Cloud-based Assessment and ICH M4Q(R2) Revision

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Pharmaceutical Quality

- A quality product of any kind consistently meets the expectations of the user – drugs are no different
- Patients expect safe and effective medicine with every dose they take
- Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects
- It is what gives patients confidence in their next dose of medicine

Patients Deserve Quality Medications

From our perspective: Patients deserve quality medications

https://www.fda.gov/drugs/news-events-human-drugs/our-perspective-patients-deserve-quality-medications

Lawrence X. Yu, Ph.D., Acting Director of FDA's Center for Drug Evaluation and Research's Office of Pharmaceutical Science, discusses the important roles of FDA and drug companies in ensuring quality drug products.

Drug quality -- a shared responsibility

Consumers expect and deserve access to safe, effective, high-quality drugs and it's up to both the FDA and manufacturers to make sure that they are available. It is FDA's job to establish standards, conduct pre-marketing reviews and inspections, and perform post-marketing surveillance and investigations to safeguard that all U.S. marketed drugs are safe, effective and of adequate quality. Drug companies have a responsibility to meet these standards to ensure that quality products reach patients.

One quality voice

Failures in drug quality put patients at unnecessary risk. When quality issues arise in manufacturing facilities, product recalls and plant shutdowns can follow, often resulting in drug shortages. By far, the most frequently cited reasons – approximately 65 percent – for drug shortages relate to manufacturing and quality issues. These

The Future of Pharmaceutical Quality

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The future of pharmaceutical quality and the path to get there

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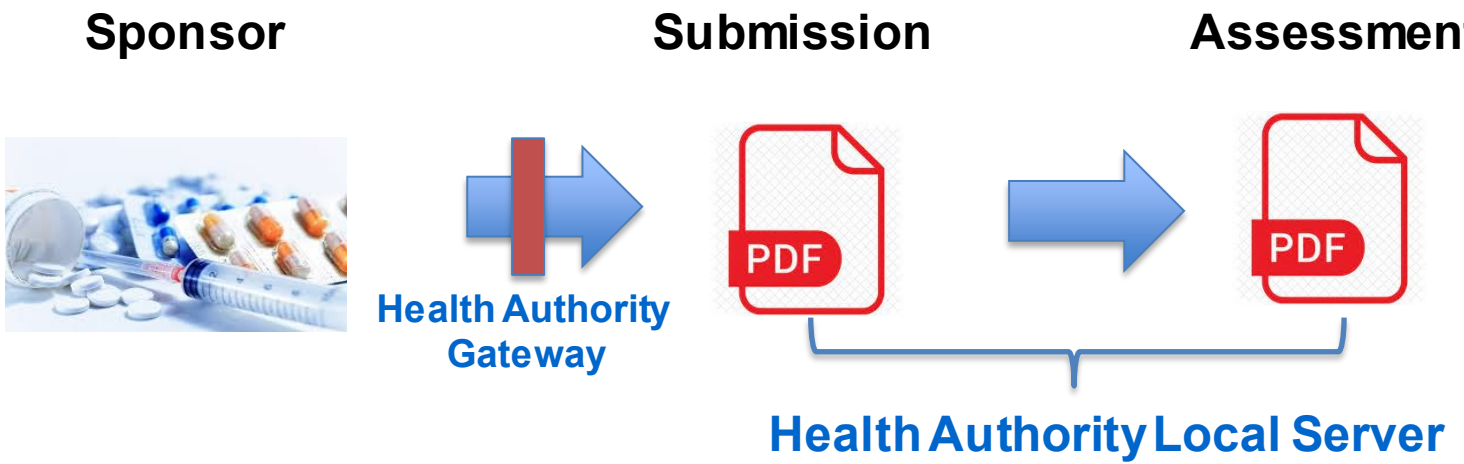
6σ

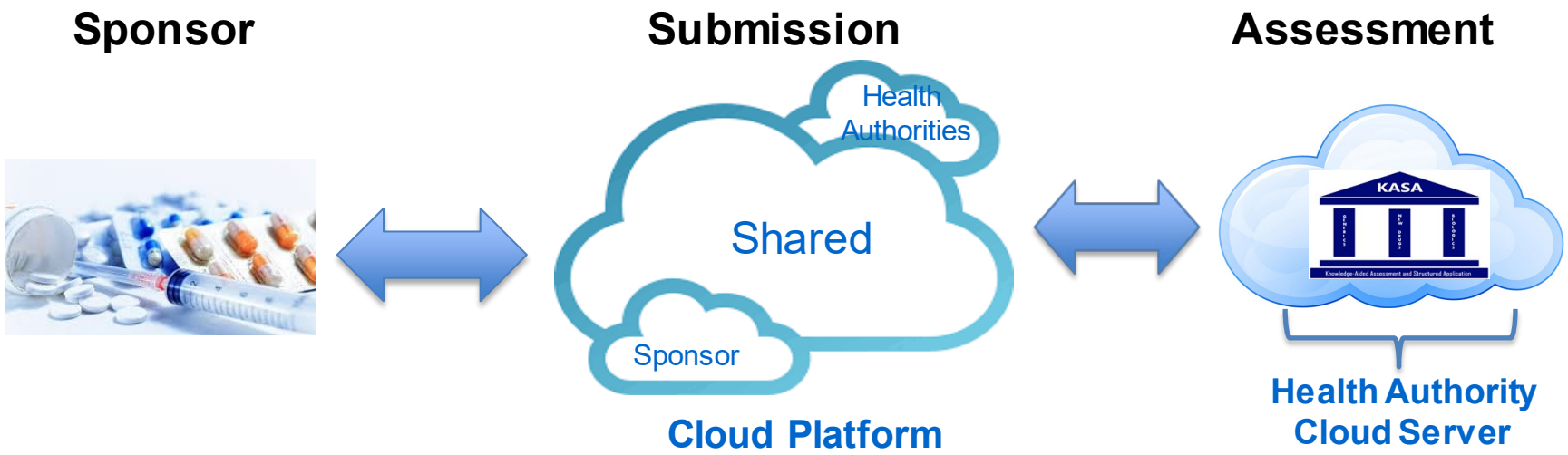
A Six Sigma Capable Process is Expected to Have No More than 3.4 Defects per Million Opportunities

Current Regulatory Submission and Assessment



Characteristics: Lengthy unstructured text narrative with dispersed information and the lack of efficient information exchange, knowledge management, and data analytics

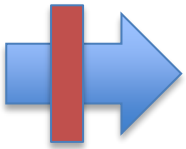
Future Regulatory Submission and Assessment



Characteristics: Both regulatory submission and review moves to structured data format enabling efficient application, information exchange, knowledge management, and data analytics

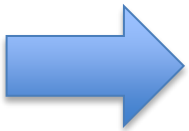
FDA's Pharmaceutical Quality Assessment is Moving into Cloud

Sponsor | **Submission** | **Assessment**



Health Authority Gateway

Health Authority Local Server



Health Authority Cloud Server

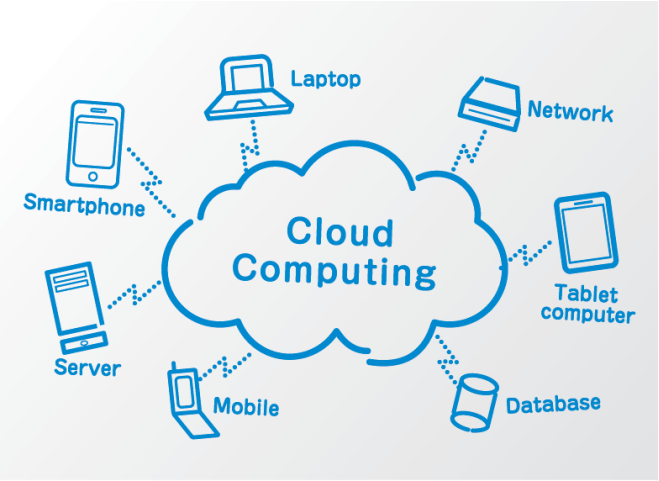
Characteristics: Lengthy submission with unstructured text narrative and the lack of efficient information exchange. Regulatory review moves to structured data enabling efficient knowledge management and data analytics

The Path to Get There?

- Cloud-Computing
- ICH M4Q Revision
- Structured Data Standard
- Regulatory Review Digitalization

World is Moving to Cloud Computing?

- Cloud computing is the on-demand availability of computer system resources, especially data storage and computing power, without direct active management by the user
- Benefits of Cloud Computing
  - Global scale
  - Flexibility and Agility
  - Elasticity
  - Efficiency and Strategic Value
  - Cost



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What's M4Q Designed to Do?

- Provides a harmonized structure and format for presenting quality information in Common Technical Document (CTD)/electronic CTD for registration of pharmaceuticals for human use
  - *Module 2 Quality Overall Summary (QOS)*
  - *Module 3 Quality*
- M4Q(R1) was developed in 2002
- Major improvement over paper/local submission formats

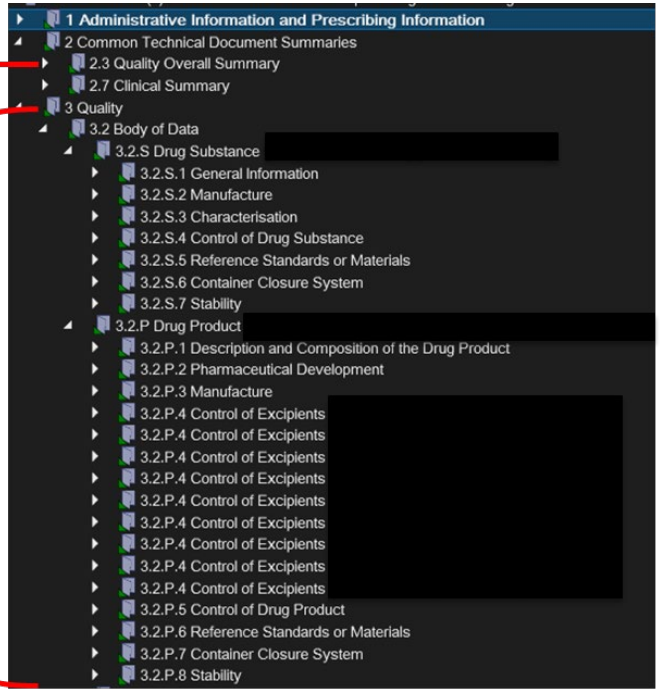
Current M4Q(R1) (2002)

- ***Module 2 CTD Summaries***

includes summarization of information from Module 3 in the Quality Overall Summary (QOS)

- ***Module 3 Quality***

Body of data displays quality data pertaining to drug substance and drug product manufacturing, analytical methods, process development, specification testing, reference standards, container closure system, and stability



ICH The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality M4Q(R1) Quality overall Summary of Module 3, Module 3: Quality, September 2002
FDA Guidance for Industry M4Q: The CTD – Quality, August 2001

What Are Perceived Problems with M4Q(R1)?

- M4Q(R1) is now due for revision to further improve registration and lifecycle management efficiency, leverage digital technologies, and accelerate patient and consumer access to pharmaceuticals. The specific drivers for this revision include:
  1. Several ICH regions have not fully implemented ICH M4Q(R1). The modernization will support and clarify global understanding of the CTD, enabling greater regulatory convergence and harmonization, and decrease redundancy.
  2. The M4Q(R2) guideline should align with modern quality guidelines Q8-Q14, and other relevant ICH guidelines that have been developed or given greater focus since the issuance of ICH M4Q(R1).
  3. The M4Q(R2) guideline should provide guidance on the location of information supporting multicomponent and/or complex products, such as antibody-drug conjugates, vaccines, ATMPs/Cell & Gene Therapies & Tissue Engineered Products or combination products that meet the definition of a pharmaceutical or biological product.
  4. The M4Q(R2) guideline should facilitate leveraging advances in digital tools, data management and standardization, and analytics to enhance efficiencies and effectiveness of regulatory submissions and assessments, although the structured pharmaceutical quality submission is beyond the scope of M4Q(R2) guideline.

What Are the Issues to be Resolved?

- The main issues to be resolved during this revision include:
  1. Expanding the scope of M4Q(R1) guideline. This M4Q(R2) guideline applies to all pharmaceutical drug substances and products (both chemical and biological) that require a marketing authorization. These may include multicomponent and/or complex products, such as antibody-drug conjugates, vaccines, ATMPs/Cell & Gene Therapies & Tissue Engineered Products or combination products that meet the definition of a pharmaceutical or biological product.
  2. Establishing the role of M4Q(R2) as the main source of the structure and location of regulatory quality information. The guideline should specify the location of lifecycle management elements. It should address diversity in requirements for quality information across ICH regions and streamline the requests for PQS and GMP information.
  3. Organizing product and manufacturing information in a suitable format for easy access, analysis, and knowledge management. The revision should facilitate inclusion of information supporting emerging concepts such as advanced manufacturing, digitalization, data management, artificial intelligence, and advanced analytical tools.

What Are the Issues to be Resolved (continued)?

4. Incorporating concepts and data expectations presented in ICH Quality guidelines and aligning with currently recognized international standards and guidelines. The M4Q(R2) should enable better use of prior knowledge and ensure that the level of detail and data of the dossier is commensurate with the risk to the product's quality.
5. Better capturing the pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure. This should address key elements of the proposed pharmaceutical product, including the Quality Target Product Profile (QTPP), manufacturing process, and overall control strategy. It may also include elements of the product and process development and understanding.
6. Enhancing the Quality Module 2 to facilitate the efficiency and effectiveness of regulatory submissions and assessments. The Quality Module 2 may discuss product quality benefit-risk considerations, summarise the pharmaceutical development, and present an overall understanding of the product quality, which may include risk and criticality assessment as per available Quality guidelines. The Quality Module 2 may also incorporate key elements of ICH Quality guidelines including lifecycle management tools to ensure product safety, efficacy, and quality.

M4Q(R2) Objectives

- M4Q(R2) guideline will improve submission and assessment efficiency, resulting in accelerated access to pharmaceuticals by (6Es):
  1. Encouraging global convergence of science- and risk-based regulatory approaches in the preparation of dossiers.
  2. Explaining and defining the organization and positioning of information for Modules 2 and 3.
  3. Enriching communication between regulators and applicants and enhancing lifecycle and knowledge management.
  4. Embracing product and process innovation.
  5. Enabling efficient use of digital tools for submission and assessment and preparing for the closely linked, upcoming ICH guideline on structured pharmaceutical quality submission.
  6. Elucidating regulatory expectations and supporting efficient assessments, decision-making, and actions.

What Are the Impacts?

- M4Q(R2) guideline would speed up patients and consumers' access to pharmaceuticals
  - For patients and consumers, it would ensure rapid and continuing access to new products by bringing a streamlined and consistent approach to the registration and lifecycle management of pharmaceuticals.
- M4Q(R2) guideline would be of great benefit to industry
  - For industry, it would clarify regulatory expectations, facilitate applying the enhanced ICH quality strategy/vision, streamline regulatory application preparation, improve the quality of submissions, facilitate data and information management, promote communication with regulators, and foster harmonisation and standardisation of data/information requirements for regulatory submissions, while increasing regulatory convergence.
- M4Q(R2) guideline would be of great benefit to regulators
  - For regulators, it would enhance benefit-risk considerations, increase access to quality data and information, streamline regulatory assessment, facilitate oversight of pharmaceutical product quality, increase consistency and efficiency in regulatory decision-making and actions, and improve communication with industry and among regulators.

M4Q(R2): Progress

- May 2020, ICH endorsed the M4Q(R2) Proposal
- April 2021, ICH approved the outline of Concept Paper
- Aug 2021, ICH formed M4Q(R2) informal WG
- Nov 2021, ICH approved M4Q(R2) Concept Paper and Business Plan

M4Q(R2): Work Plan

Expected Completion date	Deliverable
2021	✓ Final Concept Paper and Business Plan
2022	• Face to face EWG meetings and ICH M4Q(R2) Step 1
2023	• Face to face EWG meetings and ICH M4Q(R2) Step 2 and Step 3
2024	• Face to face EWG meetings and ICH M4Q(R2) Step 4
2025 and after	• Forming an implementation WG to provide training and monitor the implementation of M4Q(R2)

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Data Standards Development Approach

Data Requirements Sources

- **DSST Report**
- CDER / CVM / CBER **SME Team**
- SRS / eCTD / **FDA Initiatives** / eCo / IDMP / mp
- **FDA Terminology Groups**

Serve as foundation for data requirements

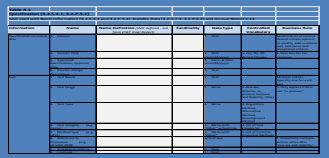
Provide additional req. and extend DSST req.

Inform representation of common touch points - Substance, Products, etc.

Leverage existing FDA terminology standards

Project Requirements Work Products

Data req. capture worksheet



PQ /CMC UML Model

Future Implementation Products

PQ/CMC Data Exchange Options: HL7 SPL & eStability; HL7 FHIR

PQ/CMC Database TBD

Adopted from the OSP-led PQ/CMC Updates on 11/03/2020

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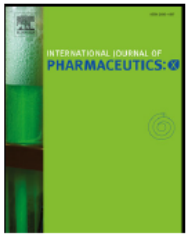

FDA's new pharmaceutical quality initiative: Knowledge-aided assessment & structured applications

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Knowledge management
Risk assessment
Risk control
Structured application

ABSTRACT

This paper describes
Structured Applicatio
lifecycle of a drug pro
perform computer-aid
plications and faciliti
summarization of pro
tiveness, efficiency, and consistency of regulatory quality oversight through lifecycle management of products and facilities, and information sharing in a standardized and structured format. Ultimately, KASA will advance FDA's focus on pharmaceutical *quality*, the foundation for ensuring the safety and efficacy of drugs.

Taking advantage of digital innovation, KASA is a system to modernize regulatory submission, review, and approvals using structured data, advanced analytics, and knowledge management

Summary

- ✓ Cloud-Computing
- ✓ ICH M4Q Revision
- ✓ Structured Data Standard
- ✓ Regulatory Review Digitalization

Acknowledgement

Thank You

FDA U.S. FOOD & DRUG ADMINISTRATION

Effective leadership Collaborative relationships

Encourage innovation **Risk-based approaches**

One Quality Voice

Patients first Team-based processes

Developing and utilizing staff expertise

Scientifically-sound quality standards

KASA
Generics | New Drugs | Biologics