CASSS CMC Strategy Forum,
Gaithersburg, MD
July 17-18, 2023

The Future of Regulatory Submission and Assessment: Impact of Digitalization

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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

Vision for future regulatory submission and assessment

Current Regulatory Submission and Assessment

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

FDA's Pharmaceutical Quality Assessment is Moving into Cloud

Applicant

Health Authority Gateway

Submission

Health Authority Local Server

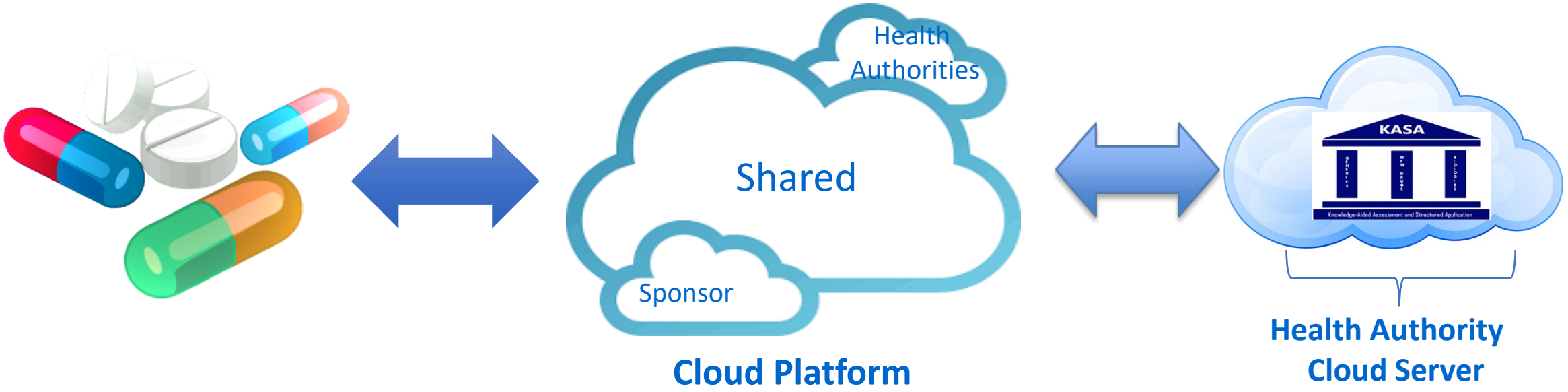
Assessment

Health Authority Cloud Server

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

Future Regulatory Submission and Assessment

Applicant | **Submission** | **Assessment**



Characteristics: Both regulatory submission and assessment move to structured data format enabling efficient regulatory submission and assessment, information sharing, knowledge management, and data analytics

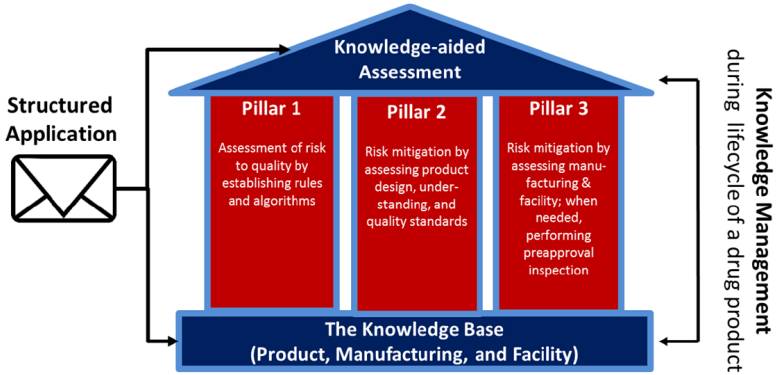
How to Get There?

- Regulatory Assessment Transformation
  - Knowledge-aided Assessment and Structured Applications (KASA)
- Regulatory Submission Transformation
  - Revision of ICH M4Q: Content and Organization
  - ISO Identification of Medicinal Products (IDMP)
  - EMA Substance, Product, Organisation and Referential (SPOR)
- Pharmaceutical Quality Electronic Data Standard and Platform
  - ICH Structured Product Quality Submission (planned, not yet started)
  - FDA Pharmaceutical Quality/CMC
  - Accumulus
- Other Related Program/Topic
  - FDA Orbis Program
  - Reliance Pathway

FDA Knowledge-aided Assessment and Structured Applications (KASA)

FDA Knowledge-aided Assessment and Structured Applications (KASA): Vision

- In 2016, FDA's KASA system was envisioned as a means of digitalizing FDA's assessment (or review) by taking advantage of:
  - Structured data (as opposed to narrative information)
  - Advanced analytics; and
  - Knowledge management



Contents lists available at ScienceDirect

International Journal of Pharmaceutics: X

journal homepage: www.journals.elsevier.com/international-journal-of-pharmaceutics-x

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

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ARTICLE INFO

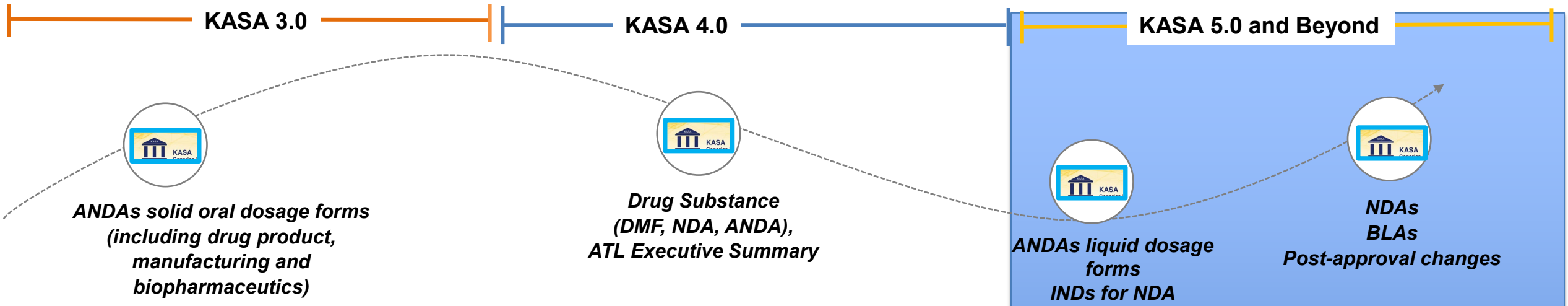
Keywords:
Pharmaceutical quality
Knowledge management
Risk assessment
Risk control
Structured application

ABSTRA

This paper d
Structured A
lifecycle of a
perform com
plications an
summarizatio
tiveness, effi
and facilities
FDA's focus

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

Roadmap for KASA IT Production: Eight Years of Making



KASA 3.0	
2021	KASA 3.0 Release (Feb. 2021): Drug product, Biopharm, and Manufacturing KASA modules for generic solid oral drug products
2022	KASA 3.2 Release (Feb. 2022): Updates to the interface and data analytics

Completed Targets

KASA 4.0	
2023	KASA 4.0 Release: Drug substance (DMF, NDA, ANDA) modules KASA 4.1 Release: ATL Executive summary

Deployed in 2023

KASA 5.0 and beyond	
2024 - 2027	ANDA liquids dosage forms INDs for NDA NDA Drug product BLA • INDs for BLA • DS/DP/viral safety • Analytics/Biosimilars ANDA, NDA, BLA Supplements

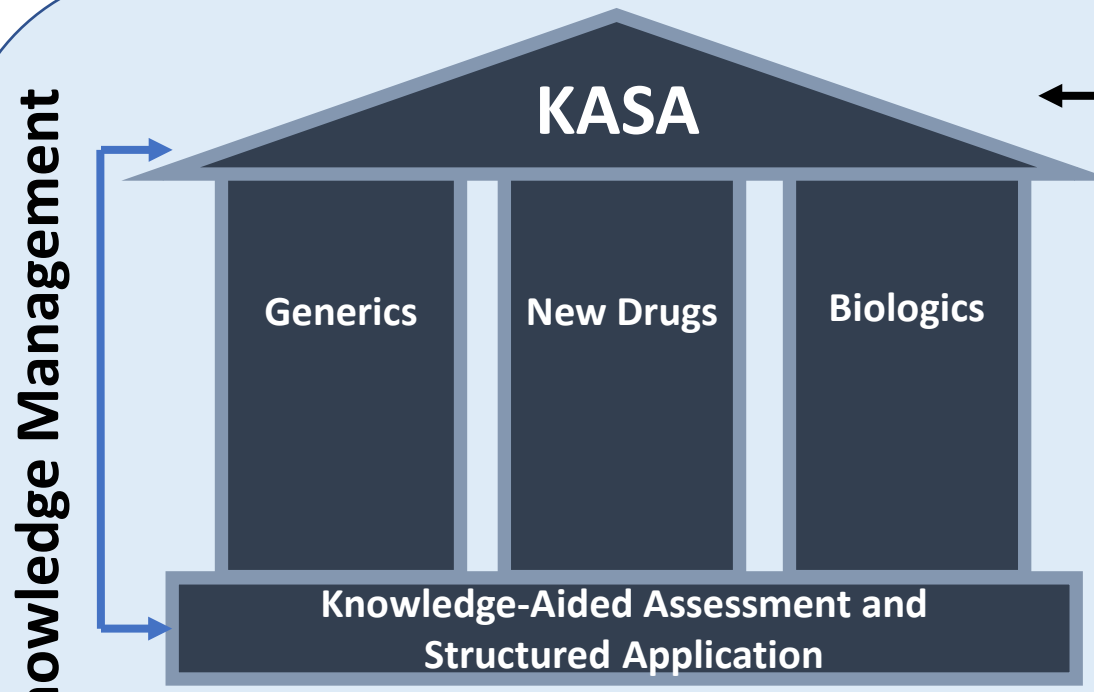
Future Targets

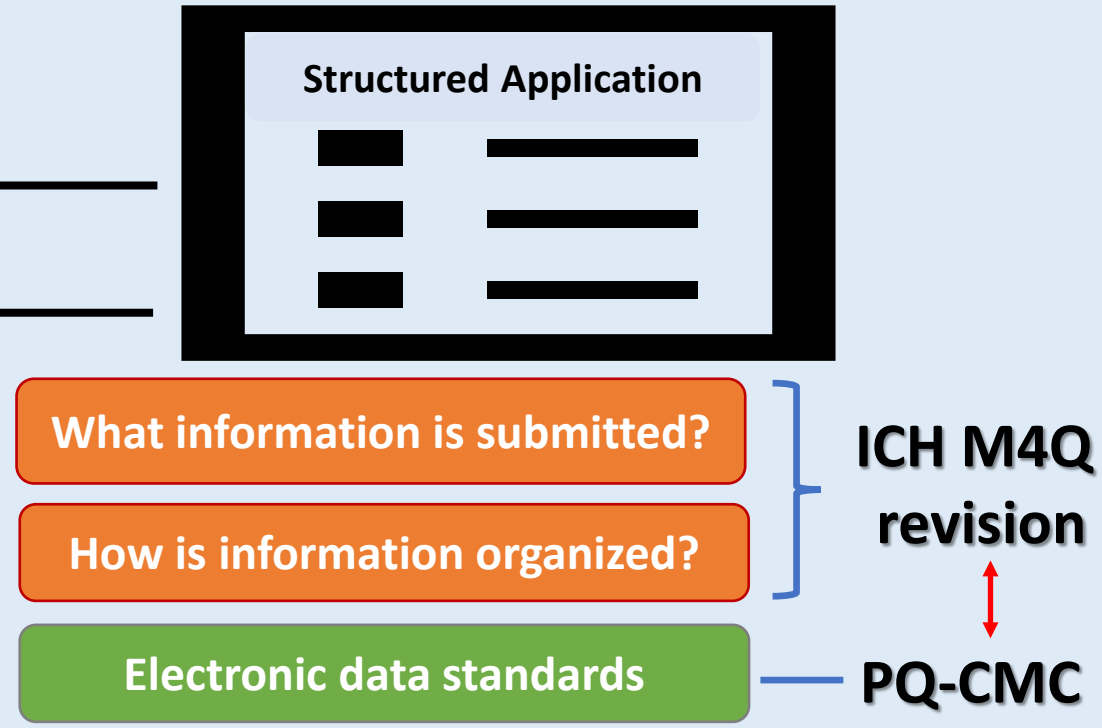
Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee Meeting (2022)

Do you support the long-term strategy for developing and implementing KASA at FDA and expanding the system from generic drugs to new drugs and biologics assessments?

Vote: Yes 13 No 0

The Future KASA System





"KA"

integrated set of tools and framework to aid regulatory assessment and knowledge management

"SA"

content and organization of submission and electronic data standards

ICH M4Q(R2), IDMP, and EMA SPOR

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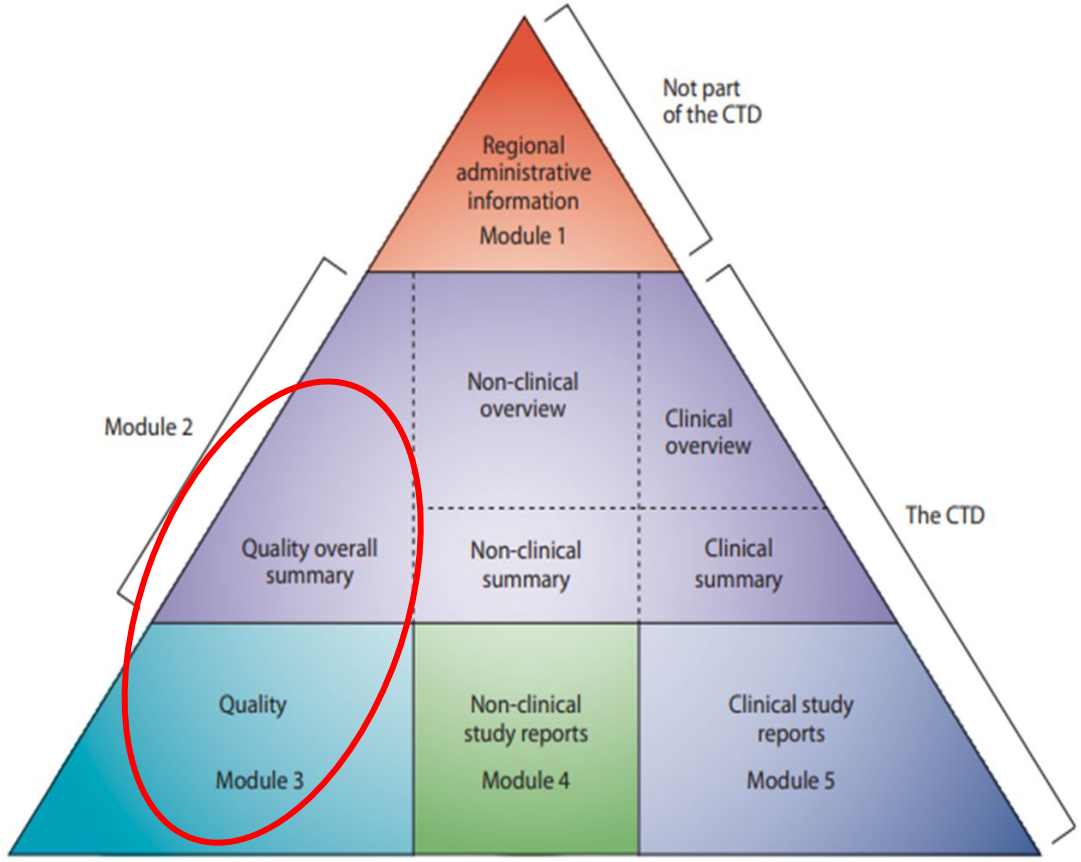
What is M4Q Designed to Do?

- Globally harmonized content and organization of quality information in Common Technical Document (CTD)/eCTD
  - Module 2.3 Quality Overall Summary (QOS)
  - Module 3 Quality
- M4Q(R1) was a substantial improvement compared to the prior state with range of submission formats and shift from paper to electronic



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

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

M4Q(R2) Establishes Module 2 as the Basis for Regulatory Assessment, Supported by Module 3

Current thinking of the EWG

Module 2

- Basis for regulatory assessment, Risk-based approach
- Comprehensive overview of the product and its components
- Product and manufacturing process understanding and overall control strategy
- Lifecycle management

Links for further details

Module 3

- Information and data repository incl. reports, data, protocols, descriptions
- Prepared for SPQS
- Supporting emerging concepts

- M4Q(R2) should enable efficient, effective, patient-centric and globally harmonised submissions, assessment and life cycle management, and minimize dossier redundancies
- Suitable for various types of submission and product modalities

Module 2

Current thinking of the EWG

- M2 should provide a sufficiently comprehensive overview of the pharmaceutical product and its components, including the Quality Target Product Profile (QTPP), manufacturing process, and overall control strategy.
- It should provide a basis for an efficient and effective regulatory submission and assessment, and product-life cycle change management.
- M2 may also support reliance-based approval.
- M2 presents and discusses the critical information, thereby providing a common understanding of the product and manufacturing process factors determining quality as well as providing product quality benefit-risk considerations.
- It may also include Product Life Cycle Management tools as per ICH Q12 guideline.
- M2 may guide the reader how the information is presented throughout the quality part of the dossier.

Module 3

Current thinking of the EWG

- M3 serves as the information and data repository that supports M2 and is presented in a globally standardized/harmonized format.
- M3 should lay the foundation for the Structured Product Quality Submission.
- M3 may comprise detailed information complementary to M2, such as reports, data, protocol, or method descriptions and should be organised in a suitable format for easy access, analysis, and knowledge management.
- Both M2 and M3 should facilitate inclusion of information supporting emerging concepts, such as advanced manufacturing, IT/software components, digitalization, data management, artificial intelligence/machine learning, and advanced analytical tools, to support regulatory assessment.

ISO Identification of Medicinal Products (IDMP)

- IDMP is a suite of five standards developed within ISO External Link Disclaimer to facilitate the unique identification of medicinal products in the context of pharmacovigilance and the safety of medications throughout the world. These standards provide an international framework to uniquely identify and describe medicinal products with consistent documentation and terminologies, as well to ensure the of exchange product information between global regulators, manufacturers, suppliers and distributors.

ISO IDMP Five Standards

- *ISO 11615, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated **medicinal product** information;*
- *ISO 11616, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated **pharmaceutical product** information;*
- *ISO 11238, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on **substances**;*
- *ISO 11239, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on **pharmaceutical dose forms, units of presentation, routes of administration and packaging**;*
- *ISO 11240, Health informatics — Identification of medicinal products — Data elements and structures for theunique identification and exchange of **units of measurement**.*

EMA Substance, Product, Organisation and Referential (SPOR)

- The European Medicines Agency (EMA) is implementing the ISO IDMP standards for the identification of medicinal products in a phased program me, based on the four domains of master data in pharmaceutical regulatory processes: substance, product, organisation and referential (SPOR) data.

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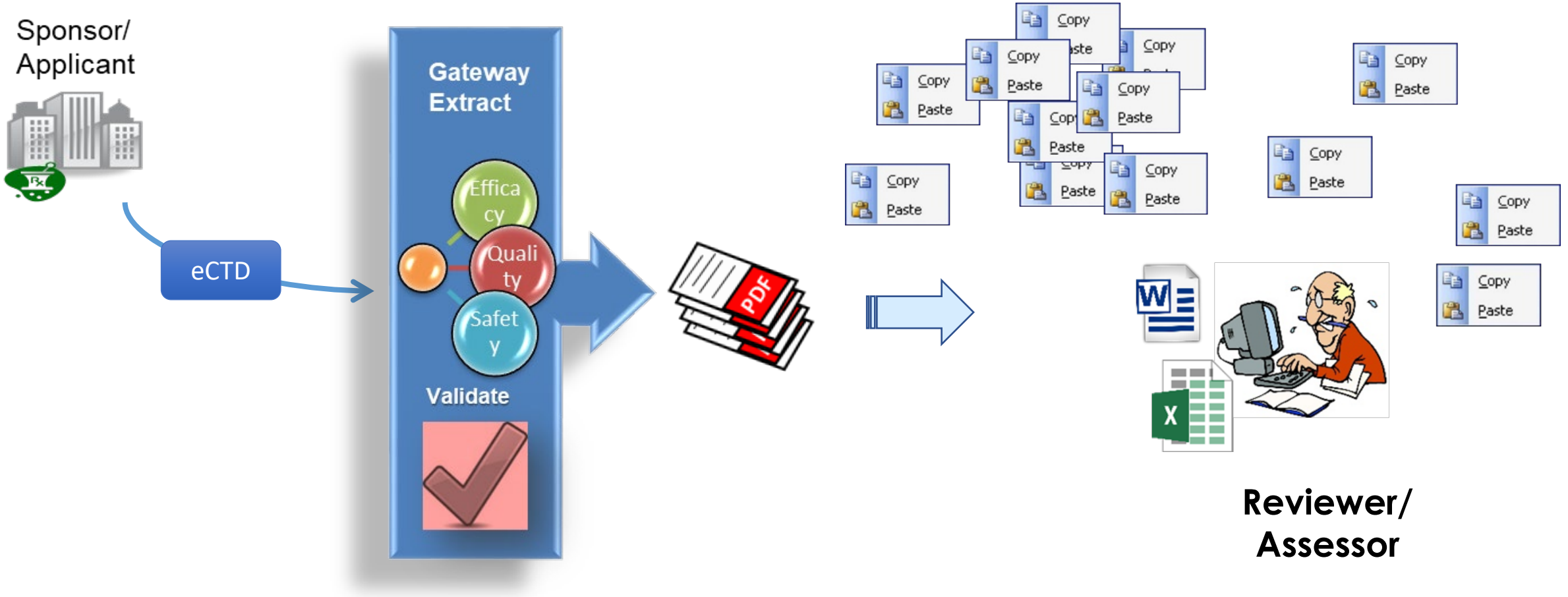
Ongoing efforts related to structured applications

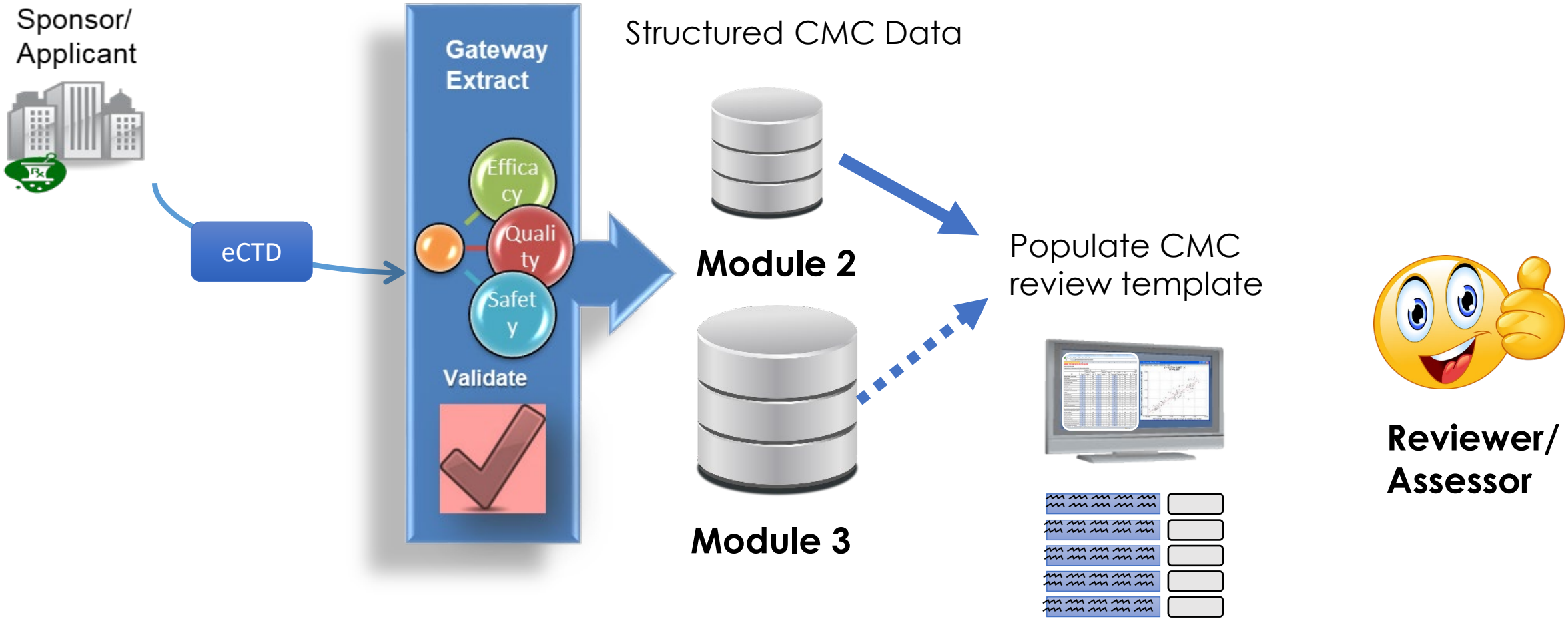
- Pharmaceutical Quality Electronic Data Standards/Platform

Current CMC Data Submissions and Review



Structured CMC Data Submission (ICH SPQS)

Future Data Submissions and Review



FDA Pharmaceutical Quality/CMC

- PQ/CMC structuring and standardization is intended to be accomplished in multiple phases.
  - **Phase 1** covers the following topics: Drug Product, Drug Substance, Quality Specification, Batch Formula, Batch Analysis and Stability
    - Substantially completed by end of 2020; ~ 33% of Module 3 data
  - **Phase 2** data standards are under development, and will cover the following topics: Drug Product Manufacturing, Drug Substance Manufacturing, etc.
    - Initiated in January 2021

For your expanded interest see *Pharmaceutical Quality/Chemistry, Manufacturing & Controls (PQ/CMC)*
Pharmaceutical Quality/Chemistry, Manufacturing & Controls (PQ/CMC) | FDA

Other Related Program/Topic

FDA Orbis Project

- Project Orbis, an initiative of the FDA Oncology Center of Excellence (OCE), is a pilot program that provides applicants with a framework for concurrent submission and review of oncology products among international partners to allow earlier registration in countries outside of the US
- Project Orbis partners include the regulatory authorities of Australia, Brazil, Canada, Singapore, Switzerland, and the United Kingdon. Israel and Japan have participants as observers

FDA Orbis Project

TABLE 2 Comparison of time-to-approval between FDA and Orbis countries[a] for Project Orbis marketing applications[3]

Application type	Median (range), in months [Number of applications]	
	FDA	Orbis countries
All applications	4.2 (0.9, 6.9) [18]	4.4 (1.7, 6.8) [20]
New molecular entities/new active substances	5.1 (3.9, 6.9) [6]	5.9 (3.9, 6.8) [7]
Supplements/variations for new indications	3.6 (0.9, 6.0) [12]	3.3 (1.7, 6.4) [13]

[a]Project Orbis partners include the regulatory health authorities of Australia, Brazil, Canada, Singapore, Switzerland, and the United Kingdom. Israel and Japan have participated as observers.

FDA Orbis Project: Assessment Aid

- The objective of the FDA Orbis project assessment aid is to focus the review on the most critical aspects of the dossier to increase review efficiency and consistency and decrease review time
- The has created an assessment aid template for applicants and has provided guidance for completing this document
- Applicants should consider what **additional time and resources** will be needed to prepare this document and incorporate these details into the overall submission plan

Regulatory Reliance

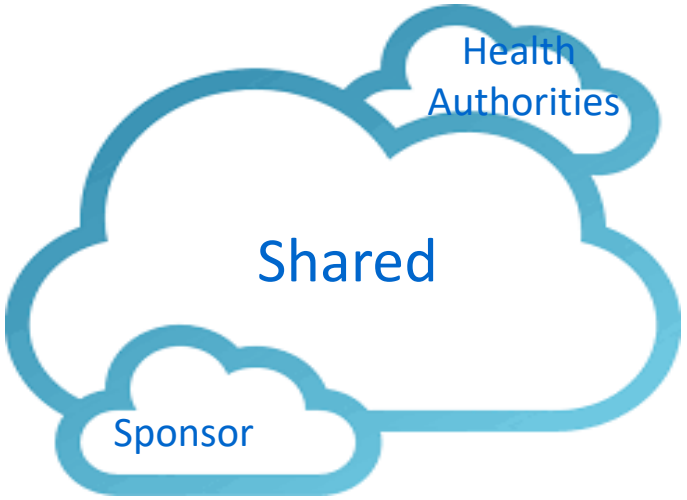
- The World Health Organization (WHO) defines regulatory reliance as
  - The act whereby the national regulatory authority (NRA) in one jurisdiction may take into account and give significant weight to assessments performed by another national regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible, and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

The End Game

Cloud-based Regulatory Submission and Assessment

Sponsor

Submission



Cloud Platform

Assessment

Health Authority Cloud Server

Thank You

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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