

Listen & Learn Focus Group on Platforms (November 2024): What have we learned?

EMA Quality Innovation Group

CBG-MEB Science Day

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Marcel Hoefnagel

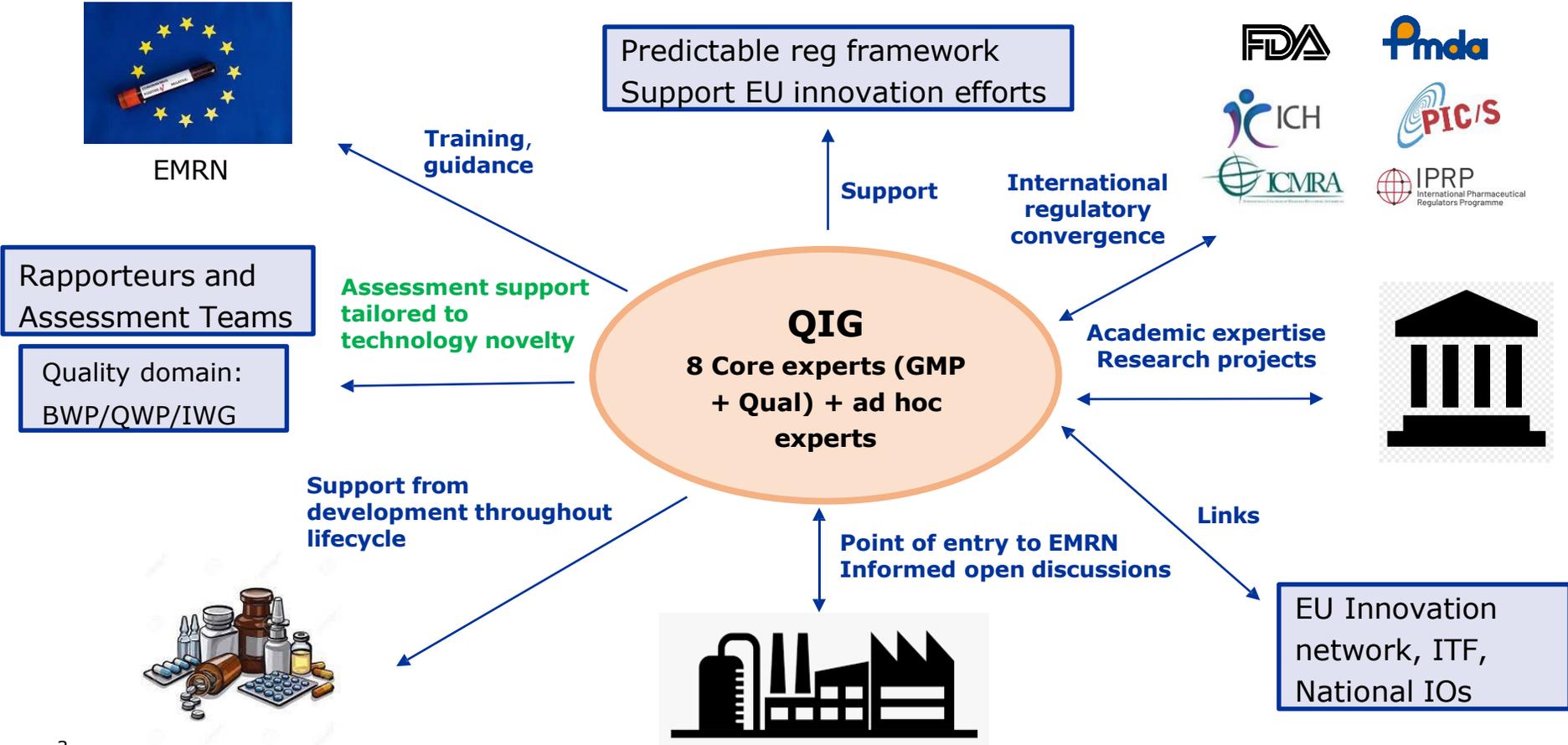
Senior Assessor CBG-MEB

GOOD
MEDICINES
USED
BETTER

- **Introduction (QIG, Set up LLFG)**
- **Use of Prior Knowledge and Platform Approaches: EU Regulatory Perspective**
- **Presentations (incl. Oligonucleotides, Vaccine Antigens, Ultra orphan, CDMO)**
- **Topics discussed**
- **Conclusion**

DISCLAIMER: Personal views only, meant to initiate further discussion; may not necessarily reflect views/opinions of MEB, EMA or EDQM.

EMA Quality Innovation group (QIG)



- **Open dialogue**
- Discuss **case studies** that use **prior knowledge** to support manufacturing platform
- Identify general **scientific challenges** with use of platforms & possible **solutions**
- Focus on **Scientific & Quality aspects** (Legal & (non)clinical aspects outside scope)

Three scenarios were foreseen for discussion:

1. Platforms for medicinal **products manufactured using prior knowledge**, such as common manufacturing platform approaches (multiple MAs)
2. Platforms for medicinal products against agents which are or have a potential to cause serious cross-border threats to health e.g. **pandemic (preparedness)** (one MA)
3. Platforms for the manufacture of **personalised or individualised medicines** ('one patient/group of patients-one product', one MA) e.g. covering different **ultra-rare orphan indications**

How to Justify Use of Prior Knowledge?

- **Aim is to obtain and demonstrate process knowledge to show that manufacturing is consistent and well-controlled**
- **Context and Relevance**
Show applicability of the prior knowledge to the new product
- Explain and **justify**
- *Clearly describe the extent of prior knowledge*

Use SA if needed*

*[Scientific advice and protocol assistance | European Medicines Agency \(EMA\) \(europa.eu\)](https://www.europa.eu)

Why Use Prior Knowledge?

- **Knowledge gains:** opportunity for systematically building a large data package for a specific area
- **Efficiency gain:** accelerate dossier development of related dossiers especially for rare conditions
- **Efficiency gain:** assist the assessment process
- **Accelerate patient access to medicinal products e.g. in emergency situations**

Examples of Use of Prior Knowledge

- **Seasonal influenza vaccines** – degree of prior knowledge accepted, relies on relatedness/prior knowledge of related authorised strains & minimises data required for annual updates.
- **COVID vaccine MAs** – first four initially approved vaccines had legally binding **specific obligations** (SOs) for deferred data (post-approval) in the context of the emergency benefit/risk. For one of these products however, use of prior knowledge avoided SOs for control strategy, specifications and stability.
- **COVID vaccine updates** – several variant updates approved for mRNA vaccines use of prior knowledge reduced submission requirements.
- **Synthetic oligonucleotide CTAs** – Prior knowledge approaches have been used to justify proposed re-test period/shelf-life.

Topics discussed during LLFG Meeting

Platform definition

- What are the minimum data required to show that a platform is established?
- Defining the fixed components and variable components of a platform
- E2E considerations for platforms

Applicability of the platform for different products

- Will the 'fixed' components comprise data which are identical for each product?
- How to permit cross-referencing of data across linked MAs?
- Approaches to demonstrate that a new product is part of platform

Lifecycle management

- How to introduce changes

Platforms based on several products for ultra rare diseases

Examples presented: Vaccines

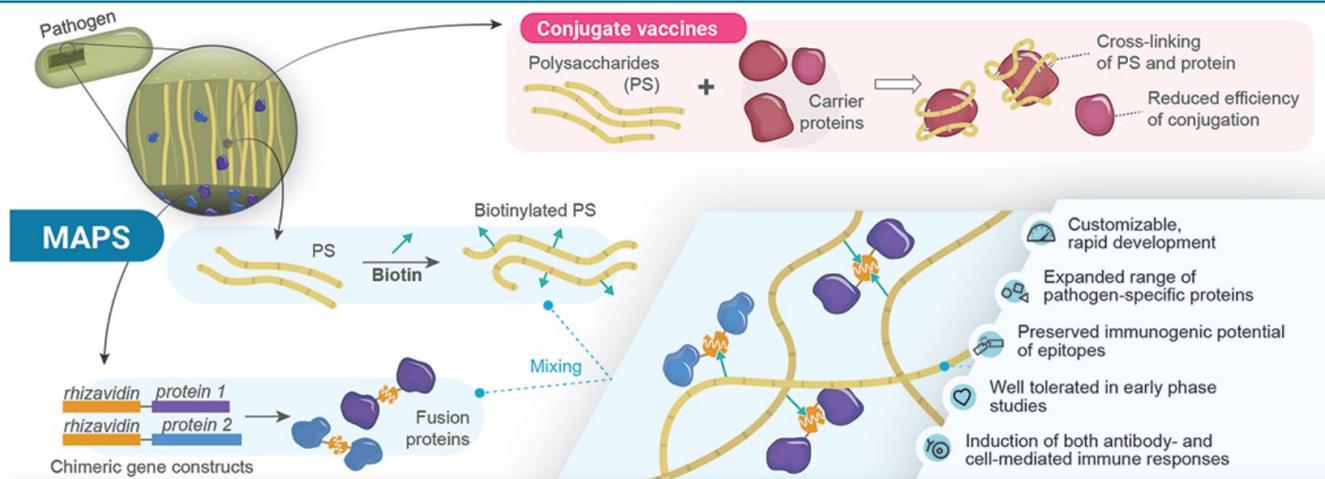
CEPI (Coalition for Epidemic Preparedness Innovations)

Platforms technologies for accelerating vaccine development

- Well-defined process (equipment, analytical methods, formulations) yield products with predictable characteristics
- Well-understood, reproducible & **antigen agnostic**

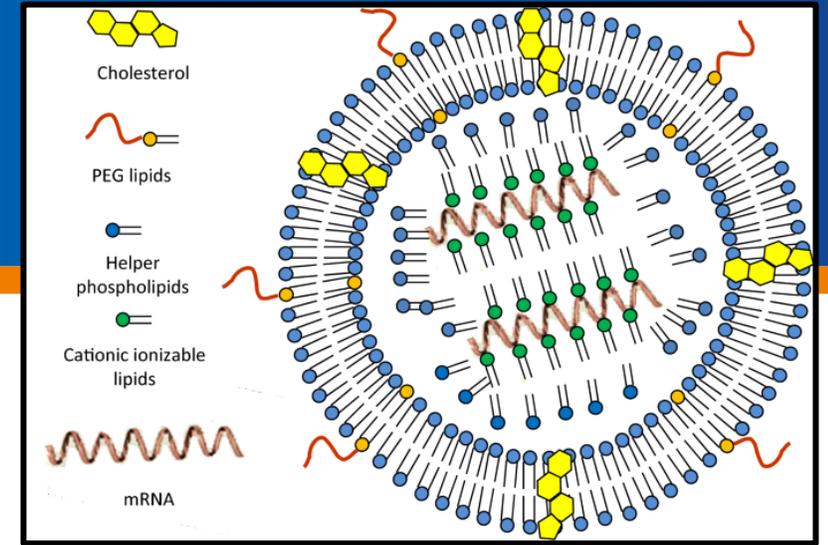
PDA/GSK: MAPS technology, a cutting-edge platform manufacturing

- MAPS (Multiple Antigen Presenting System) Technology, novel vaccine platform, for multivalent vaccines against *S. pneumoniae* (**Conjugate antigens; Carrier Protein with Polysaccharides attached**)
- Polysaccharides, a leading serotype is identified based on properties (e.g., structure, sensitivity to hydrolysis, size, viscosity)
- Platform knowledge (evolving experience) to inform modelling strategies for optimization



MAPS offers a multifaceted and customizable vaccine platform, with the potential to induce

Nucleotide products



Moderna: mRNA-lipid nanoparticle (LNP) platform technology to support specification setting and determination of product shelf life

- mRNA-LNP technology platform (shared lipid composition, manufacturing processes & analytical methodologies)
- leverage shared scientific principles & manufacturing processes between products enhance development efficiency

EPOC: Application of platform approach to oligonucleotide drug substances

- Same basic unit operations: solid phase synthesis, cleavage, purification & isolation
- Strong understanding how various steps impact quality attributes
- E2E: Synthetic oligonucleotides of identical length, synthesized using identical process, starting materials, reactants, etc.
- E2E is too restrictive, **consider modular approach** using quality risk assessment
- Case study: Prior knowledge to support control strategy; Single full scale Process Validation & Stability batch

Fondazione Telethon ETS: Optimising development of gene therapies for rare genetic diseases

- **Lentiviral vector transduced CD34+** stem cell gene therapies
- Platform for efficient development (avoid repeating testing) esp. for clinical studies

Prime editing: Platform technologies

- Ex vivo gene editing of HSC (Haemopoetic Stem cells)
- Prime editing guide RNA (pegRNA) targets specific DNA sequences, nicks one strand and reverse transcriptase incorporates corrective genetic sequences
- **Modular CMC approach** de-risks manufacturing process, quality, regulatory, clinical & analytical strategies
- Modular platforms particularly valuable for rare diseases, small patient populations

Viralgen - Platform strategy (CDMO perspective)

- Platform strategy for Adeno-associated viruses (AAVs)
- Transgene as unique element (Variable) & Capsid as Fixed component per AAV serotype
- Leveraging historical data (N>100 batches) to standardise processes
- Quality by Design approach to establish control strategies

BioSpring Strategy for implementation of a platform approach for synthetic oligonucleotides

- Define Family of oligonucleotides based on sequence, same manufacturing process, CQAs, CPPs, CMAs, & risk assessments
- Set acceptance criteria using statistical tools
- Criteria defining platform robust enough per family

How to use data from different sponsors to support individual products?

CDMO = Contract Development & Manufacturing Organisation

ISPE: Prior knowledge in investigational medicinal products' (IMPs)

- mRNA Investigational Medicinal Products **QbD principles to apply prior knowledge**
- Key challenges: limited batch numbers for IMP, assessing mathematical models for Design Space robustness

CMC Statistical Network Europe: Statistical approaches to develop data-driven prior knowledge into a platform

- **Statistical Methods for Prior Knowledge Integration:**
 - Data-driven approaches to prior knowledge: more efficient drug product development
 - Use prior knowledge models for risk assessments, improve FMEAs & reduce experiment design resources

FMEA= fail mode and effect analysis

Platform definition

- **Definition of Platform (some considerations)**

- Differences between a platform and prior knowledge / manufacturing understanding
- Platform could streamline prior knowledge
- Platform as design space; Mathematical model
- Platform to accelerate development on more robust control strategy

- **E2E considerations for platforms**

- Some end-to-end manufacturing platforms: combination of fixed platform-specific and flexible components
- Modular approach proposed: platform consisting individual manufacturing steps (modules) and cross-referenced across multiple programs, (e.g. critical starting material like viral vectors for ex vivo gene therapy or sgRNA for gene editing)
- Is part of manufacturing (module) eligible for platform?

- **What are the minimum data required to show that a platform is established?**
 - How Many products (n>1)?
 - Ideally, one approved product
 - Platform based on developmental data, clinical trial data, and/or data from approved products
 - Relevance & adequacy of supporting data to be justified
 - Mathematical model may support robustness (e.g. acceptance criteria or shelf life)
- **Defining the fixed components and pre-defined intentionally variable components of a platform**
 - Constrained vs flexible definition (define fixed and variability elements)
 - When does it stop being a platform?
 - Scientific knowledge; published knowledge can be used too

- **Applicability of the platform for different products**
 - Justify applicability of platform for any new product
 - How much process adaptation (variation) is acceptable?
 - Should 'fixed' components comprise identical data for each product?
 - Having families of related platforms?
- **Lifecycle management**
 - Platform lifecycle maintenance; link to multiple products with their own lifecycles?
 - Will it be static or define processes/ parameters which will change?
 - Introduction of changes/improvements in the platform (Via Worksharing procedure?)
 - Does a platform stifle innovation?

- **Platform based on several products for ultra rare diseases**

- Approaches to validate a manufacturing platform based on different products, prior to one is approved as medicinal product
- For rare diseases, find a balance between how much data/many products is needed
- B/R of the product also impacts data requirements (Ultra orphan vs prophylactic vaccine)

- **Platform data in the dossier**

- Can you base Process validation on platform data (from previous product)?
- How can CDMO use platform characterisation data from multiple sponsors?
- Can it be in a closed part?
- Several stakeholders stated preference for PTMF. However legal aspects are outside the scope
- Minimise the amount of de novo data that regulators need to assess for new products

- Leveraging Prior knowledge accelerates product development/ patient access on more robust control strategy
- Different interpretations what constitutes a platform (definition)
- In addition to E2E, consider modular approach (across multiple products)
- Data to support a platform: developmental, clinical trial, modelling and/or approved products
- Justify data (applicability & robustness)
- For ultra-rare diseases manufacturing platforms different products to support process validation
- Value of mechanism to (confidentially) access CDMO data in accelerating product development
- Lifecycle management considerations for platform and related products

Acknowledgements



QIG LLFG Organising Committee Members

EU

Marcel Hoefnagel, MEB, The Netherlands, QIG Chair
Leticia Martinez Peyrat, ANSM, France, QIG Member
Barbara Stubbe, FAGG, Belgium, QIG Member
Christina Meissner, AGES, Austria, QIG Member
Silke Schüle, PEI, Germany, QIG Member
Marcos Timón, AEMPS, Spain, QIG Member
René Thürmer, BfArM, Germany, QIG Member
Ciara Turley, HPRA, Ireland, QIG Member
Sean Barry, HPRA, Ireland
Tone Agasoster, NOMA, Norway
Greger Abrahamsen, NOMA, Norway

EMA

Ragini Shivji, Quality Office, European Medicines Agency
Dolores Hernan, Quality Office, European Medicines Agency
Evdokia Korakianiti, Quality and Safety Department, European Medicines Agency
Veronika Jekerle, Quality Office, European Medicines Agency
Peter Twomey, Inspections Office, European Medicines Agency
Giampiero Lorenti, Inspections Office, European Medicines Agency
Miguel Rodriguez, Inspections Office, European Medicines Agency

Mail address QIG: qig@ema.europa.eu

Questions

www.slido.com

Code: 2250950

