Specific Regulatory Strategies for Process Validation for Biologics

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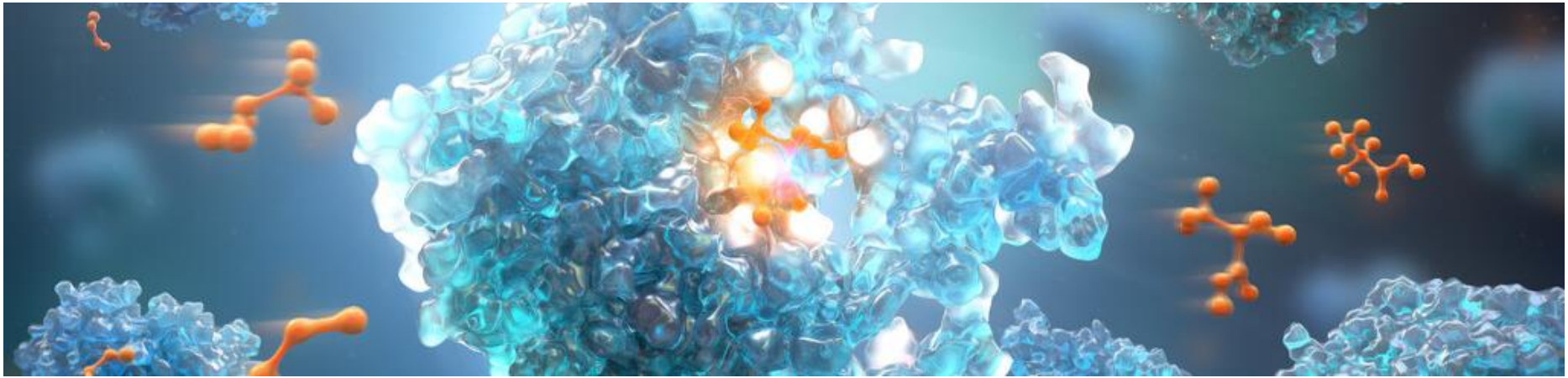
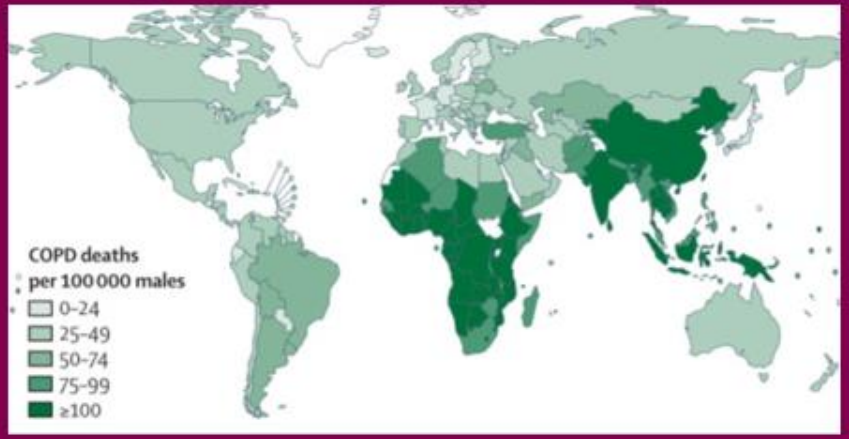
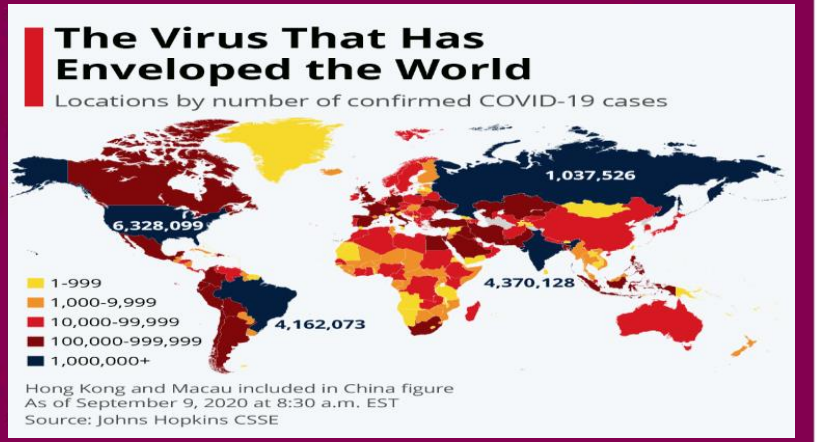


Global patients are waiting……

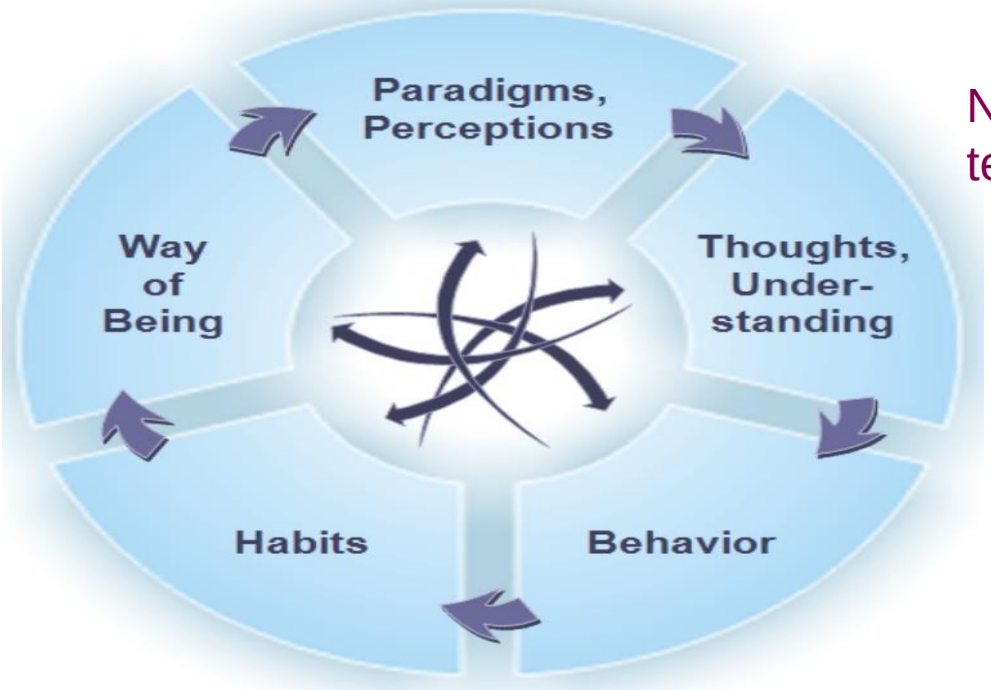


Our goal has to be to try and bring numbers to zero, globally, as soon as we safely can



The world of CMC is changing: A paradigm shift?

New guidance e.g. Q12



New modalities and technologies

Regulatory pathways: Accelerated and reliance

Discussion on and acceptance of accelerated CMC approaches with Agencies: 2019 EMA report

….and then there was COVID

Accelerated CMC/Regulatory approaches –why?

Quality remains at the heart of development and manufacturing, and safety and efficacy are not compromised

- Both Agencies and Industry share a common goal of delivering safe, efficacious quality products to patients
- No published guidance for CMC requirements within Accelerated pathway guidance (except COVID)
- Agencies negotiate CMC requirements for innovative medicines for unmet medical need (e.g. Medical Breakthrough Therapy, PRIME, SAKIGAKE)
  - Based on sound science & requires negotiation – safety & efficacy. **Benefit: risk**
  - Cross regional or Assessor consistency not always seen
- 'Non-traditional' approaches often needed in CMC development to ensure **CMC data package keeps pace with clinical studies**.

CMC data will be on critical path to submission and approval more often

Benefit :Risk: Accelerated CMC development

Benefit to patients/opportunity

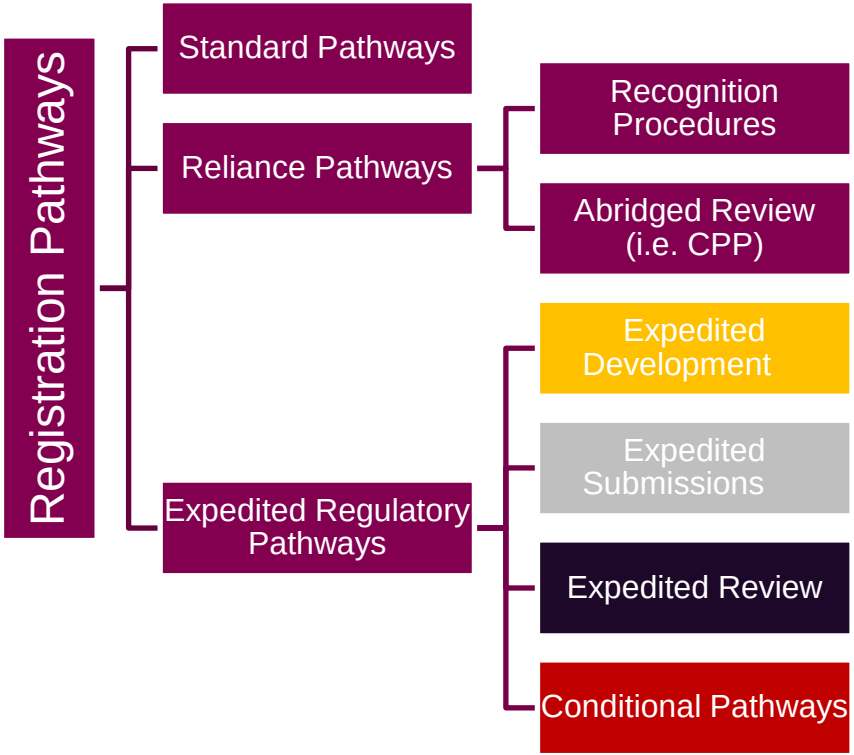
- Fast Access to new Medicines (Unmet Need)
- Increase in level and intensity of regulator/industry interaction (e.g. rolling assessment)
- Apply clinical benefit vs CMC risk and accept necessary post approval activities/ commitments, which will likely be increased compared with traditional approaches

Increase in CMC /Regulatory Risk:

- Clinical Acceleration results in need for 'non-traditional' CMC data to allow CMC to keep pace
- '*Can we not start CMC dev. earlier?'* : not all of it – need time to develop and generate data based on final dose, modality, process, analytical methods, device, supply chain, scale, stability data etc.

Still need to meet Company and Assessors' needs to confirm process is acceptable, but in a different, scientifically rationale and/or risk based way

Alternative Regulatory Pathways: Expedited development, submissions and reviews



PRIME: Unmet Medical Need
Major Therapeutic Advantage

- Medical Breakthrough :
- Serious or life-threatening disease
- Potential for substantial improvement over existing therapies

SAKIGAKE:
- innovative treatments for serious target disease

Many Agencies developing Expedited Reviews e.g. China, Taiwan, Brazil, Switzerland, Kuwait, Australia, Saudi Arabia, S.Korea, Singapore etc.

CMC Challenges with Expedited Development Programs

Stability Challenges

- Less time to accrual real time data on commercial product to set shelf life
- Fewer batches to set realistic SL specifications
- Need to apply modelling and forced degradation data

Analytical Methods Challenges

- Less time for optimization & validation
- Bridge between results from earlier vs later methods

Manufacturing Challenges

- Less time to scale up & optimize manufacturing process
- Understanding of criticality & interactions not fully mature
- Challenge for Process Performance Qualification requirements and timing
- Too few batches to assess manufacturing consistency
- Need to scale up and out post approval

Control strategies

- Less time to develop and finalise control strategy and mature specifications
- Need to apply prior and platform knowledge

Strategies for being Agile:

EMA/FDA Workshop with Ind. stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies , report 2019)

Process validation from EMA report, 2019

- **Commercial supply of clinical batches** post-approval
- **Decoupling of AS and FP** process validation activities
- Deferral of process validation studies/restricted control strategy
- Reinforce value of **concurrent validation or CPV**
- Mechanisms to **submit delayed validation data**
- Tailoring validation packages
- **Widening control strategy post-approval through PACMPs** (i.e. agreement on the principle of "relaxing" control strategy post-approval when supportive data is available)
- The extent that **Prior Knowledge** can compensate for a deferral of certain process validation data
- ***'launching with only clinical manufacturing*** *is feasible if the facilities are GMP compliant. Comparability exercise could be done after the BLA is approved when comparability from clinical to commercial manufacturing is carried out. If analytical differences are observed, additional clinical data may be required ' p24 of report*

Alternative knowledge/technical approaches to biologics process validation

Potential increase in risk

- Use of prior knowledge/platform data to support reduced /later process validation
- Validation of selective manufacturing process parts
- Register a constrained process & revise post approval (Increased number of CPPs, IPCs and narrow process ranges)
- Decoupling: Use clinical DS to manufacture DP PPQ
- Commence commercial launch from clinical manufacturing site

Potential Regulatory strategies/tools

Benefit : risk : strong scientific risk based CMC approaches

Early Agency Engagement to agree CMC development and submission approaches

Use of rolling review: pre-submission, during review, post approval

Use of flexible PACMPs (timeline, scope, detail), – existing change management procedures and as in ICHQ12

Use of product lifecycle management plans – ICH Q12: product lifecycle planning

Process Validation Protocol with a Post Approval Commitment

Process validation: Use limited amount of process validation data at submission

- Integrating prior knowledge i.e. early batch data and/or platform data into PV justification
- Potentially register a constrained process & revise post approval (Increased number of CPPs due to uncertainty, IPCs and narrow process ranges)

Regulatory strategy:

- Negotiate provision of PV data during review
- Concurrent Validation –aim to complete post approval
- Continued/ongoing process verification

Application in practice

- Products of unmet medical need, have successfully applied this strategy for synthetic and biologic products

Question: Could this be more widely accepted globally

Process validation: Non-sequential DS/DP Proc. Val based on benefit: risk

- Use commercial DS for launch
- Decoupling: Use clinical DS to manufacture DP PPQ

Regulatory strategy:

- Negotiate provision of PV data during review
- Submit Process Validation Protocol/scheme and Post Approval Commitment

Application in practice

- AZ experience where Agencies agreed to launch with use of “unvalidated” Clinical Drug Substance

Question: Could this be more widely accepted globally

Process Validation: Develop master protocols/SOPs to support continuous verification

- Develop master protocol for product validation/verification
- Determine how controlled in QMS and at sites: SOPs
- Share with Agencies so understand plan and activities to be undertaken

Regulatory strategy:

- Negotiate provision of PV data during review
- Submit Process Validation Protocol/scheme and Post Commitment

Applied in practice

- AZ products of unmet medical need, have successfully applied this strategy for synthetic and biologic products

Questions: could this approach be applied globally and information be supplied post approval or even managed within Company QMS?

Post approval impact : will be more PACs

Need to achieve global capacity for drug supplies and prevent drug shortages

- Normal process for major change takes **3-5years** for global approvals
- This could cause, delay in access to medicines for patients or drug shortages
- Need to find a way of aligning - globally

Regulatory strategy for PA changes:

- Data requirements and timings agreed through scientific advice
- Use of reliance or recognition applied across Agencies
- NRAs recognise risk (based on ICH Q9), applying benefit: risk thinking, allowing companies to manage aspects of changes, within their PQS
- Concepts such as ‘established conditions’ e.g. as described in ICH Q12 clearly defining areas to be covered by change management and areas to be managed within a company PQS.
- Use of flexible PACMPs for types of change, could be applied globally.
- Use of Exceptional Change Management procedures for critical medicines e.g. EMA, could be applied globally

Process validation approaches applied to COVID therapeutics or vaccines:

Wish from Industry: One science, one product, one Reg. process - globally

EMA: QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE DURING THE COVID-19 PANDEMIC, April 2020

'for crucial medicines for treatment of COVID-19 patients and where delay in supply may affect those treatment , it is acceptable to conduct process validation concurrently rather than prospectively'

FDA: Development and Licensure of Vaccines to Prevent COVID-19:Guidance for Industry, June 2020

Validation data from the manufacture of platform-related products may provide useful supportive information

Data/process validation protocols, study reports, data from engineering lots, and drug substance process performance qualification. Recommends 2011 guidance be used

CEPI/WHO Regulatory Advisory Group

Questions posed on use of these type of validation strategies e.g. concurrent – reliance requested. Response to be posted on WHO site.

Further build Agency interactions

Use of ICRMA and CEPI/WHO Regulatory Advisory Group to align Agency thinking

Flexibilities and further opportunities for vaccines and other therapies observed for COVID

What is working well - flexibilities:
-Good engagement and early steer on strategies with some Agencies
-Agreed use of platform or prior knowledge data
-Consideration of agile CMC approaches, based on data, e.g. process validation approaches
-Ability to apply ECMPs for supply changes in EU
-Agreement to use rolling reviews and submit proposals and draft M3 document

Further Opportunities:
- Adoption of the flexibilities globally: further engagement with Global Agencies on CMC principles
- Gain agreement to apply 'same' dossier for many markets: same product - same science, development strategies, control strategies, specifications, process validation etc.
- Recognition or reliance for initial licence and apply this **post approval**, including comparability assessment for supply chain changes
- Mutual recognition of inspections

Great opportunity to work together to meet the needs of Global patients, based on benefit: risk - the world is waiting

Key messages: Agile Process validation Regulatory Strategies

There is no one-size-fits-all solution and a combination of approaches may be necessary to avoid delayed submission/ approval for products on an accelerated path

Elements impacting the timing of the approval such as process validation, need to be adapted or waived to avoid delay in getting medicines to global patients
e.g. applying platform knowledge, use of concurrent validation or making such activities post-approval etc.

Quality remains at the heart of development and manufacturing, and safety and efficacy are not compromised

Any questions?