EMA /US FDA Workshop on

support to quality development in early access approaches

Use of Prior Knowledge to Establish Flexible Enhanced Model-based Control Strategies

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Control Strategy : how will it differ in Early Access?

Quality Risk Management
QTPP, CQAs

Control of cell banks

Control of raw materials

Specifications
Release Testing
Stability

Right time release

ICH Q10 - Control Strategy Definition

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

PPQ/CPV
Process Development

Manufacturing process description, design space

In-process testing, process controls document

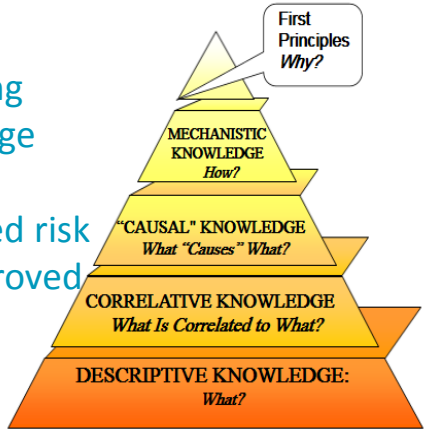
Predictive models

- **Control strategy defined by <u>current</u> product and process understanding, and already accepted that this should evolve with time : need to build on ability to do this for early access approaches**
- **Reality is Early access submissions will have limited commercial manufacturing experience and clinical experience with commercial DP**
- **There may also be limited commercial, if any, DP lots used in clinical trials**
- **Therefore we need to explore how existing guidance e.g. ICH Q8, Q9 and Q10 can be applied in early access approaches and captured for global application**
- **Much will depend on the <u>risk: benefit for the patient</u>, which will drive the level of comfort in a particular early access control strategy**

Control strategies built including knowledge

The knowledge pyramid

Increasing knowledge enables decreased risk and improved controls



Regulatory pathways needed for control strategy evolution with knowledge

Slide 11 May 2008

FIP International Pharmaceutical Federation

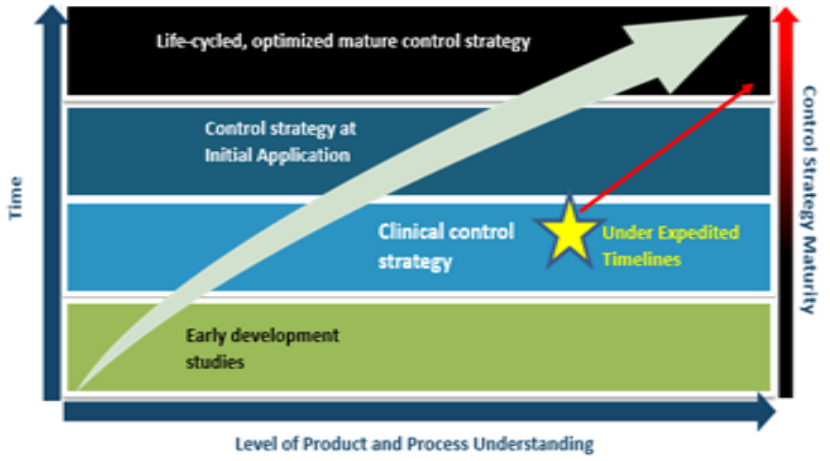
World Health Organization

Courtesy from Ajaz Hussain

Elements, applied across any modality, guarantee quality and a predictable and reliable supply chain:

- A knowledge based process development (verification or validation)
- Intelligent controls that maintain optimal states (maintain the PPQ state or even more optimal states)
- Appropriate specifications limits
- Stability de-riskers that match the supply chain.

Control strategy Maturity Model

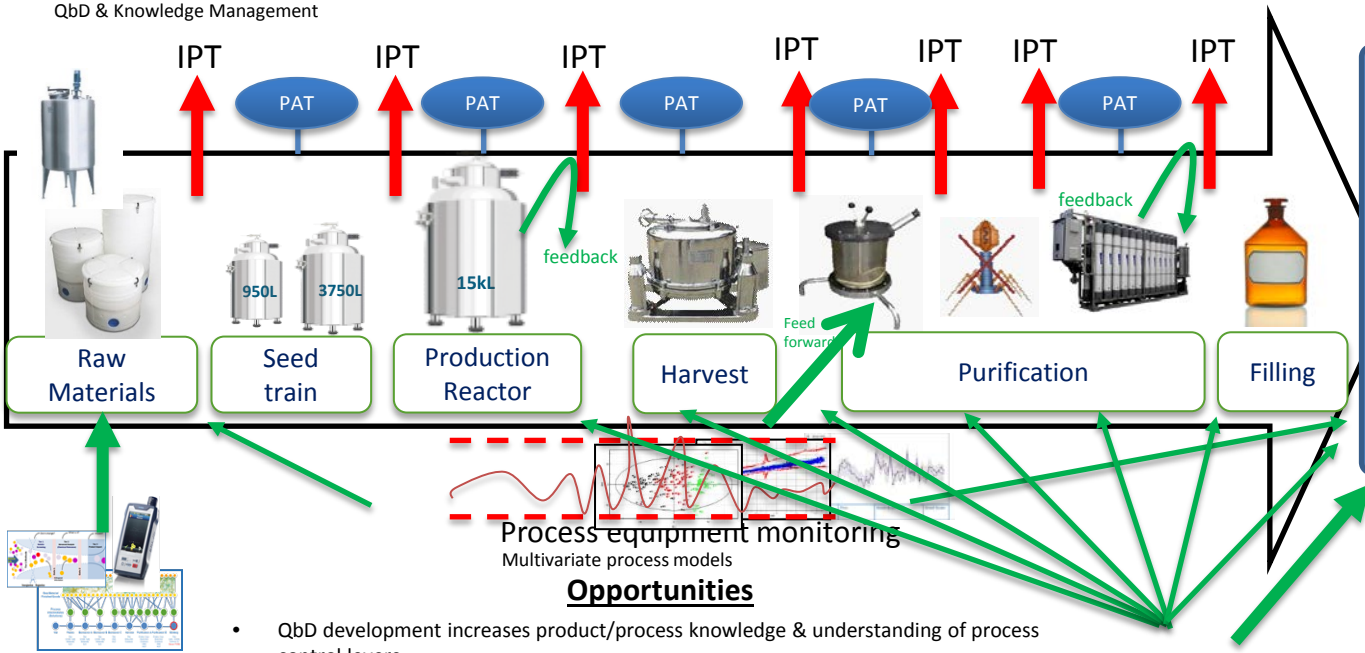


efpia

Control strategy with manufacturing innovation

QbD & Knowledge Management

IPTs tested on manufac floor or QC Lab



Prospective RM Controls

Opportunities

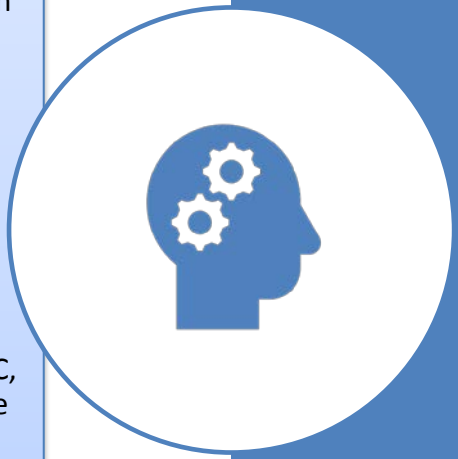
- QbD development increases product/process knowledge & understanding of process control levers
- Extensive RM knowledge allows control (prospective)
- Predictive process models for consistency and product quality
- IPTs tested on the manufacturing floor (where applicable)
- Real-time monitoring and PAT for adaptive control
- Batch release based on testing at point of control & process/product understanding

Batch release testing at point of control (Real or right time quality)

- **Helps build confidence at an earlier stage in a Control strategy**

Potential approaches for agreement to control strategies in early access approaches

1. Proposal is, similar to IMPD submissions, control strategies (and release specifications) are based primarily on scientific strategies and prior knowledge, greater initial **reliance on risk and scientific understanding** with outline of QMS oversight in MAA
2. **Use of prior knowledge** (e.g., non-product specific process, attribute and clinical data; in-vitro / relevant animal data; data from small scale process studies) to establish control strategy with minimal full scale data
3. The approach for molecules with **little or no platform prior knowledge** also needs consideration using aspects of early studies, extrapolation and prediction to establish early, potentially small scale, control strategies via use of innovative control approaches to reassure of safety and efficacy.
4. **Can we just do everything earlier**? Not possible as developing process and product and refining formulation, process and testing, in line with clinical development.
5. **Performance based adaptive process control** (e.g., advance process control (APC)) can also be used to focus control on the final output for high risk attributes through set-point adaptation rather via fixed parameter limits – giving early confidence in control strategy.
6. **Intelligent process control strategies** (like those used in other advanced industries) could be used to increase product and process capability. To develop models for APC, significant amounts of data and intricate process knowledge/ experience (experience with the overarching control strategy) is required.
7. **Post approval Commitments** (e.g. PACMPs and other forms of post-approval commitments) could be used for:
   - Agreement on process and timeline for re-evaluation of control strategies, reporting unexpected trends, and OOS results similar to that currently used in the IMPD, for example after specified number of lots and considering additional clinical and/or commercial experience is an option
   - Agreement on a systematic roadmap for post-approval APC implementation
   - Limitations however from this approach
8. **Global harmonisation ; different acceptance of submission and approval strategies for leveraging development data/lots and therefore many benefits to global patients of harmonisation**



Examples of approaches that may be used for Flexible Enhanced / Model-based Control Strategies for early access pathways

Enabled by:

Technology benefit to patients

- Predictive process modeling
- PAT (at-line, in-line, off-line)
- Adaptive process controls
- Increased Raw Material controls

Quality systems and Business Systems benefit to patients

- Right-time Testing or release testing
- Automation and execution systems
- Robust continuous monitoring
- Knowledge management and use of prior knowledge

Regulatory benefit to patient

- Post-approval change management working with strategies agreed during approval
- Wider and consistent Reg acceptance of PACMPs to minimize change implementation globally
- Elements of QbD submission principles
- Ongoing Engagement & collaboration with Agencies pre and post approval
- Integrated Control Strategy
- Potential for continued review during Inspections?

Envisaged that aspects of the above approaches may be applied to a particular product

Key considerations for Global early access control strategy agreement to meet patient needs

Scientific understanding and risk vs benefit to patient

- **Use of scientific and technical tools to build early patient availability and reliable supply: balance simple fast filing vs implementation of global changes: use of PACMPs defined at an early stage – need to be flexible**
- **Need for dialogue pre and post approval**
- **Try for agreed approach across Agencies and Assessors for a parameter, product or modality to ensure sufficient reassurance**

Examples of opportunities for alignment of approach between Agencies

- Raw material/excipient release and testing – relying on vendor data for majority of testing
- Differing Global compendia requirements
- Use or not of peptide maps
- Classification of key excipients and critical vs non critical process controls
- Application of real time testing and RTRT
- Use of PACMPs and lack of global harmonisation or even acceptance as a regulatory tool for modifications of control strategy post-approval
- Impurity clearance testing – global acceptance of strategy of validating out removal during process validation
- Etc.

Recommendation:

- Use existing regulatory tools consistently – work together to achieve this.
- Generate a timely meeting paper and Q&A type document for existing ICH guidance, to build harmonisation for global early access control strategies

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Back-ups

Definitions

- Advanced Process Control (APC)= the discipline for applying control strategies and/or employing analysis and computation mechanisms to recommend optimized machine settings and detect faults and determine their cause
- Process Analytical Technology (PAT) = system for designing, analyzing, and controlling manufacturing through timely measurements (that is, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality