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U.S. FOOD & DRUG ADMINISTRATION

Genesis of M4Q: A Regulatory Perspective

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Presentation Outline

Broader FDA Modernization Efforts Influencing Regulatory Submission Modernization

Vision for Future Regulatory Submission and Assessment

ICH M4Q(R2) Update

Examples of FDA Modernization Efforts

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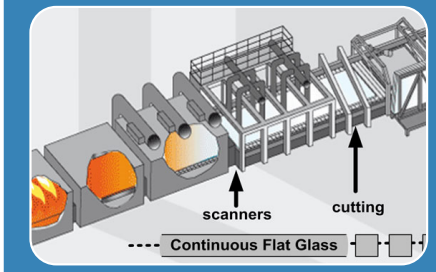
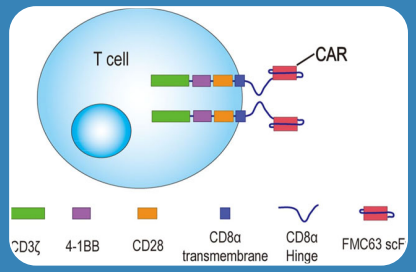
Modernizing FDA's Data Information Technology (IT) & Bioinformatics

- 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 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

- Strengthening staff capacity to support 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

Drivers & Vision for Future Regulatory Submission and Assessment

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Application Assessment Challenges

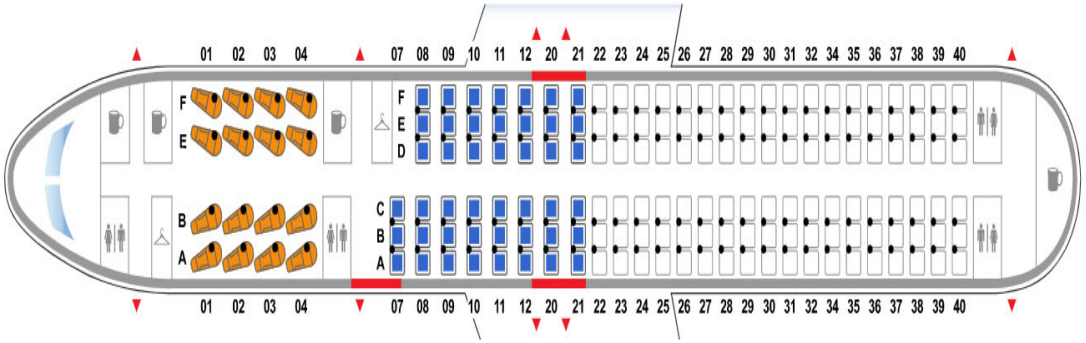
External Challenges

- 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

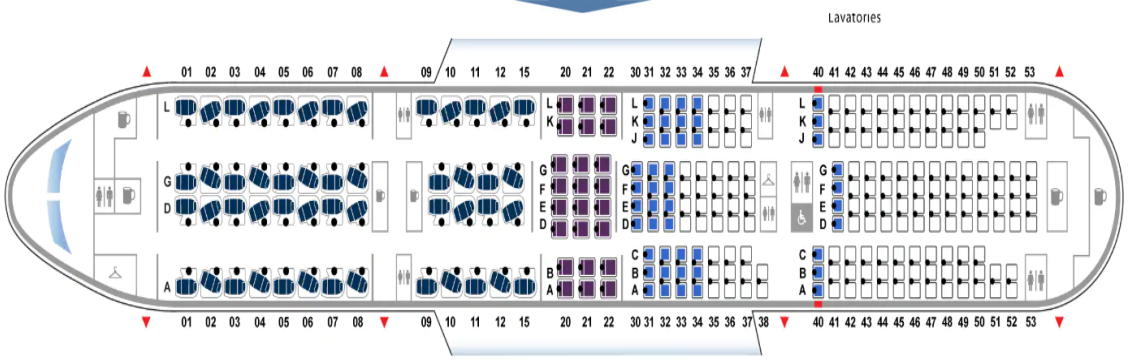
Internal Challenges

- 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



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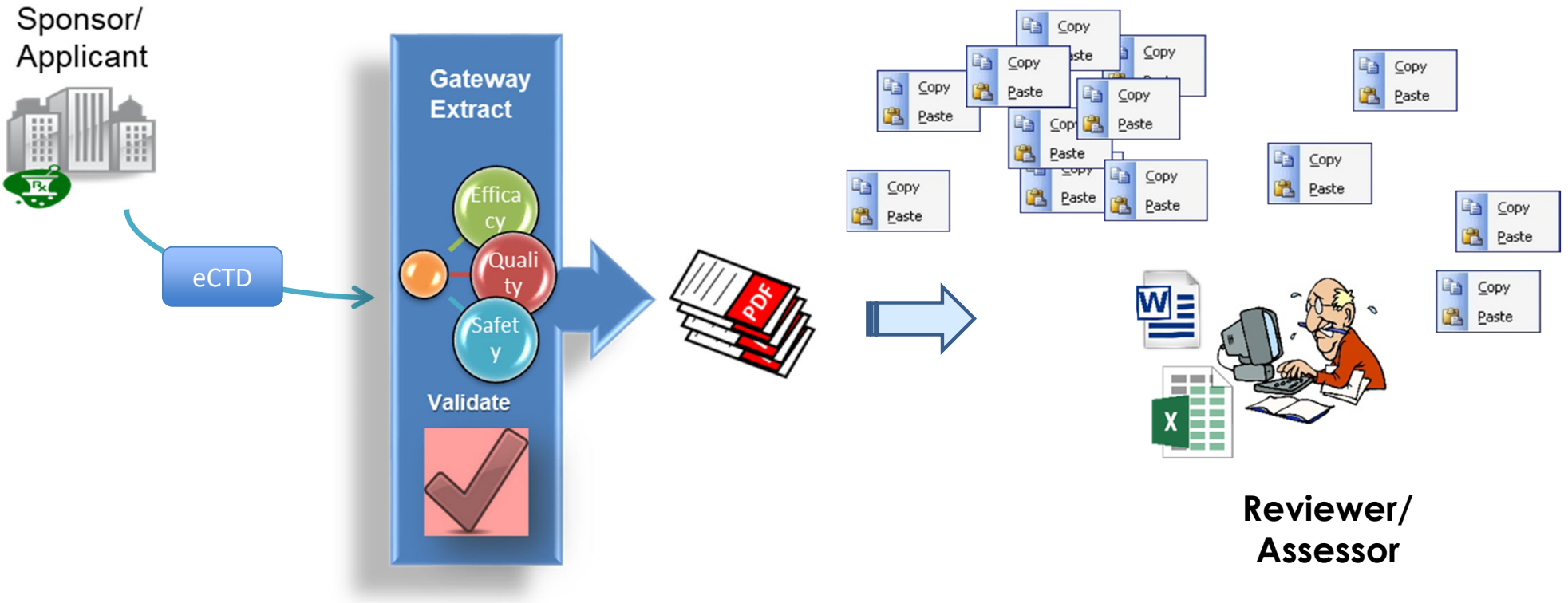
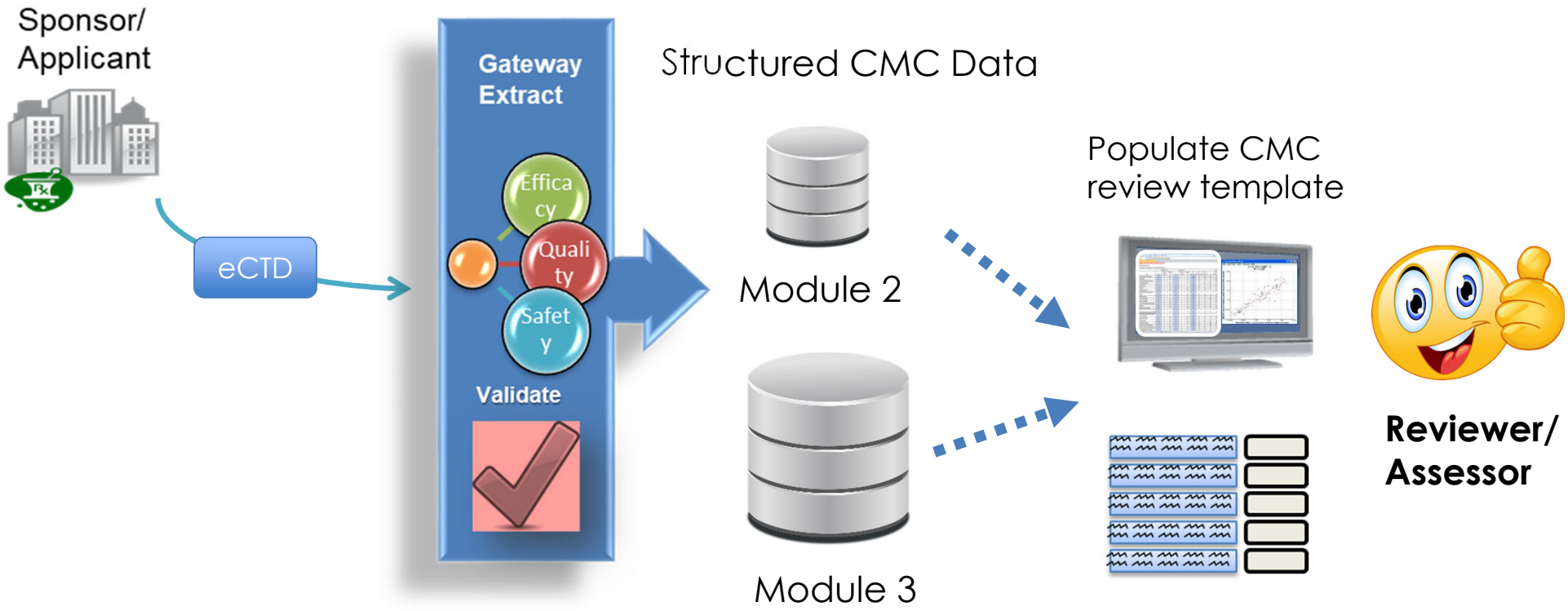
Current CMC Data Submissions and Review



Structured CMC Data Submission

Future Data Submissions and Review



GOAL: Move away from the narrative information, towards structured data to capture & manage knowledge

Building Bocks Enabling Digitalization of Regulatory Submission

Paper to E-Submission M4Q(R1)

M4Q(R2)

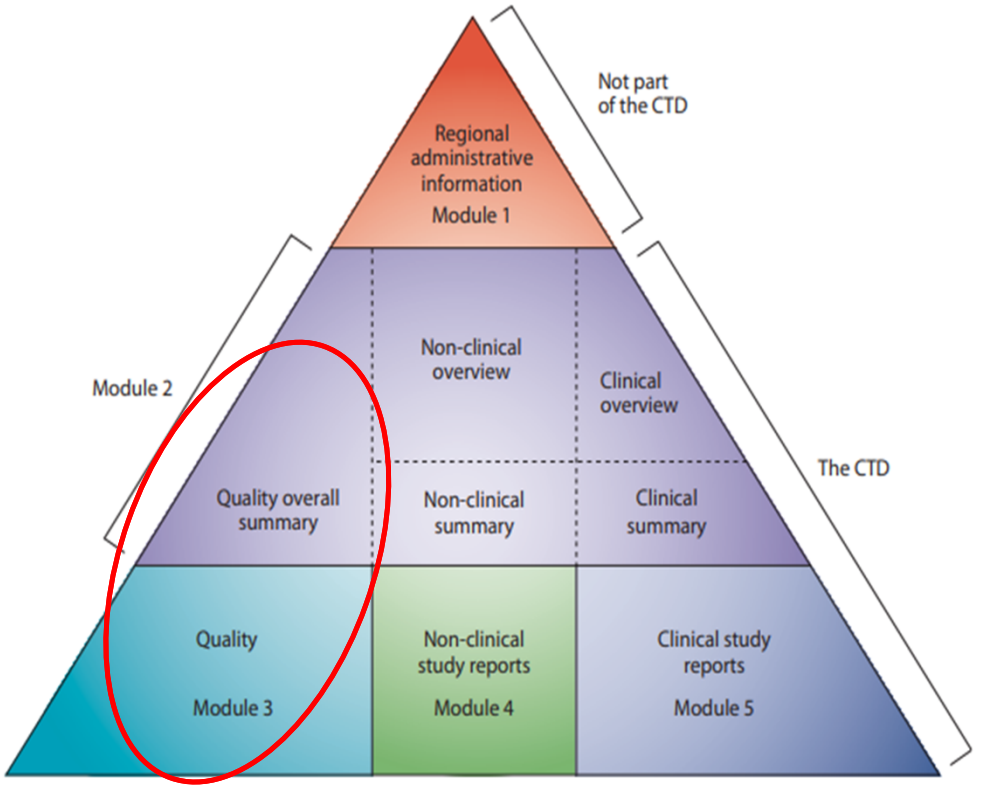
PQ/CMC KASA IDMP/SPOR SPQS

Health Authority Cloud Server

ICH M4Q(R2) Update

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 along with a 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(R1) Implementation

2001

2023

- 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

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

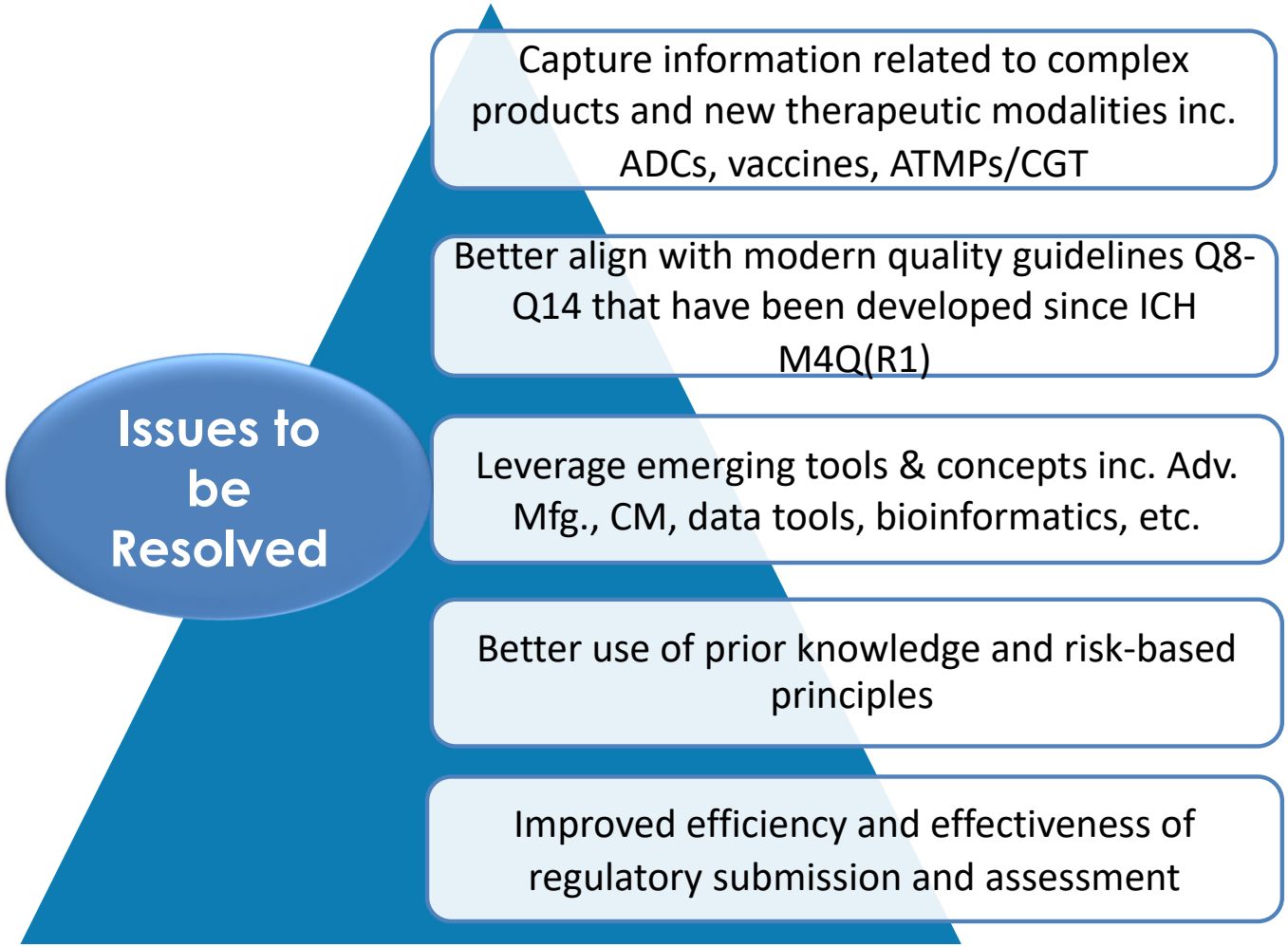
ICH Elected a Step-wise approach to Modernize Regulatory Submission

ICH M4Q(R2) will define content and organization of informaton in Module 2 and Module 3

When M4Q (R2) reaches step 2, the work on Structured Product Quality Submissions (SPQS) will be begin

Therefore, M4Q(R2) will think ahead but not work on developing data models for structured data

What are perceived problems?



Benefits of Revised M4Q

Benefits to Patients and Consumers

M4Q(R2) guideline would streamline patients' and consumers' access to lifesaving therapies

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

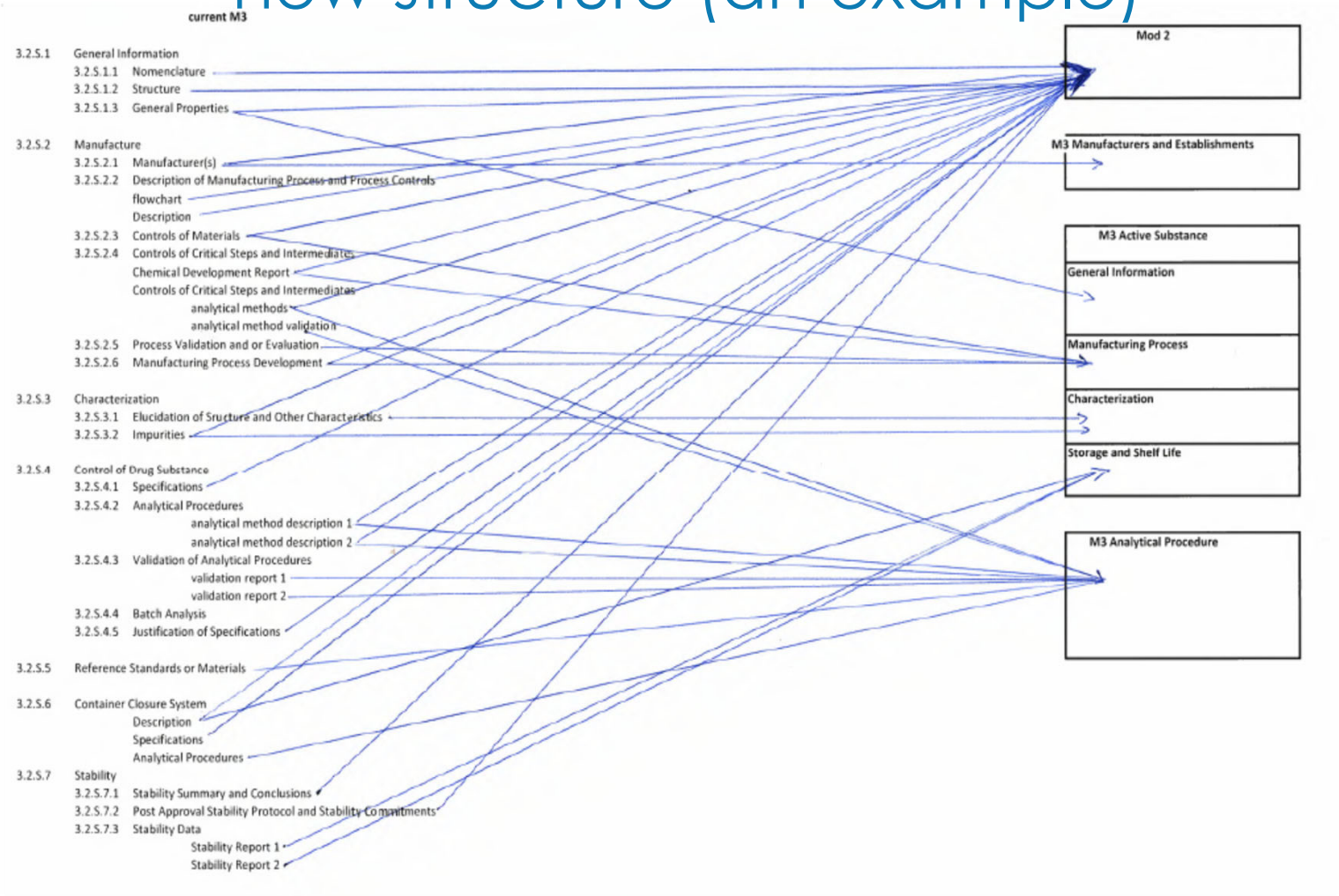
Current thinking of the EWG

- 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.

Points to consider for new CTD organization as M4Q(R2) work progresses

- **Transformative change** compared to the current state how information is presented and organized
- New organization needs to support **initial approval** and **lifecycle management**
- Needs to work for **all product types** from **generic products to complex C&GTs**, including **devices**
- Be able to accommodate products relying on **DMF**
- Capture Q12 and non-Q12 applications
- Needs to be at the right **level of detail**
- May facilitate **reliance-based review/approval**

Mapping the current M4Q sections to the new structure (an example)

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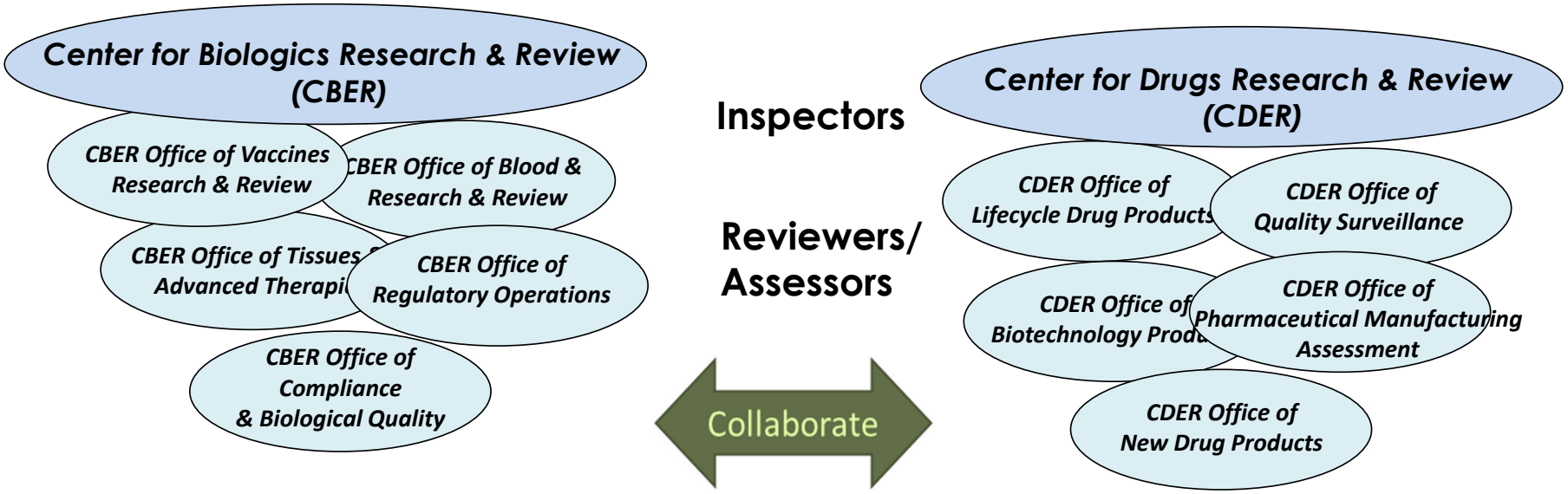
FDA Support of ICH M4Q(R2)



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Big Thanks!

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Collaborate

Q & A