CaSSS 2022 CMC Strategy Forum Europe
October 17-19
Brugge, Belgium

U.S. FOOD & DRUG ADMINISTRATION

FDA Perspective on Opportunities for Modernization of Regulatory Submissions

Ingrid Markovic, Ph.D.
Senior Science Advisor
Office of the Center Director, CBER | US FDA
CBER ICH M4Q Lead & CBER ICH Quality Lead

Presentation Outline

Broader FDA Modernization Efforts influencing Regulatory Submission Modernization

Future vision & Drivers for Regulatory Submissions Modernization

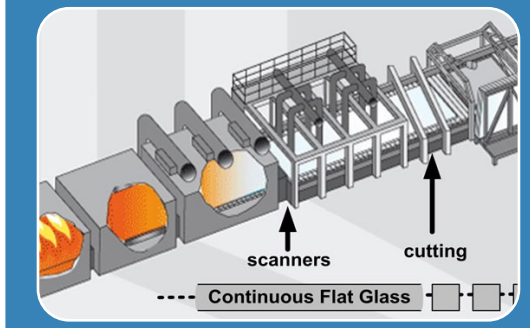
Possible Solutions & Enablers And How They Might Work Together

Examples of FDA Modernization Efforts

U.S. FOOD & DRUG ADMINISTRATION

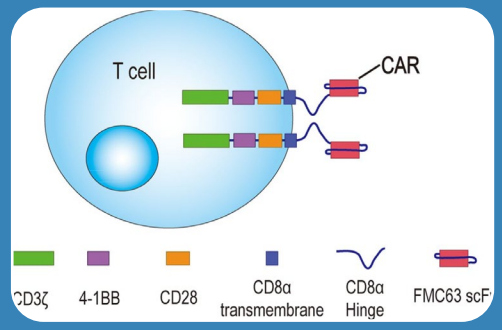
Modernizing FDA's Data Information Technology (IT) & Bioinformatics

- Substantial increase in bioinformatics submissions (genomic data & computational biology approaches) in past 4 years – many in pre-IND or early IND
- Cloud/cloud-based technologies to receive, process & store large volumes of data
- Critical to advance novel technologies and products (e.g., cell and gene therapy products, vaccines, live biotherapeutics)



Advancing Utilization and Implementation of Innovative Manufacturing

- PDUFA VII commitments geared to facilitate adoption of innovative manufacturing technologies (e.g., best practices, case studies, regulatory submission strategies leading to better understanding of overcoming the barriers to adoption of Adv Mfg.)
- CBER CATT & CDER ETT- discussion platforms for novel tech at any stage of development



Investing in Cell and Gene Therapy Programs (specific to CBER)

- Strengthening staff capacity for review of cell and gene therapy products
- Development of regulatory tools and scientific technologies, external collaboration and outreach, & enhancing communication
- Harmonization, enhancing regulatory consistency, review standards, training, etc.

Vision for future regulatory submission and assessment

Application Assessment Challenges

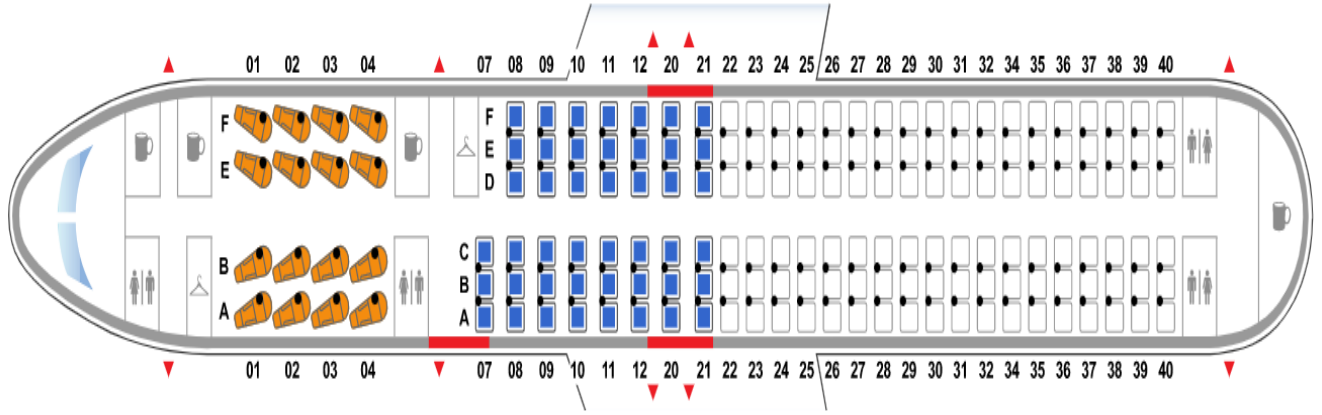
External Challenges

- Volume & complexity of new applications
- Accelerated timelines
- User fee program expectations
- Commissioner, Congress, the pharma industry, and the public expectations
- Complexity of Biological Products under CBER purview

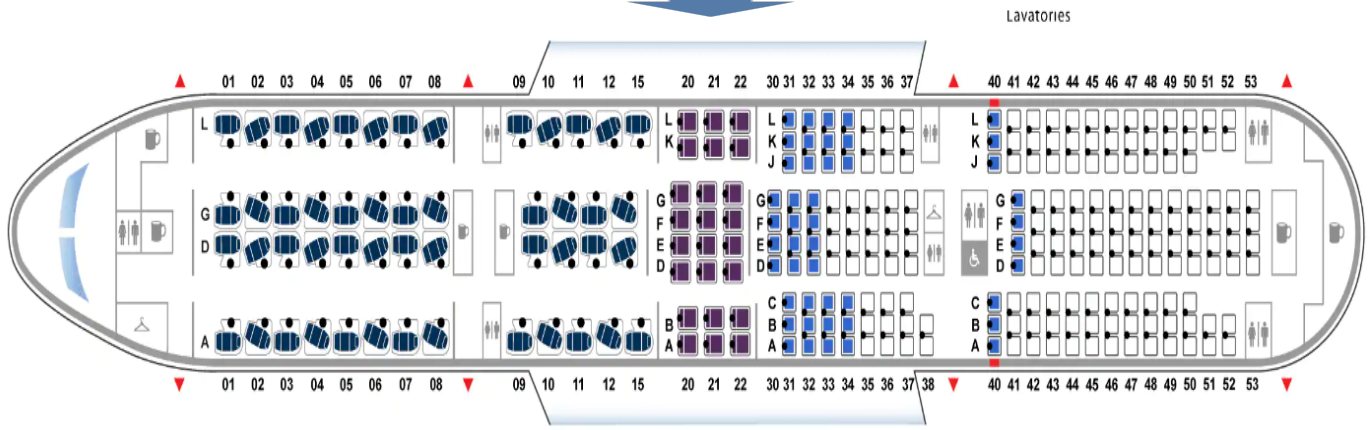
Internal Challenges

- Regulatory assessments traditionally based on freestyle narratives (or unstructured text) and summarization of application information with cut/paste of data tables.
- Cumbersome knowledge sharing and knowledge management
- Potential for subjective assessment based on the assessor's expertise and knowledge at hand

Increase in submission size and complexity with accelerated timelines



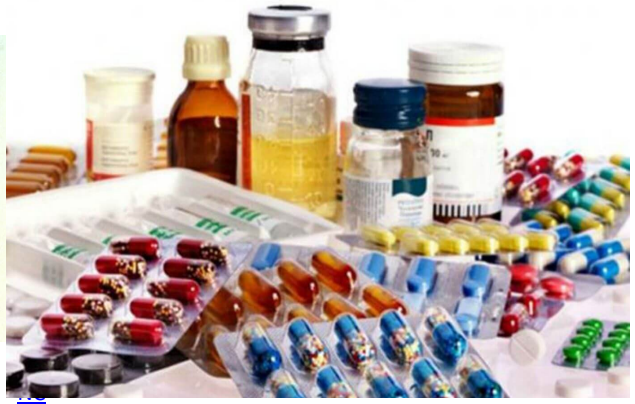
Boeing 727



Boeing 777

Advancing Forward

We recognize the need to modernize
(20th → 21st century technology)



Move from narrative information to **structured data*** in order to best capture/manage knowledge

* **Structured data** is highly specific and is stored in a predefined format, where **unstructured data** is a conglomeration of many varied types of **data** that are stored in their native formats

7

U.S. FOOD & DRUG ADMINISTRATION

Possible Solutions & How they Might Work Together

Complementary Opportunities for Submission Modernization

KASA

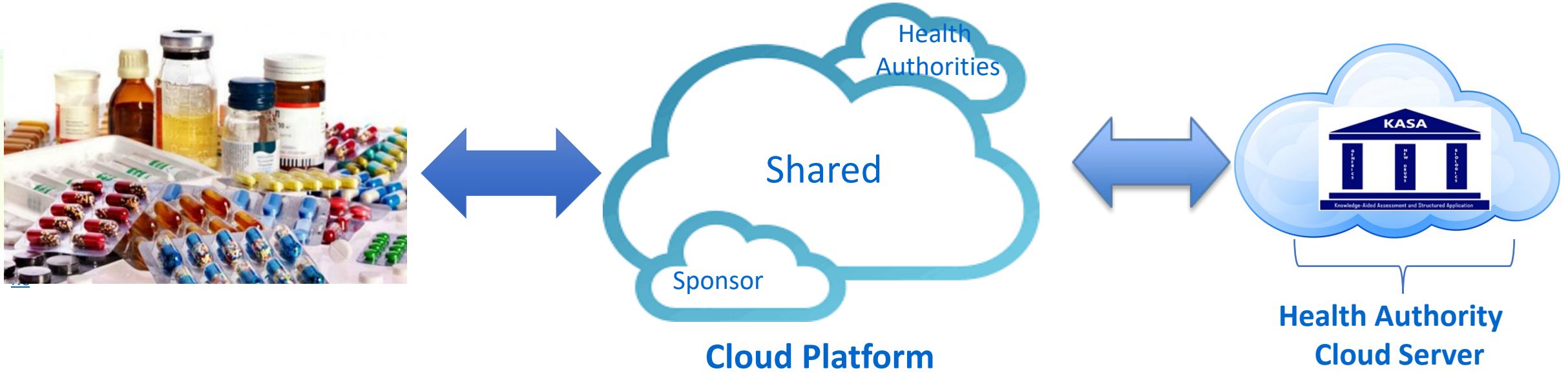
eCTD & M4Q(R2)

Structured Data PQ/CMC ICH SPQS

Harmonization

Future Regulatory Submission and Assessment

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

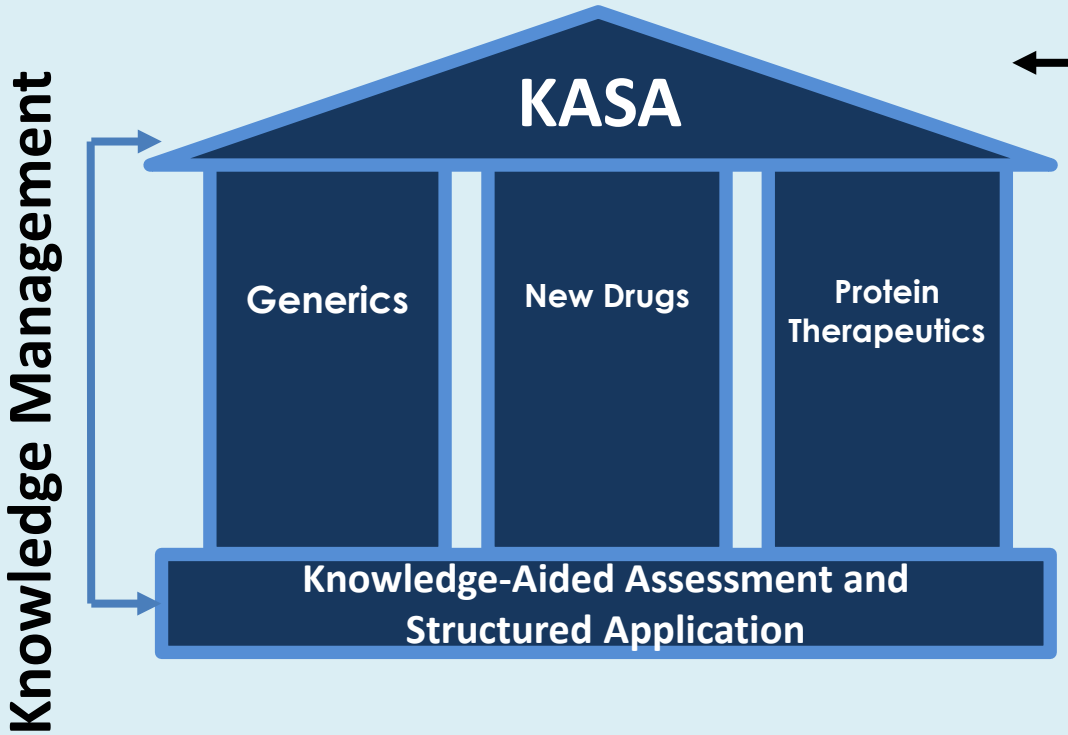


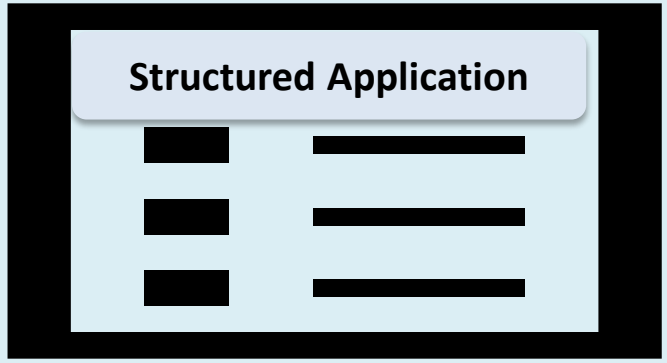
Characteristics: Both regulatory submission and assessment move to structured data format enabling efficient regulatory submission and assessment, information sharing, knowledge management, and data analytics

KASA

U.S. FOOD & DRUG ADMINISTRATION

The Future KASA System (under evaluation for complex biologics)





What information is submitted?

How is information organized?

ICH M4Q revision

Electronic data standards

PQ-CMC

"KA"

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

"SA"

content and organization of submission and electronic data standards

Key Objectives of KASA System for Biological Products
(under evaluation for complex biologics)

1. Capture and **manage knowledge** during the lifecycle of a drug product

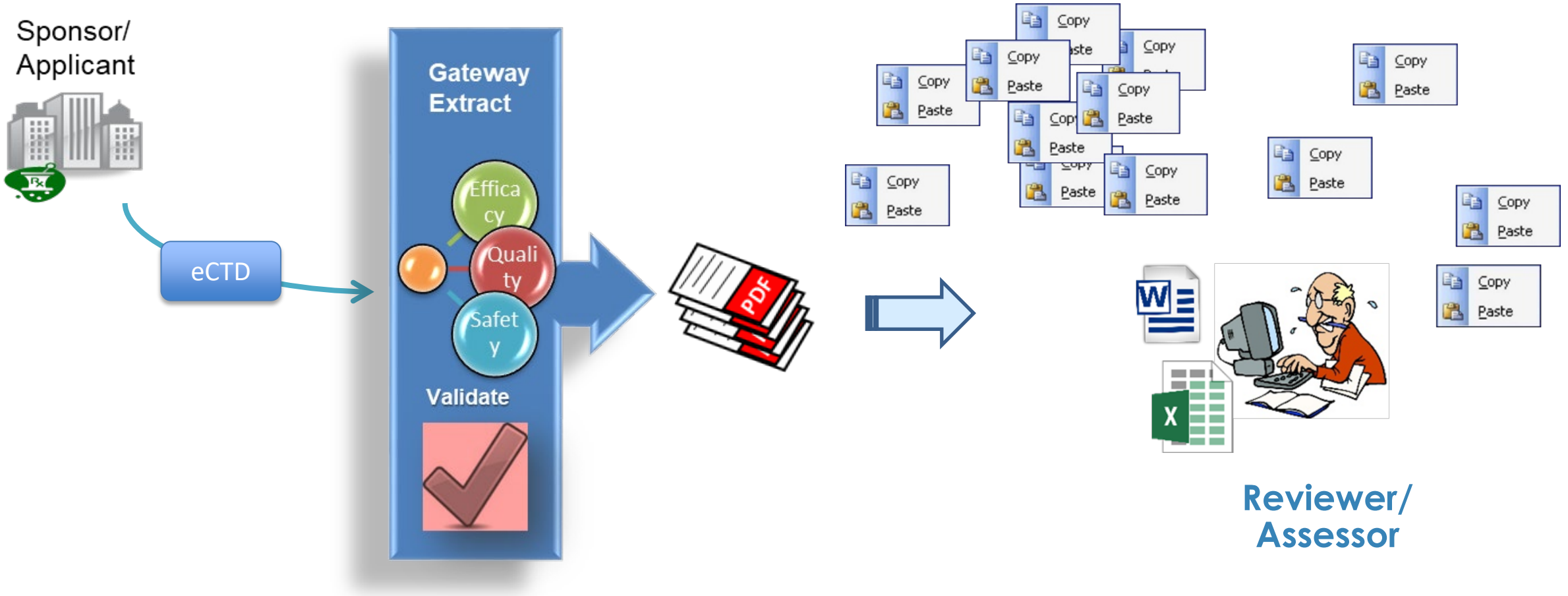
2. Establish **rules and algorithms to facilitate risk** identification, mitigation, and communication for the drug product, manufacturing process, and facilities

3. Perform **computer-aided analyses of applications** for a comparison of regulatory standards and quality risk across the repository of approved drug products and facilities;

4. Provide a structured assessment that **radically eliminates text-based narratives** and summarization of information from the applications.

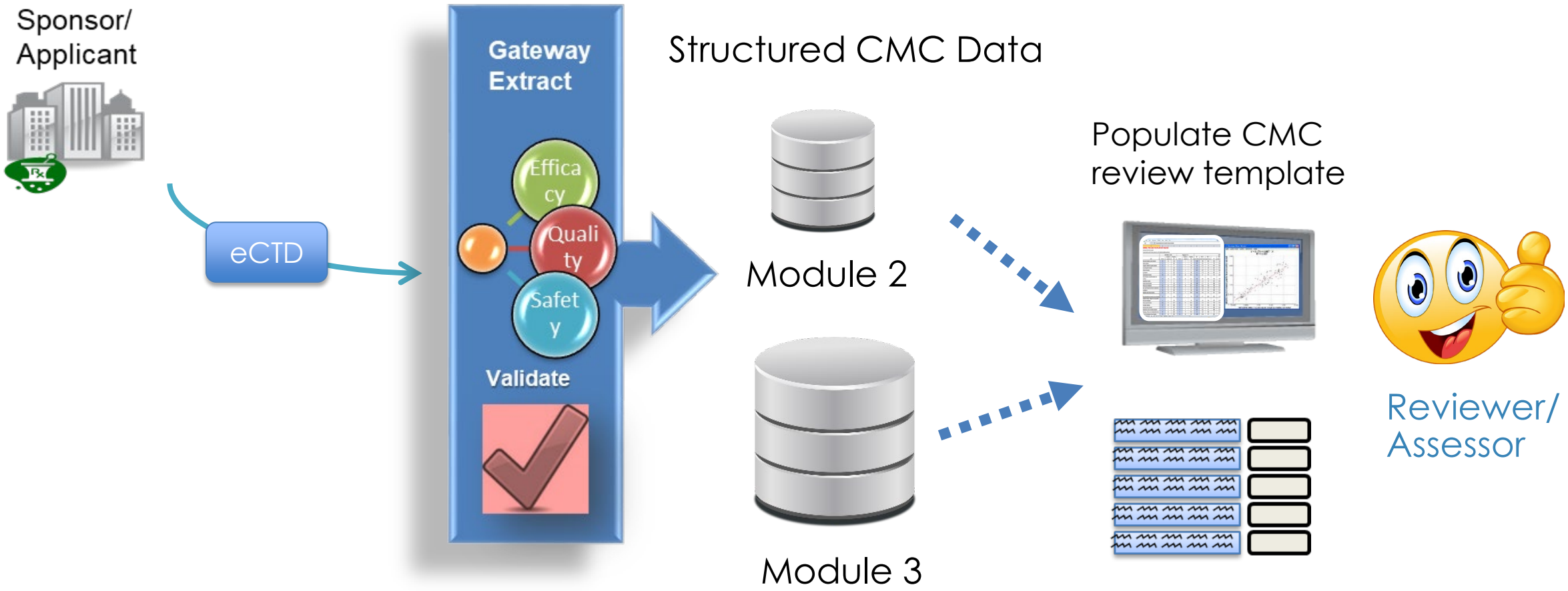
FDA Pharmaceutical Quality Electronic Data Standards (i.e., PQ/CMC)

Current CMC Data Submissions and Review



Structured CMC Data Submission (ICH SPQS)

Future Data Submissions and Review



PQ/CMC Data Elements – Phase 1

(Substantially completed by end of 2020; ~ 33% of Module 3 data)

#	PQ/CMC Data Groupings	High level eCTD Reference	Total Elements
0	Application Sponsor	3.2.S.2.1, 3.2.P.3.1	6
1	Specification	(3.2.S.4.1, 3.2.P.5.1; 3.2.S.4.4 and 3.2.P.5.4; 3.2.S.7.1; 3.2.P.8.1)	7
2	Test	(3.2.S.4.1, 3.2.P.5.1)	11
3	Acceptance Criteria	3.2.S.4.1, 3.2.P.5.1)	7
4	Batch Lot Information	(3.2.S.4.4; 3.2.P.5.4; 3.2.S.7.1; 3.2.P.8.1)	29
5	Batch Analysis	(3.2.S.4.4; 3.2.P.5.4; 3.2.S.7.1; 3.2.P.8.1)	10
6	Stability Study	(3.2.S.7.3; 3.2.P.8.3) / 3.2.S.7.1,3.2.S.7.2, 3.2.P.8.1, 3.2.P.8.2	12
7	Nomenclature Drug Substance	(3.2.S.1.1; 3.2.S.1.2)	12
8	Drug Substance Characterization	(3.2.S. 3.1)	4
9	Description & Comp. Drug Product	(3.2.P.1)	18
10	Batch Formula	(3.2.P.3.2)	9
11	Drug Sub. Control of Materials	(3.2.S.2.3)	13
12	Drug Product Control of Excipients	(3.2.P.4.1)	16
13	Drug Substance Impurities	(3.2.S.3.2)	11
14	Drug Product Impurities	(3.2.P.5.5)	12
15*	~~Analytical Methods Validation~~	~~(3.2.S.4.3; 3.2.P.4.3; 3.2.P.5.3)~~	~~10~~
	Total		**181**

- Piloted with 7 industry participants
- Evaluated suitability, appropriateness of data elements and terminologies
- Continuous improvement in conjunction with KASA data structure

* SMEs developed data standards but deferred the refinement to later stage.

PQ/CMC Data Elements – Phase 2
(Initiated in January 2021)

Categories of PQ/CMC data in eCTD Module 3 and Module 2 QOS

1. Specification(drug substance/drug product/excipients)
2. Batch Analysis (drug substance/drug product)
3. Stability(drug substance/drug product)
4. Nomenclature of Drug Substance
5. Composition of Drug Product
6. Batch Formula
7. Impurities
8. Manufacturing Process
9. Annual BLA Lot Distribution Report
10. CMC Changes in Annual Report – NDA/ANDA/BLA/NADA/ANADA
11. Analytical Procedure Validation
12. Facility Information

Categories 1 -7

PHASE 1

Categories 8 -12

PHASE 2

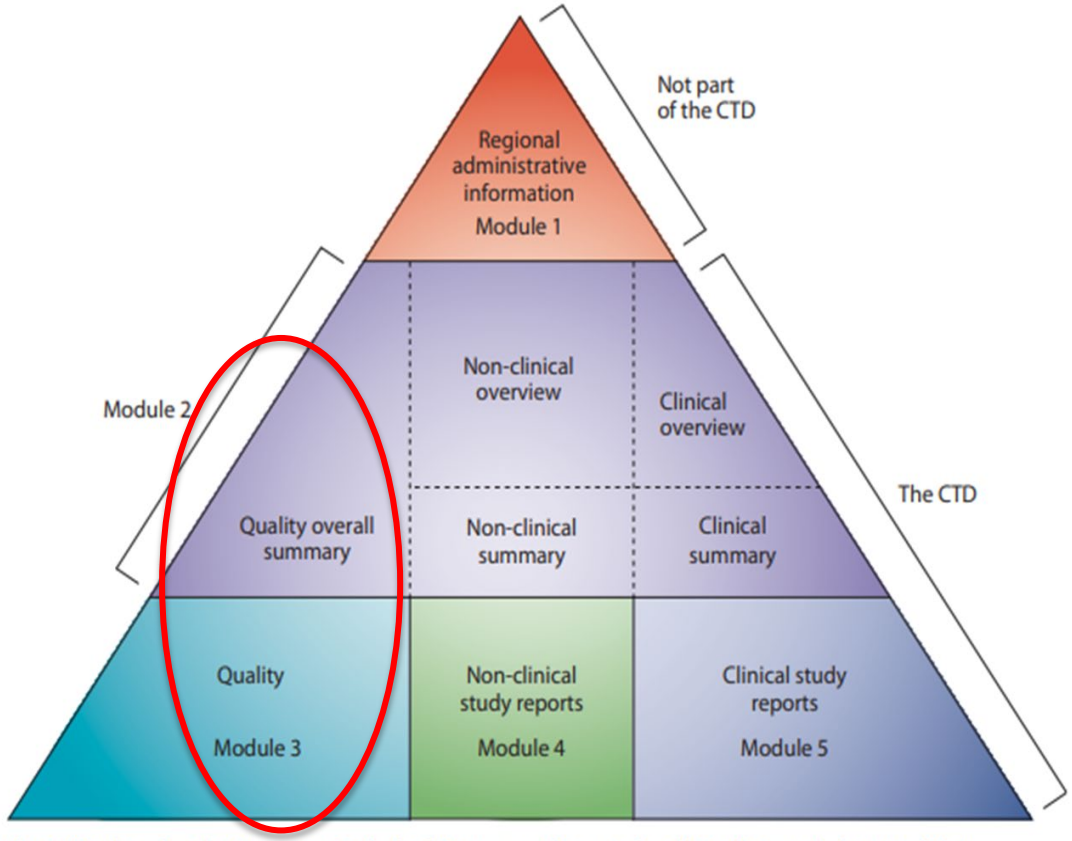
18

ICH M4Q(R2)

U.S. FOOD & DRUG ADMINISTRATION

What is 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
- Substantial improvement over wide range of submission formats



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(R1) Implementation Status

https://www.ich.org/page/ctd

2001

2019

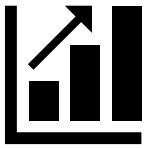
- FDA, United States - August 2001
- HSA, Singapore - January 2003
- EC, Europe - March 2003
- MHLW/PMDA, Japan - July 2003
- Swissmedic, Switzerland - July 2004
- TITCK, Turkey - December 2006
- Health Canada, Canada - June 2012
- TFDA, Chinese Taipei - November 2012
- MFDS, Republic of Korea - June 2016
- NMPA, China - February 2018
- ANVISA, Brazil - August 2019

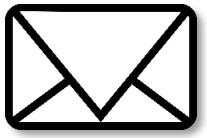
21

Top Benefits of Revised M4Q

Benefits to regulators

- Enables harmonization and standardization of information submitted in biologics application
- Enhances review efficiency and consistency of regulatory decision-making and actions
- Eliminates the need for transcription, enables use of analytics and knowledge management
- Improves communication with industry

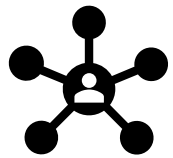




Top Benefits of Revised M4Q

Benefits to industry

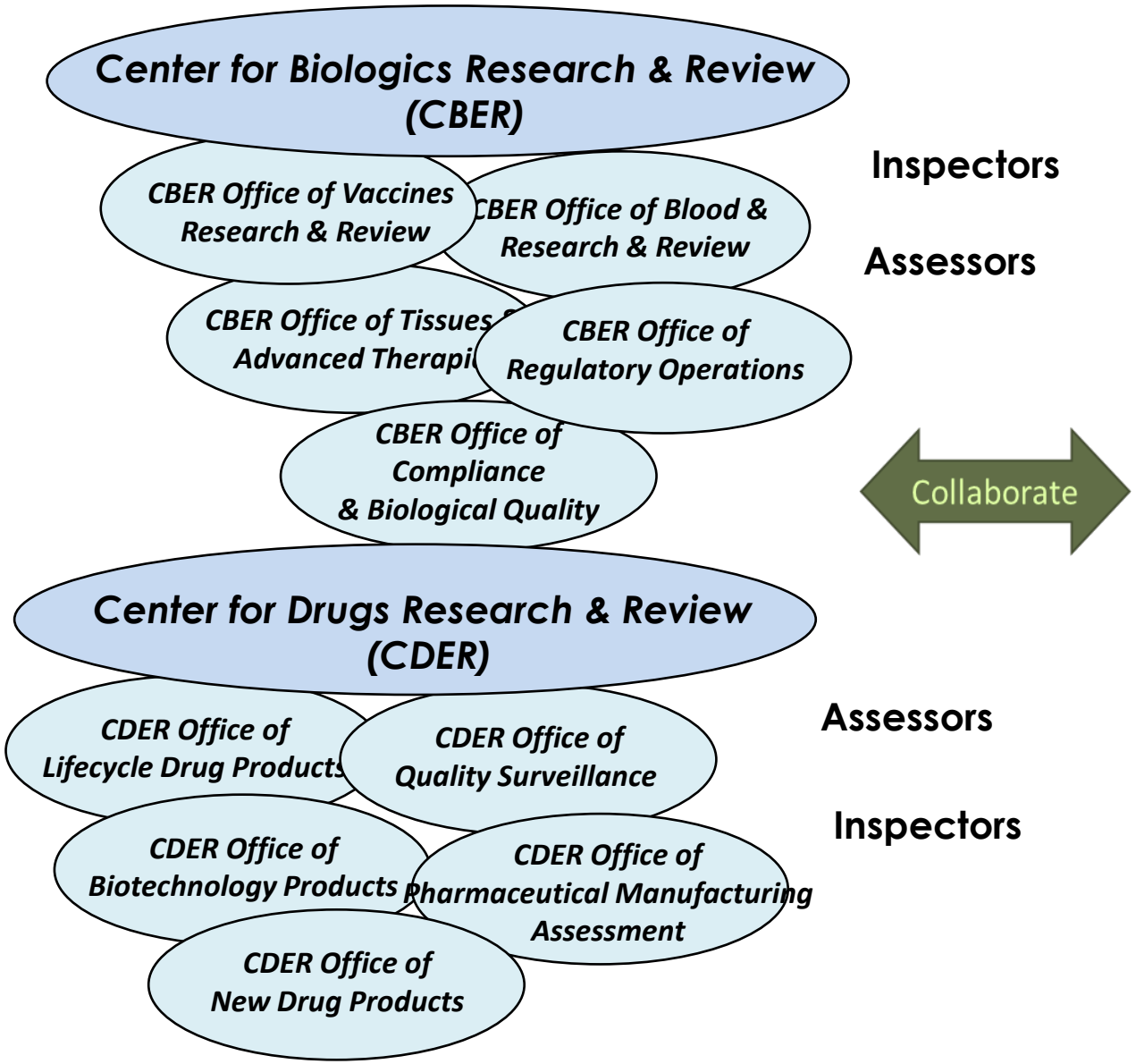
- Enables harmonization and standardization of information submitted in biologics application
- Enhances efficiency regulatory application preparation
- Clarifies regulatory expectations
- Improves quality of submissions, enables use of analytics and knowledge management



23

US FDA Support of ICH M4Q(R2)

Rapporteur: Lawrence Yu, US FDA/CDER
Rapporteur Supporter Larisa Wu



M4Q(R2) EWG Revision of M4Q(R1)

EC, Europe
Klara Tiitso
Mr. Antonius (Ton) Johannes van der Stappen

EDA, Egypt
Dr. Sara Shatat

EFPIA
Henrik Kim Nielsen

FDA, United States
Dr. Ingrid Markovic
Dr. Susan Rosencrance

Global Self-Care Federation
Ms. Christelle Alliens-Müller

Health Canada, Canada
Dr. Hugo Hamel

IFPMA
Ms. Sheila Inada

IGBA
Mr. Javier Monvoisin

JPMA
Mr. Hiroki Ito
Ms. Tomoko Yamato

MFDS, Republic of Korea
Dr. Naroo Kang

MHLW/PMDA, Japan

NMPA, China

Disclaimer: Expert Working Groups members are appointed by their nominating ICH Member or Observer party and are responsible for representing the views of that party, which may not necessarily reflect their personal views. Working Group experts do not respond personally to external inquiries but are directed to forward any inquiries they receive to their nominating party or the ICH Secretariat for a response on behalf of either their ICH party or the ICH Association as appropriate. For questions to the ICH Secretariat, please use the contact form on the ICH website.

Acknowledgements

- **FDA M4Q(R2) Team**
  - Lawrence Yu
  - Susan Rosencrance
  - Larisa Wu
  - CBER & CDER Members of the FDA internal WG
- **FDA PQ/CMC WG**
  - Geoffrey Wu (Lead)
- **KASA WG**
  - Lawrence Yu & Susan Rosencrance (SM Leads)
  - Joel Welch (LM Lead)

Collaborate

M4Q(R2) EWG Revision of M4Q(R1)

ANVISA, Brazil
Ms. Ellen Nogueira

APIC
Dr. Sabina Jurca
Dr. Rudy Peeters

BIO
Ms. Kathy Lee

CDSCO, India
Dr. Rubina Bose

EC, Europe
Klara Tiitso
Mr. Antonius (Ton) Johannes van der Stappen

EDA, Egypt
Dr. Sara Shatat

EFPIA
Henrik Kim Nielsen

FDA, United States
Dr. Ingrid Markovic
Dr. Susan Rosencrance

Global Self-Care Federation
Ms. Christelle Alliera-Müller

Health Canada, Canada
Dr. Hugo Hamel

IFPMA
Ms. Sheila Inada

IGBA
Mr. Javier Marcoiain

JPMA
Mr. Hiroki Ito
Ms. Tomoko Yamato

MFDS, Republic of Korea
Dr. Narae Kang

MHLW/PMDA, Japan
Dr. Isao Takayama
Dr. Seiko Usami

NMPA, China
Dr. Yonghui Liu

PhRMA
Mr. Rodrigo Palacios
Dr. Sarah Pope Mikairaki

SFDA, Saudi Arabia
Mr. Hamoud Alharbi

TFDA, Chinese Taipei
Ms. Yi-Ying Lin

Thank you!