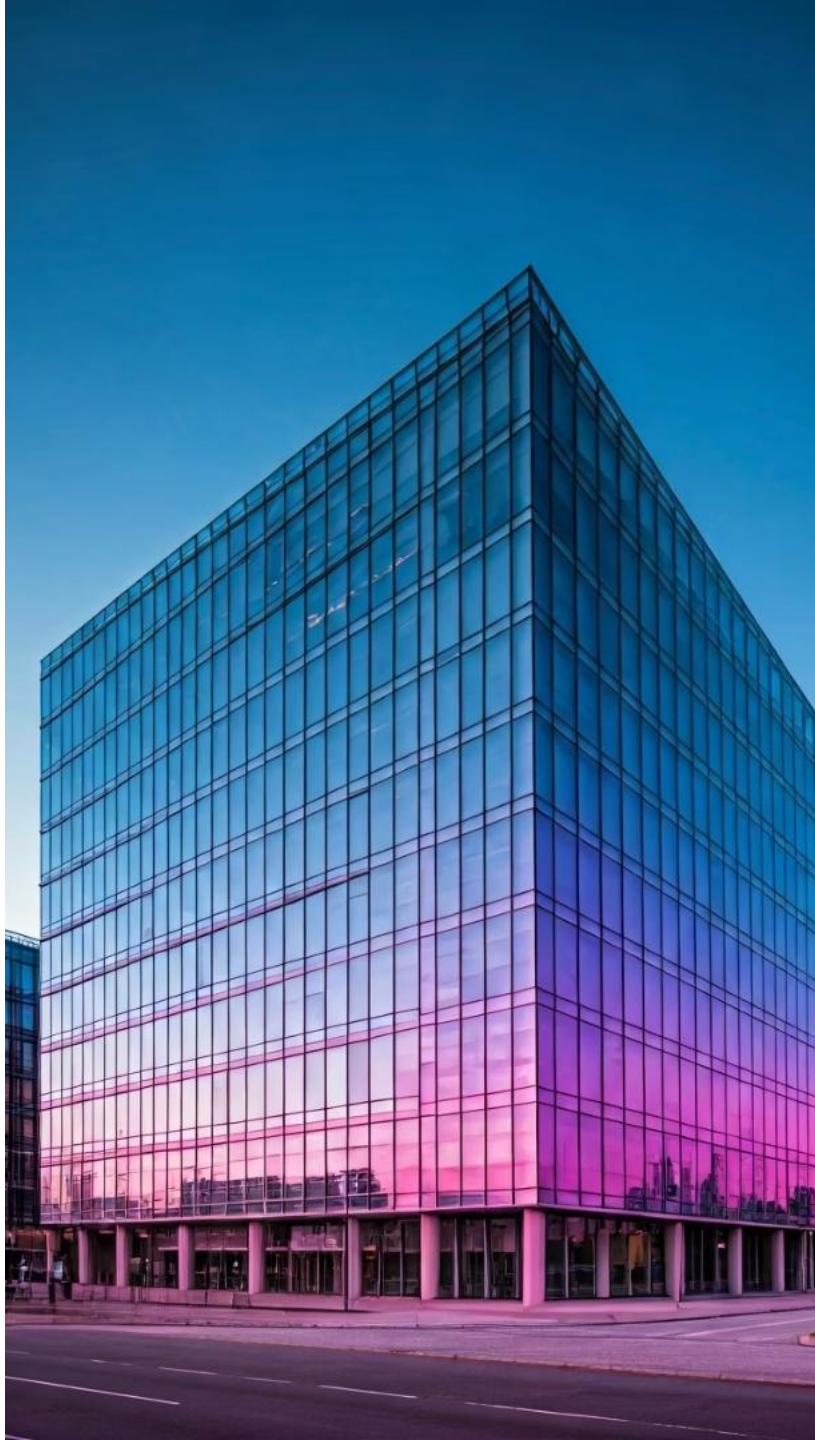
Safety

Geographical scope

- Geographical plans are crucial for success
  - Parallel global submissions? Reliance approach?
  - Single region registration? Which countries?
  - Legislation alignment or discrepancies?
  - Medical treatment approach?
  - Where were/have been clinical trials performed?
- Long term commercial & manufacturing plans understanding helps streamline & prioritize

Crucial role of Regulatory Intelligence

- Mapping of regulatory landscape can make a difference between winning or losing
- Legislation and regulatory requirements
  - Early access pathways
  - Options (vs. needs) for engagements with Health authorities
  - Necessary pre-authorization steps
  - Content expectations
  - Systems and technical requirements
- Competitors presence and activities
  - Existing portfolio registration (= direct competition)
  - R&D pipeline (= emerging competition)
  - EPARs, PARs, (AUSPARs etc.), EMA 70 depository etc.



One Drug. Three Countries. Three Coatings. Why?

- You'd expect the same tablet to look the same everywhere, right?
  But guess what — one formulation might wear three different coats across the globe.
  Not for style — but for science, climate, and culture.

Climate	Regulatory	Culture
• Stability zone concerns drive R&D / formulation considerations	• Excipients regulations differ regional by region, restrictions may imply to limited amount or actual presence in the medicinal product	• Japan: mini-tablets or fast-dissolving coatings are preferred due to patient swallowing concerns. • US patients often expect a glossy, professional finish. • In India, color coding is common — red for pain, green for digestion — and coatings often reflect this.

Taken from: https://www.linkedin.com/posts/dev-soni-00b268151_formulation-coating-pharma-activity-7334605234423353346-XyX8/?utm_source=social_share_send&utm_medium=android_app&rcm=ACoAAAPJRGoBCYRYpfU4Do2DHWPXWJiBAq9O4ro&utm_campaign=whatsapp

Regulatory Pathway

Centralised
Single application, evaluation and authorization for all EU markets

Decentralised
Simultaneous authorization in multiple EU member states

Mutual Recognition
Extends existing national authorization to other member states

National
Single member state authorization for local market only

EUROPE

GCC, EAEU

CH, UK, others

Centralised procedure (EMA)

The **centralized procedure** is **mandatory** for certain medicinal products in the **EU**. These include:

- **Human medicines** containing a **new active substance** for treating:
  - **HIV/AIDS**
  - **Cancer**
  - **Diabetes**
  - **Neurodegenerative diseases**
  - **Autoimmune and other immune dysfunctions**
  - **Viral diseases**

- **Medicines derived from biotechnology processes**, such as **genetic engineering, vaccines etc.**

- **Advanced-therapy medicines**, including **gene therapy, somatic cell therapy, and tissue-engineered medicines**

- **Orphan medicines** (for **rare diseases**)

- **Veterinary medicines** used as **growth or yield enhancers**.

Pre-submission activities

What everything should be done upfront?

Pre-submission Activities

Scientific Advice

Seek feedback on development plans to align with authority expectations.

- Clinical trial design
- Safety data planning
- Submission planning

Pediatric Investigation Plan (PIP)

- Mandatory for MAA application
- Ideal between Phase 2/3

Orphan designation and/or unmet medical need

- Orphan designation must be requested and once granted,
- Its relevancy is re-assessed regularly!

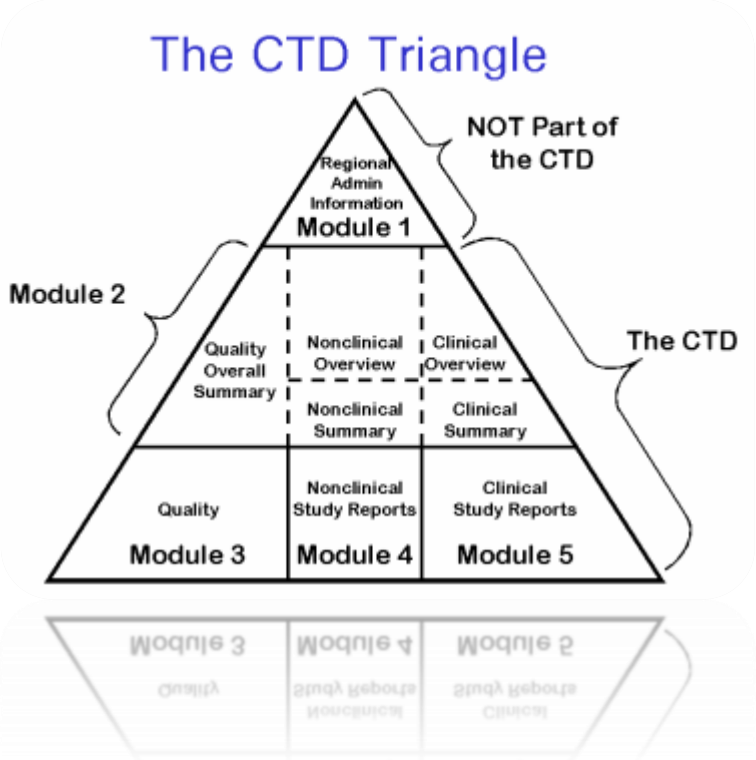
Other time/cost consuming studies gating MAA submission

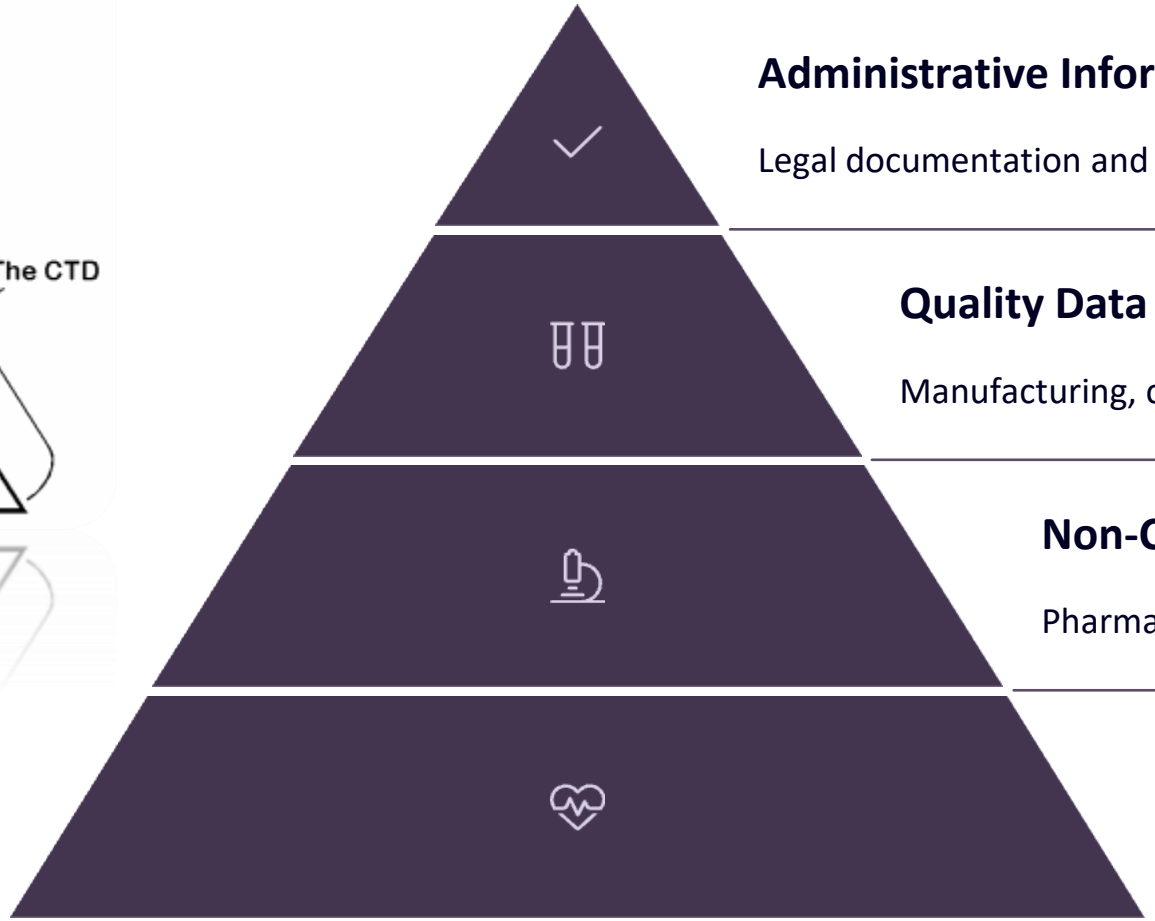
- ERA
- Nitrosamines
- Brand name confirmation: Name review group (EMA) or national authorities
- Readability assessment
- …

Preparing Marketing Authorisation Application (MAA)

What to do with all of the so far generated data?

Two-way thinking about the CTD content





Administrative Information

Legal documentation and application forms

Quality Data

Manufacturing, controls, stability

Non-Clinical Data

Pharmacology, toxicology studies

Clinical Data

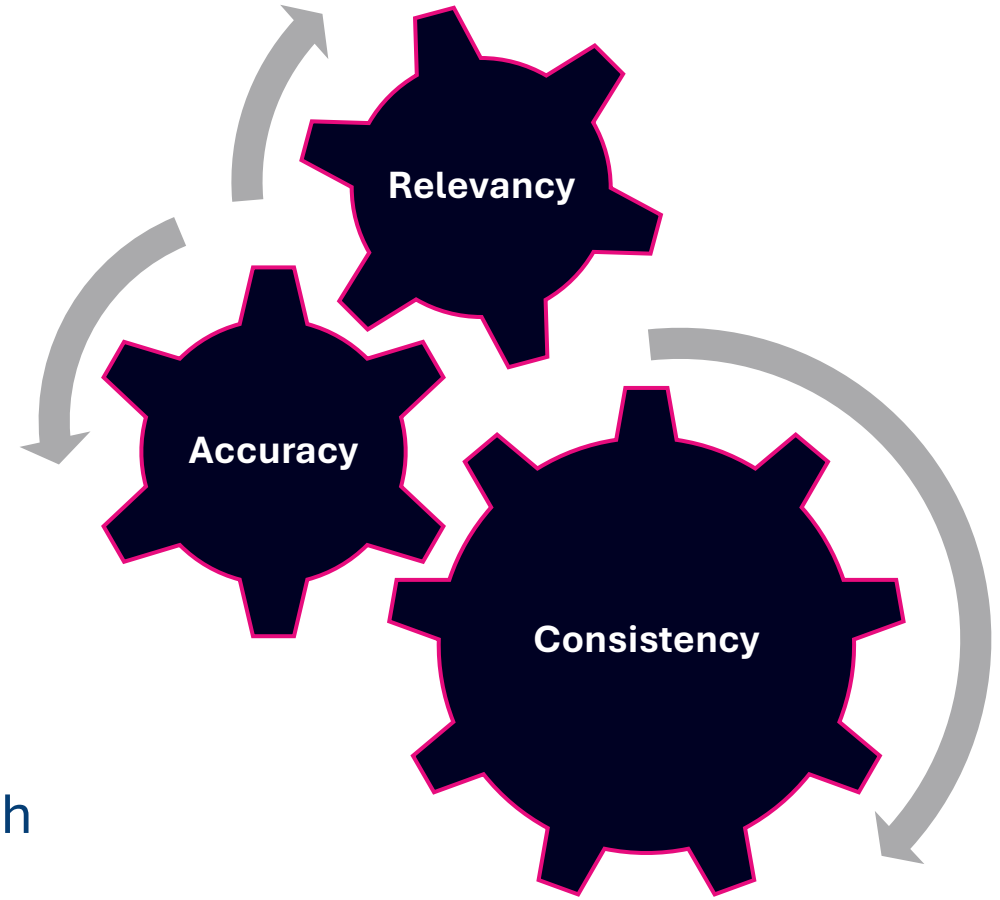
Efficacy, safety, risk-benefit analysis

Data approach

- Main goal of registration process is to provide a proof that the product is
  - Of consistent and adequate quality
  - Safe enough
  - Efficacious enough
- In other words: the product has positive benefit/risk ratio

- Strategy for each area should reflect that

- Gap analysis to be run for data available, data to be created and data to be created based on health authority requests
  - Concious decisions
  - Risks & risks mitigations
  - Potential future health authority questions identification



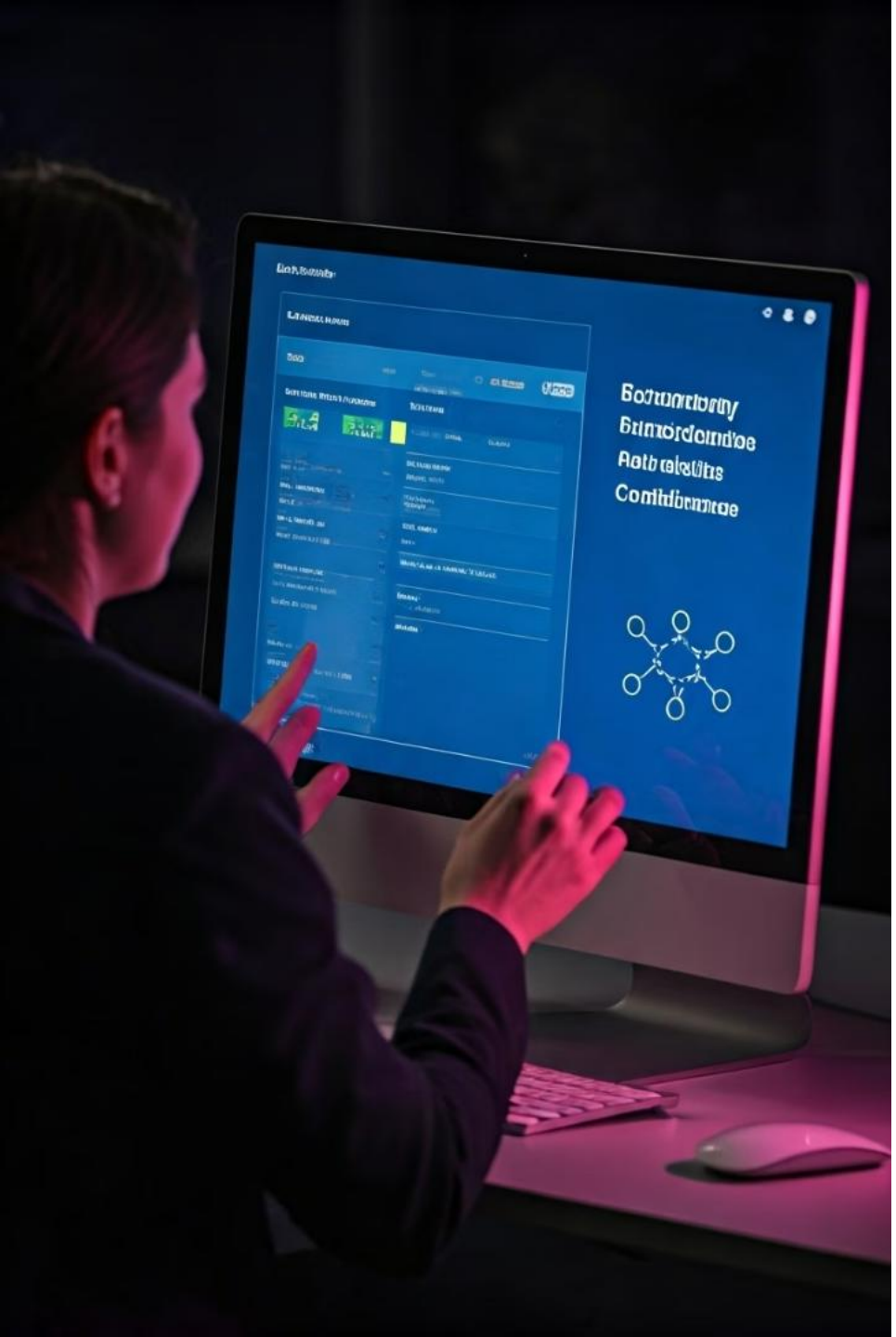
Why final QC check matters?

- Imagine an innovative CTD dossier data package
  - ❑All documents present?
  - ❑All documents readable?
  - ❑All documents formatted properly?
  - ❑All hyperlinks working properly
  - ❑Does eCTD envelope contain the correct data?
  - ❑Are all other eCTD validation criteria fulfilled?

First EMA initial CP application (127 boxes):

Submission and Validation Phase

Submission done – what´s next?



Submission and Validation

Dossier Submission

Submit complete electronic CTD to relevant authority portal.

Validation Check

Authority reviews for technical completeness.

Authority reviews for procedural correctness.

Address Deficiencies

Respond promptly to validation questions.

Supply missing information within specified timeframes.

Assessment Start

Assessment starts only post written confirmation of validation!

Scientific evaluation and review process

Strategic considerations at every step of the assessment

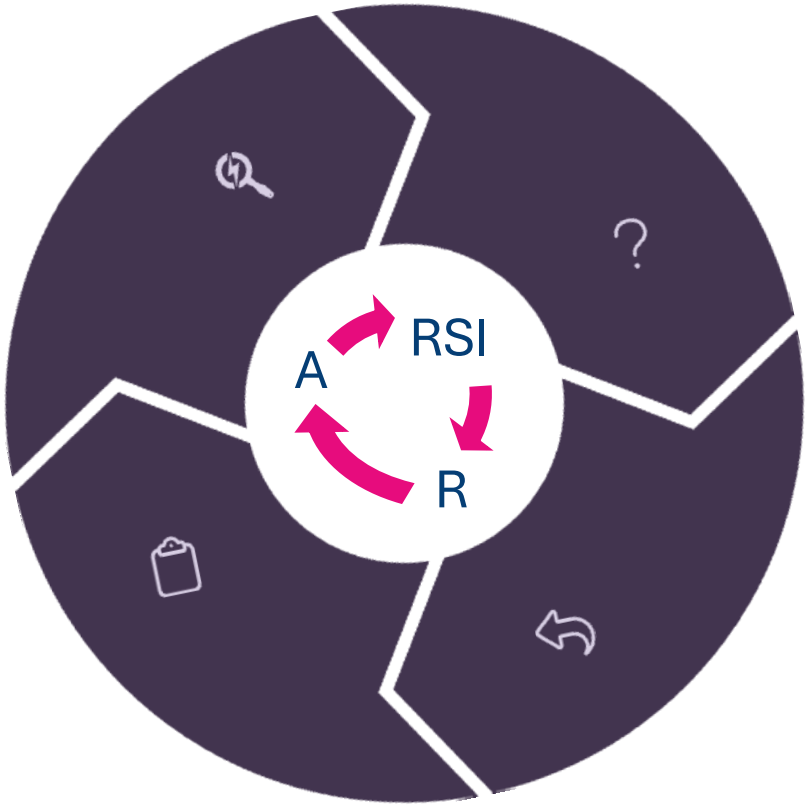
Scientific Evaluation and Review Process

Initial Assessment

- Rapporteurs/RMS examine dossier and prepare preliminary assessment report (pAR)
- Co-Rapporteurs/CMS team provides additional feedback → updated assessment report

Final Assessment

- Assessors complete assessment report (= final AR)
- Committee finalizes benefit-risk evaluation



List of Questions

- Authority issues formal queries at Day 120 (RSI)
- Stop clock allows applicant time to respond (usually agreed with the HA upfront, can be updated in exceptional cases)

Sponsor Response

- Company provides additional data during clock stop
  - Response document!
  - Additional data
- Formal, eCTD response

Final Opinion, Decision & Post-Approval Obligations

Assessment is finalized, what´s next?

Final Opinion, Decision & Post-Approval Obligations

Final Decision Timeline

- CHMP opinion/RMS approval: Day 210
- EC decision (for CPs): +67 days
- National implementation: +30 days

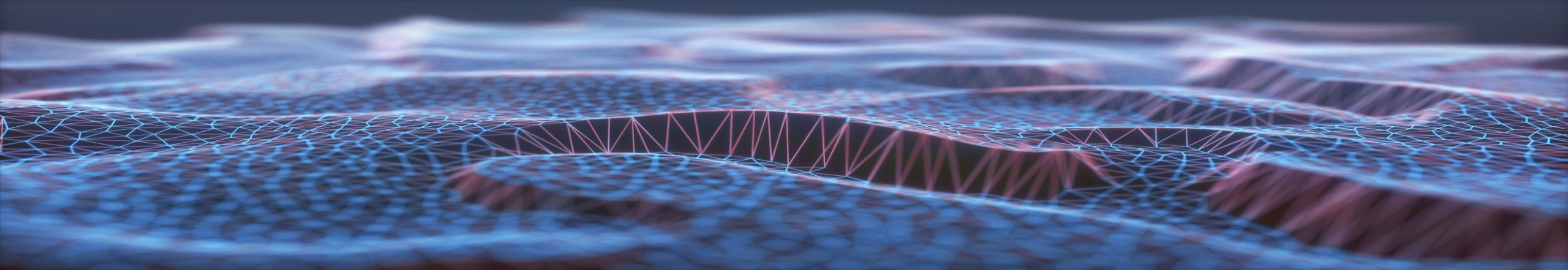
Final MA

Post-Approval Requirements

- Risk management plan implementation
- Periodic safety update reports (PSURs)
- Post-authorization efficacy studies (PAES)
- Variation management for changes

Post-Approval Measures (PAM)

- Commitments provided & agreed during assessment
- Different types depending on nature of the content
- Deadlines for additional data submission must be kept, otherwise the MA is under risk



Summary and Success Factors

Early Engagement

Consult with authorities during development phases. Seek scientific advice to align expectations before clinical trials begin.

Quality Documentation

Ensure comprehensive, well-organized dossiers. Address all regulatory requirements with clear, compelling data packages.

Responsive Communication

Maintain open dialogue with assessors. Provide prompt, thorough responses to authority questions during review.

Lifecycle Management

Plan for post-approval obligations. Develop robust systems for ongoing regulatory compliance and product updates.

List of abbreviations

- HA = Health Authority
- EC = European Comission
- MA = Marketing Authorisation
- MAA = Marketing Authorisation Application
- PIP = Pediatric Investigation Plan
- CP = Centralized Procedure
- DCP = Decentralized Procedure
- MRP = Mutual Recognition Procedure
- IRP = International Rcognition Procedure
- NP = National Procedure
- TPP = Target Product Profile
- RSI = Request for Supportive Information
- RFI = Request for Further Information
- DL = Defficiency List
- LoQ = List of Questions

- RMP = Risk Management Plan
- PSUR = periodic Safety Update Report
- EC = European Comission
- PAES = Post-authorization efficacy studies
- PAM = Post-Approval Measures