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Health Products Regulatory Authority

Collaboration on international initiatives

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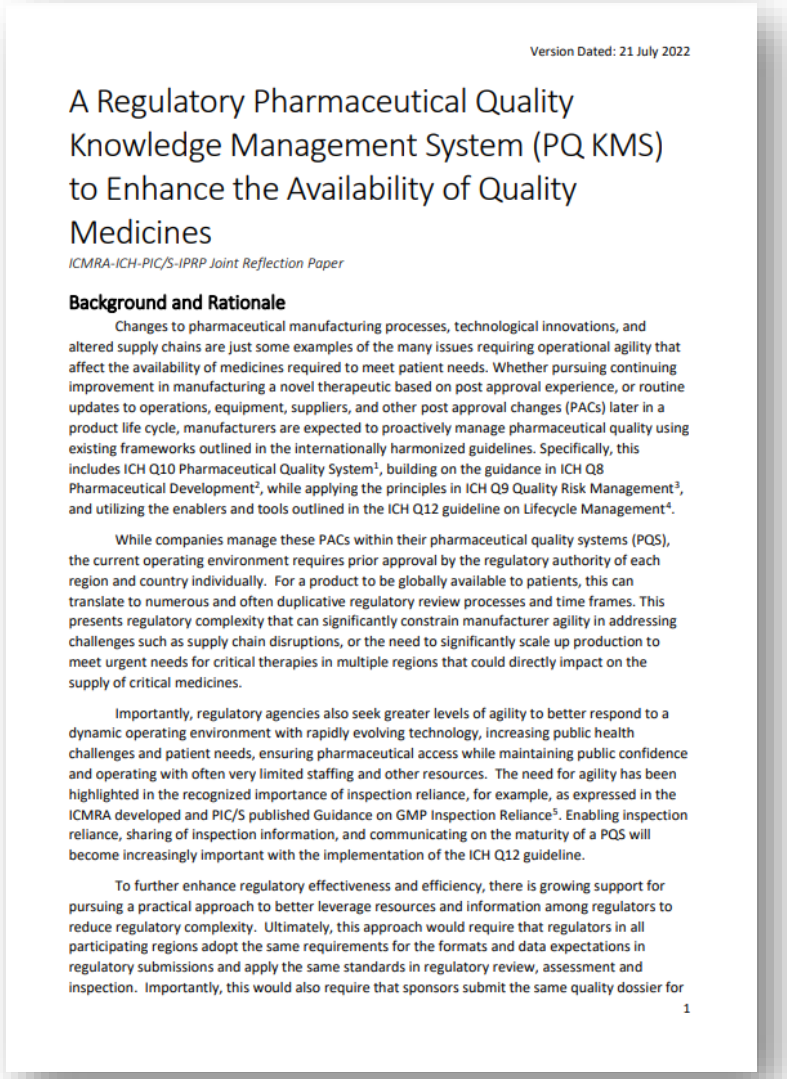

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A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines

ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper

Background and Rationale

Changes to pharmaceutical manufacturing processes, technological innovations, and altered supply chains are just some examples of the many issues requiring operational agility that affect the availability of medicines required to meet patient needs. Whether pursuing continuing improvement in manufacturing a novel therapeutic based on post approval experience, or routine updates to operations, equipment, suppliers, and other post approval changes (PACs) later in a product life cycle, manufacturers are expected to proactively manage pharmaceutical quality using existing frameworks outlined in the internationally harmonized guidelines. Specifically, this includes ICH Q10 Pharmaceutical Quality System[1], building on the guidance in ICH Q8 Pharmaceutical Development[2], while applying the principles in ICH Q9 Quality Risk Management[3], and utilizing the enablers and tools outlined in the ICH Q12 guideline on Lifecycle Management[4].

While companies manage these PACs within their pharmaceutical quality systems (PQS), the current operating environment requires prior approval by the regulatory authority of each region and country individually. For a product to be globally available to patients, this can translate to numerous and often duplicative regulatory review processes and time frames. This presents regulatory complexity that can significantly constrain manufacturer agility in addressing challenges such as supply chain disruptions, or the need to significantly scale up production to meet urgent needs for critical therapies in multiple regions that could directly impact on the supply of critical medicines.

Importantly, regulatory agencies also seek greater levels of agility to better respond to a dynamic operating environment with rapidly evolving technology, increasing public health challenges and patient needs, ensuring pharmaceutical access while maintaining public confidence and operating with often very limited staffing and other resources. The need for agility has been highlighted in the recognized importance of inspection reliance, for example, as expressed in the ICMRA developed and PIC/S published Guidance on GMP Inspection Reliance[5]. Enabling inspection reliance, sharing of inspection information, and communicating on the maturity of a PQS will become increasingly important with the implementation of the ICH Q12 guideline.

To further enhance regulatory effectiveness and efficiency, there is growing support for pursuing a practical approach to better leverage resources and information among regulators to reduce regulatory complexity. Ultimately, this approach would require that regulators in all participating regions adopt the same requirements for the formats and data expectations in regulatory submissions and apply the same standards in regulatory review, assessment and inspection. Importantly, this would also require that sponsors submit the same quality dossier for

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ICMRA
International Coalition of Medicines Regulatory Authorities

ICH
harmonisation for better health

IPRP
International Pharmaceutical Regulators Programme

PIC/S

https://www.icmra.info/drupal/sites/default/files/2022-08/pqkms_joint_reflection_paper.pdf

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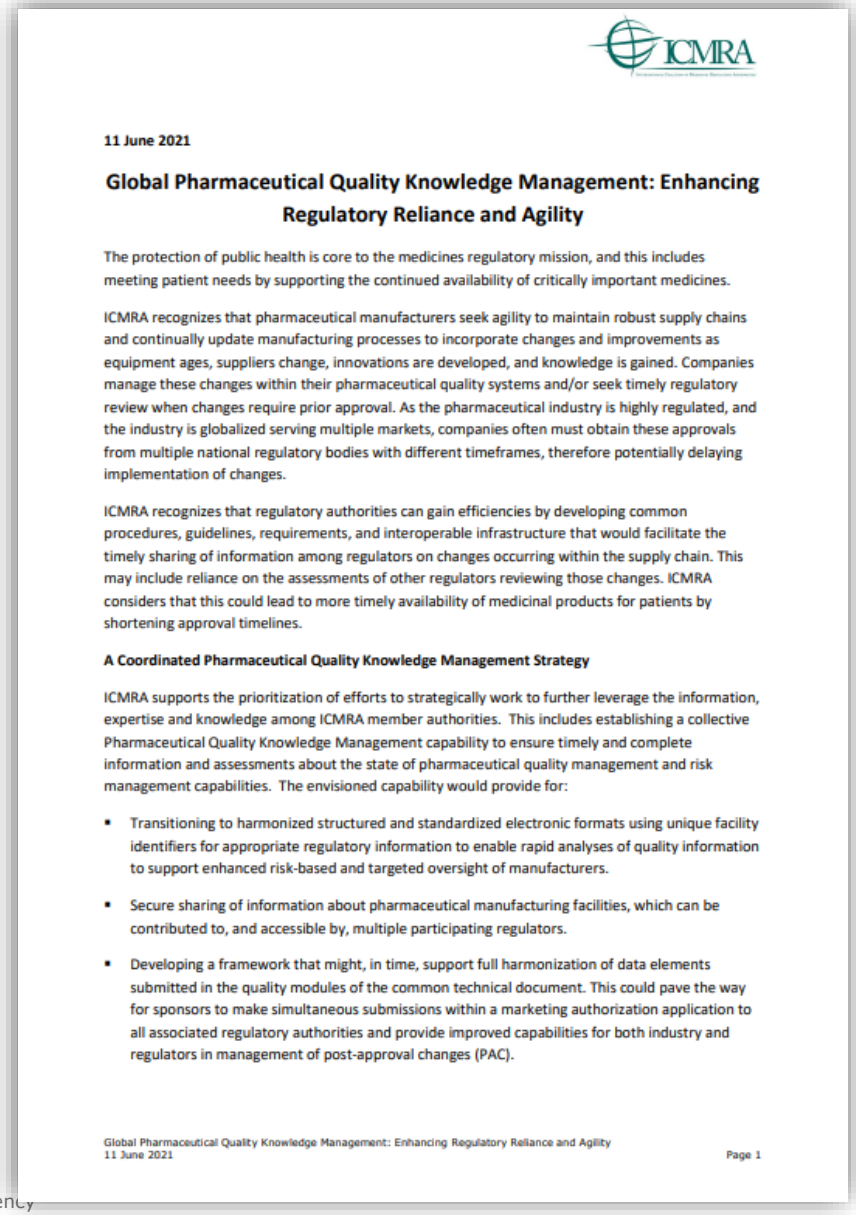
PQ KMS ICMRA Strategic Priority

Leveraging Collective Knowledge and Intelligence

"Transitioning to ***harmonized structured and standardized*** electronic formats…to ***support risk-based*** and ***targeted oversight***"

"Developing a framework that might, in time, ***support full harmonization of data*** elements submitted in the quality modules of the common technical document."

"Enabling ***more extensive mutual reliance***…so that regulators can be assured of the comparability of the assessments and related determinations…"



ICMRA

11 June 2021

Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility

The protection of public health is core to the medicines regulatory mission, and this includes meeting patient needs by supporting the continued availability of critically important medicines.

ICMRA recognizes that pharmaceutical manufacturers seek agility to maintain robust supply chains and continually update manufacturing processes to incorporate changes and improvements as equipment ages, suppliers change, innovations are developed, and knowledge is gained. Companies manage these changes within their pharmaceutical quality systems and/or seek timely regulatory review when changes require prior approval. As the pharmaceutical industry is highly regulated, and the industry is globalized serving multiple markets, companies often must obtain these approvals from multiple national regulatory bodies with different timeframes, therefore potentially delaying implementation of changes.

ICMRA recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain. This may include reliance on the assessments of other regulators reviewing those changes. ICMRA considers that this could lead to more timely availability of medicinal products for patients by shortening approval timelines.

A Coordinated Pharmaceutical Quality Knowledge Management Strategy

ICMRA supports the prioritization of efforts to strategically work to further leverage the information, expertise and knowledge among ICMRA member authorities. This includes establishing a collective Pharmaceutical Quality Knowledge Management capability to ensure timely and complete information and assessments about the state of pharmaceutical quality management and risk management capabilities. The envisioned capability would provide for:

- Transitioning to harmonized structured and standardized electronic formats using unique facility identifiers for appropriate regulatory information to enable rapid analyses of quality information to support enhanced risk-based and targeted oversight of manufacturers.
- Secure sharing of information about pharmaceutical manufacturing facilities, which can be contributed to, and accessible by, multiple participating regulators.
- Developing a framework that might, in time, support full harmonization of data elements submitted in the quality modules of the common technical document. This could pave the way for sponsors to make simultaneous submissions within a marketing authorization application to all associated regulatory authorities and provide improved capabilities for both industry and regulators in management of post-approval changes (PAC).

Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility
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https://www.icmra.info/drupal/sites/default/files/2021-06/pqkms_statement.pdf

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Objectives of the regulatory PQ KMS project

- Strengthen international collaboration to support global development, manufacture, and supply of medicinal products
- Better leveraging of resources and information among regulators to reduce regulatory complexity
- Standardization and harmonization of **structured electronic data** for regulatory submission
- Develop a framework to support full harmonisation of data elements submitted in Module 3
- Move towards regulators adopting the same requirements for the **format** and **data expectations** in regulatory submissions and apply the **same standards** in regulatory review, assessment and inspection
  - Unique product identifiers
  - Unique facility identifiers
  - A commonly agreed data standard for information exchange

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Proposed areas of harmonization work

Harmonisation of data elements and standards

Alignment of regulatory assessment and expectations

Harmonizing inspections, structured data format for inspection reports

Collaborative assessment and hybrid inspection pilots

Cross-organizational collaboration, unique Identifiers

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Benefits of the regulatory PQ KMS project

- Harmonized data expectations facilitating further convergence, collaboration and reliance in assessment and inspections between regulators
- Secure sharing of confidential and non-confidential information among regulatory authorities
- Rapid integration and analyses of quality information that will support efficient and enhanced risk-based and targeted oversight of manufacturers.
- Developing a framework to support the possibility for simultaneous filing of common data sets to all regulatory authorities
- More extensive reliance among regulators on the supervision of manufacturing facilities → structured data formats for inspection reports.

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Moving toward harmonised and structured manufacturing/CMC data

- Currently the submission and assessment of quality related data in Module 3 is very manual and labour intensive
- Different data and submission requirements between international regulatory agencies create significant challenges for CMC data management of global medicines
- This data must be submitted to regulatory authorities through electronic or paper based documentation to support clinical trials, new product approvals, and lifecycle management
- Moving from unstructured data in PDFs to structured machine readable CMC data submitted using cloud based systems provides huge opportunities for advanced analytics and machine learning approaches, which to date have been underutilised in CMC
- With the proper infrastructure, there is an opportunity to significantly increase the efficiency of regulatory submission and review, and support regulatory decision making

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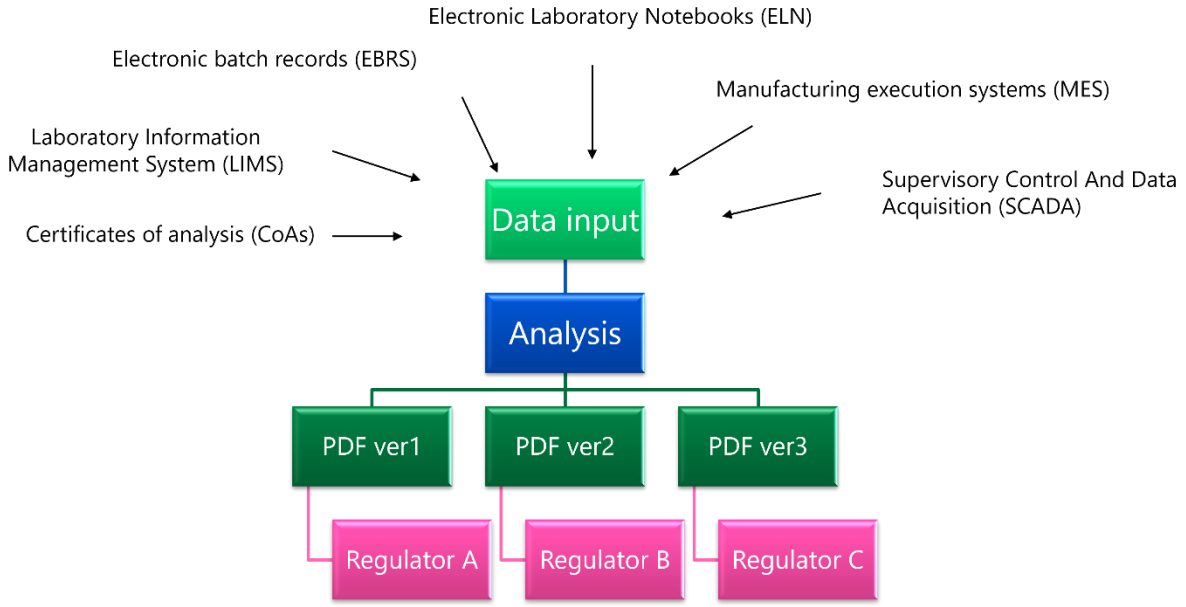
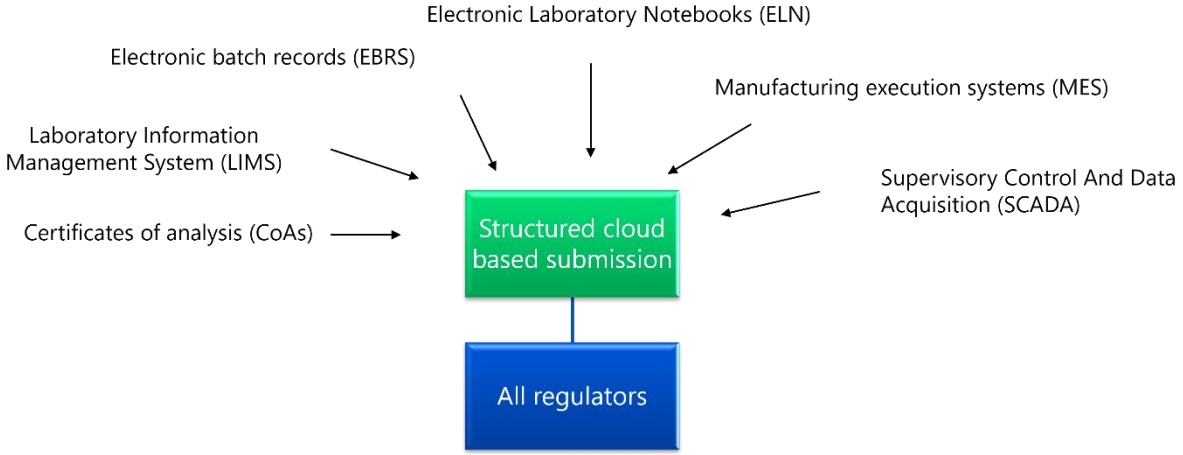
Current state



- Data in PDF format is static and needs multiple rounds of author and reviewer approval before changes can be made
- A typical Module 3 can contain 100s of PDFs with 1000s of pages of narrative text
- Data embedded in PDFs cannot be easily analysed by regulators
- Different global regulatory requirements result in numerous versions of the same PDF adapted to suit local needs

Future state



- Cloud based structured data is dynamic and can be updated rapidly as new information is generated
- Potential to increase the speed and efficiency with which CMC data can be transmitted to regulators
- Facilitate the use of data analytics tools by regulators
- Supports regulatory harmonisation and reliance
- Complements Pharma 4.0 approaches

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Use of machine learning, data analytics, and AI in manufacturing and CMC

- Manufacturing processes are data rich; collection of this data is an enabler for:
  - Improving knowledge & decision making
  - Enhanced process control and increased process capability
  - Real time monitoring, prediction and control
  - Improving overall product quality
- Machine learning and AI may offer opportunities to improve regulation, either by being more efficient and freeing resources or by enhancing support for regulatory science and decision making
- Some current examples of machine learning and AI used for CMC data
  - Using training and validation data sets to replace human visual inspection of vials and syringes by AI
  - Using natural language processing (NLP) to examine deviation reports
  - Using machine learning (e.g. neural network) for predictive stability modelling
  - Applying machine learning models and predictive analytics to quality defect reports and make predictions about the effectiveness of a company's PQS

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Potential impact of data analytics on regulation of CMC

- Big data approaches are already being used by industry to analyse manufacturing data
- However, the big data approaches designed for the clinical space may not be readily transferred to CMC data
- Therefore there is a need to consider the impact of big data, machine learning and AI on regulation of CMC in the medium to long term
- For new data analytics approaches, it remains to be decided which data is required for Module 3 and which data can be part of the PQS and examined during GMP inspections
- There are GMP considerations including regulatory focus on data integrity, security & management of data (GMP Annex 11)
- Do we have the right experts? - writing code, data analytics, AI, Bayesian statistics, data visualisation techniques etc. Need for inspectors to assess systems and to understand concepts, model metrics and statistics?
- How to deal with algorithms which adjust manufacturing processes in real time. Current regulation was not devised with this possibility in mind
- Need for future regulatory guidance?

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