Regulatory updates from the EU

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Disclaimer: The opinions expressed are my own and do not necessarily represent those of the HPRA or EMA
Outline

• PRIME scheme
• Adaptive Pathways and CMC challenges
• Process validation for Adaptive Pathways
• Recent trends in quality/CMC questions from EU regulators
Launched in March 2016 and aims to provide enhanced interaction and early scientific and regulatory support

- Rapporteur assigned early in development to provide continuous support and help build knowledge
- Kick-off meeting with multidisciplinary participation from the EU network to discuss the proposed development programme
- Enhanced scientific advice at key development milestones with a dedicated EMA contact point
- Optimisation of benefit/risk data during development will enable accelerated assessment
Reinforce scientific and regulatory advice
- Foster early interaction with dedicated rapporteur
- Multidisciplinary expertise
- Parallel scientific advice with HTAs
- Applicants will be advised on milestones

Optimise development
- Focus on efficient development
- Robust data generation
- Guidance on development plan and regulatory strategy

Enable accelerated assessment
- Facilitated by knowledge gained throughout development and scientific advice
- Intensive guidance will lead to better informed development plans

Nonclinical → Phase I → Exploratory → Confirmatory → Evaluation → Post-authorisation

SMEs Academia
Eligibility (CHMP)
SA 1 (SAWP)
SA 2 (SAWP)
SA n (SAWP)
Accelerated Assessment confirmation (CHMP)

Early CHMP Rapporteur appointment

Proof of principle
Proof of concept
• **Who can apply?** Applicable to medicines in indications with unmet clinical need and where there is therapeutic innovation

• **What’s needed?** Data to support the claim that the product has the potential to bring a major therapeutic advantage to patients

• **Will the outcome of applications be published?** An overview of the number of recommendations adopted will be published in the CHMP Monthly report including the type of data supporting the eligibility request

• **What happens if application is unsuccessful?** Applicants not qualifying for PRIME support can still apply for accelerated assessment prior to filling
Benefits of prime

- Better informed development plans
- Regular checkpoints
- More streamlined scientific advice
- Improved quality of MAAs
- Shortened timeframe for review
CMC considerations for PRIME

• Use the regular scientific advice procedures to discuss plans for process validation, scale up, stability etc

• **Opportunity** to get continuous feedback on pharm development and process validation activities

• Engage with regulators on areas which are challenging
Medicine’s Adaptive Pathways to Patients (MAPP)

Adaptive pathways

Treatments in high medical need areas where collection of data via traditional routes is difficult and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.
Adaptive Pathway is based on 3 principles

- Iterative development
  - Expansion of target population or progressive reduction of uncertainty

- Progressive gathering evidence through real-life data

- Early involvement of patients and health-technology-assessment bodies in discussions on a medicine’s development.

- Optimises use of regulatory tools and flexibility
- The evidence generated addresses not only the needs of regulators, but of HTA bodies as well
- No change to the **principles** of the benefit vs risk approach
- Acceptance of uncertainty balanced by continued evidence generation
Widening of indication

The sponsor could follow one of two strategies for approval in the overall target population.

Reduction of uncertainty

The sponsor could follow one of two strategies for reduction of uncertainty.
CMC challenges for Adaptive Pathways

- May be few batches manufactured
- How will process validation look – concurrent process validation?
- How to set specifications based on few batches?
- Stability studies may be ongoing, need to identify stability indicating assays early
- Less time to scale up and optimize manufacturing process
- Analytical methods need to be validated early in development

CMC solutions for Adaptive Pathways

- Regulators will need to shift some emphasis to post approval
- Much of this can be captured in the PACMP
- Will need a well thought out plan in the MAA to generate data post-approval
- Greater emphasis on lifecycle validation
- Greater reliance on prior/platform knowledge
- Leverage data from early development lots - comparability
- ICH Q12 approaches to product lifecycle
CMC questions for Adaptive Pathways

• Where does the balance lie in limited data versus regulators acceptance of risk?

• Can specifications and control strategy be reassessed post-approval?

• Is there flexibility to adjust the control strategy, specifications etc. once validation is complete

• How will post approval extension of shelf life look?

• Can the recent process validation guideline help in terms of post-approval process validation?
Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission
Process validation guideline and the Adaptive Pathway

- Prior knowledge can be used as supportive information in the justification of operating ranges
- Use of continuous process verification: in-line, on-line or at-line controls, use of PAT and Multivariate Statistical Process Control as enablers, depends on level of process understanding and/or prior knowledge
- Concurrent validation – in exceptional circumstances (e.g. where there is a very strong benefit-risk ratio for the patient), it may be acceptable not to complete a validation programme before routine production starts

Products under accelerated programmes

- Can leverage ongoing process verification
- Provide a protocol that indicates how process knowledge, control strategy and characterisation methods will be use to assess product quality throughout the lifecycle
- Protocol includes tests and acceptance criteria that will be used to further demonstrate that the process remains in a validated state
Trends in questions raised in the quality/CMC section of the dossier
Quality questions raised by Rapporteurs/BWP in dossiers submitted in 2015

- Major objections are the exception rather than the rule
- Major Objections identified in manufacturing process description, potency assay, manufacturing process development, comparability
- In general, recombinant proteins have slightly more questions (however this is based on a small sample size)
Distribution of other concerns

Based on 20 MAA applications for mAbs and recombinant proteins received in 2015.
The three most consistent areas for questions are:

- Process Development (S.2.6)
- Process validation (S.2.5)
- Specifications (S.4.1, S.4.5, P.5.1, P.5.6)
Process development questions

Common questions in S.2.6 relate to the control strategy, designation of criticality and risk ranking approaches

• How was criticality of CPPs/non-CPPs decided?
• If using a risk ranking approach, explain why a certain cut-off was chosen, it can sometimes seem arbitrary
• Provide data to show that any small scale studies which underpin the control strategy are representative of the full scale process
• Make it clear how the range of each PAR is justified
• Avoid using non-ICH terminology where possible
The balancing act of specification setting

Clinical qualification

Historical batch data

Manufacturing consistency

Statistical analysis
Common questions around setting specifications

- Need to be **clinically qualified** - indicate which batches were used in which clinical trials
- Where the proposed specifications are higher/lower than any batch used in the clinical studies, a justification should be provided
- If there is a choice of batches available during the clinical trials, consider which batches/how many to use with an eye to future specification setting
- How to clinically qualify specifications when there's a low number of batches e.g. in adaptive pathway procedures?
- How to clinically qualify specifications of biosimilars?
- Using “assay variability” to justify widening the specs ... needs to be linked to actual variability seen during analytical validation
- Statistical approaches need to be properly justified
Are regulators open to reducing the number of specification tests post-approval?

- Variations to move specification tests to IPCs or to remove entirely are becoming more common

- Replacement of e.g. potency assays, purity assays with data modelled from process knowledge

- Once a sufficient number of batches have been manufactured, predictive models can be developed to reduce regulatory burden

- Quid pro quo for investing in gathering greater knowledge of the process

- More open to discussion on this than in the past
Protein sequence variants – an emerging trend?

- Point mutation
- Amino acid misincorporation
- Mutated gene copies
- Mistranslations
- DNA rearrangement
- Missplincing
- Bioreactor amino acid depletion
- Mischarging of tRNAs
- Codon-anticodon mispairing

Can lead to significant difficulty at the time of MAA!
Remedies

• Cannot rely solely on changes to mass or charge

• Combine HPLC-MS/MS with Mascot based error tolerant search (ETS)

• MS methods can miss sequence variants in part of the protein that give very small or large tryptic peptides - consider using a second enzyme

• Deep sequencing of DNA, transcriptome sequencing (RNAseq) during cell line development

• If sequence variants persist into commercial manufacture how will they be controlled, how will the specification be clinically qualified?
Conclusions

- New pathways have been developed to facilitate faster patient access to medicines
- Closer interaction and dialogue during product development will lead to faster review times
- More options for staged approval
- More openness to alternative process validation schemes
- Some areas of the dossier still remain common areas of questions
Thank you for your attention