

Date: December 5, 2024

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Subject: Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Elements and Terminology; Informational Chapter A; Docket FDA-2023-N-1443-0001

Dear Sir or Madam:

Accumulus Synergy's and its Pharmaceutical Quality Industry Policy Subcommittee appreciates the opportunity to provide comments on Information Chapter A of the Food and Drug Administration's Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Exchange. Our comments address general considerations on PQ/CMC as well as provide specific feedback on the taxonomical categories and valid values.

Comment Overview

Innovative technologies have been rapidly adopted by various industries to meet the growing demand for real-time information exchange. However, the life sciences and regulatory ecosystem is unique in that it collects proprietary, confidential, and personal information through research, development, manufacturing, and marketing. This raises concerns about the potential exposure of sensitive information to unauthorized users, leading to hesitance in adopting new solutions.

Pharmaceutical Quality (PQ) data, also known as Chemistry Manufacturing and Controls (CMC) data, is collected and stored in different systems throughout the drug development and marketing lifecycle. Despite its importance and frequent transfers between organizational entities, the utility of this data has been limited until the

recent publication of the PQ-Industry (PQI) data standard. Additionally, CMC documentation is not easily accessible in the public domain, creating challenges for the development and adoption of the necessary technical innovations.

The highly diverse nature of CMC details presents a significant barrier to consistent and efficient access to critical therapeutics worldwide. We commend the Agencies for their efforts to establish a standard that supports interoperable data exchange for regulatory purposes, and we encourage the continued refinement of this initiative.

The draft PQ/CMC data standard requires further development to enhance its utility and reusability. It is crucial to clarify how Informational Chapter A aligns with the Foundational Data Standards and Terminology for PQ/CMC outlined in Chapter 1. As the data components are harmonized and standardized, the Agency should also explore how the framework may be adjusted to accommodate modalities beyond small molecules.

Importance of Interoperability

The Universal Realm FHIR Implementation Guide is designed for the standardized exchange of structured pharmaceutical quality data on an international scale, facilitating communication among biopharmaceutical companies and their stakeholders. This data standard structure creates a common framework for exchanging product quality information across biopharmaceutical manufacturing organizations. It aims to enhance technology transfer, improve monitoring of facilities, and support the development of advanced manufacturing methodologies.

Ensuring Reusability

To facilitate the ecosystem's transition from documents to data, the Pharmaceutical Quality - Industry (PQI) project developed an initial set of 19 profiles of FHIR resources and bundles that can be reused across PQ data domains. We recommend that the Agency ensure its PQ/CMC resource complements other FHIR-based PQ resources. This will enhance

reusability, system interoperability, and ultimately promote the efficient use of PQ data to support various CMC industry and regulatory use cases.

PQI FHIR Resource Profiles

<ol style="list-style-type: none"> 1. Activity Definition – Test 2. Composition – Drug 3. Device Definition – Drug 4. Diagnostic Report – Drug Analysis 5. Document Reference – Drug 6. Ingredient – Drug 7. Manufactured Item Definition – Drug 8. Medication – Batch Information 9. Medicinal Product Definition – Drug Product 10. Observation – Test Result 	<ol style="list-style-type: none"> 11. Observation Definition – Test Method 12. Organization – Drug 13. Packaged Product Definition – Drug 14. Plan Definition – Drug 15. Procedure – Drug 16. Specimen – Drug 17. Specimen Definition – Drug 18. Substance – Drug 19. Substance Definition – Component Drug
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PQ Data Domains (Bundles)

<ol style="list-style-type: none"> 1. Analytical Procedure 2. Batch Analysis 3. Batch Formula 4. Product Batch Information 5. Substance Batch Information 6. Product Compatibility 7. Product Composition 8. Reference Standards 9. Container Closure System 10. Product Specification 11. Substance Specification 	<ol style="list-style-type: none"> 12. Drug Product 13. Product Microbiological Attributes 14. Product Excipients 15. Substance General Properties 16. Substance Characterization 17. Impurities 18. Manufacturing 19. Organizations 20. Process Validation 21. Stability
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This modular approach to organizing PQ/CMC data promotes continuous innovation and accelerates efforts toward international harmonization and consensus. Specifically, it involves cascading standardization at various levels, which fosters agreement on the use of controlled lists and vocabularies. Additionally, this approach can be expanded to other therapeutic areas, such as devices and biologics. Collectively, these initiatives

will help both the industry and regulators achieve improvements in data management and quality, regulatory compliance, and operational efficiencies.

Application of PQ Data Standards

Protein therapeutics are commonly delivered using drug delivery devices. As new product types are introduced into the Product Quality/CMC (PQ/CMC) framework, it is likely that these products will incorporate delivery devices more frequently than the initial solid oral dosage forms. Therefore, it is advisable for the PQ/CMC controlled terminology to include elements related to devices and combination products sooner rather than later. There are HL7 FHIR specifications regarding medical devices (DeviceDefinition) that are currently being utilized for IDMP and could similarly be adopted for PQ/CMC.

Specific Feedback/Recommendations

The Agency has developed a framework specifically designed for small molecules. We recommend that the Agency explore options to expand this framework by adding values within the existing Main Taxonomical Categories. Additionally, we suggest creating new Categories to encompass a wider range of product types, such as Biologics, Devices, and Combination Products, in order to facilitate high-quality submissions.

Valid Value	Value Identifier	Feedback/ Recommendation
1.0 Active Ingredient		
Biological Activity	1.1	Recommendation: Consolidate values further describing the active ingredient so that the Active Ingredient foundation is easier to interpret and implement/ differentiate/associated with other taxonomical values like Material Properties and relate back to other guidance such as Chapter 1:
Structure	1.2	
Physiochemical Properties (include subclasses like Molecular Weight, Subclass Profiling, or Extinction Coefficient, solubility)	1.3	

		Specification Test Type
2.0 Structure		
Higher Order Structure	2.2	Feedback: Doesn't contain quaternary structures or an element (if applicable)
Beta Sheets	2.2.8	Description: Evaluation of content of common arrangement (Beta Sheets) in the secondary structure of protein(s)
3.0 Function		
Recommendation: Reconsider the grouping logic of this taxonomy at the first level to ensure the values would support use of new modalities		
Binding	3.2	Recommendation: Change Value Name to "Binding Evaluation"
4.0 Process-related Impurities		
Recommendation: Change 4.0 to Impurities and then have sub-values to reflect manufacturing process and/or product-related Impurities		
5.0 Material Properties		
Recommendation: If the Agency agrees with our later recommendation to create a new taxonomical category for Safety Assurance, then consider renaming this section to "Formulation Properties" where subcategories like identity, description (appearance), quantity, pH, etc. can be included.		
6.0 Formulation		
Recommendation: The Agency should ensure the valid values are inclusive of all therapeutic proteins such as: Complexing Agent, pH adjustment, Preservative, Water for injection, and stabilizer		

We recommend adding a category for Performance to the proposed Main Taxonomical Categories in order to prepare the PQ/CMC standard for supporting products beyond small molecules, such as biologics and devices. This enhancement will provide broader utility across the drug development and regulatory lifecycle, especially in future iterations of the standard.

7.0 Performance		
7 – Performance Injection	7.1	Performance attributes relating to administration of the therapeutic protein product using an injection drug delivery device
7 – Performance Inhalation and Nasal	7.2	Performance attributes relating to administration of the therapeutic protein product using inhalation or nasal drug delivery device
7 – Performance Transdermal and Topical	7.3	Performance attributes relating to administration of the therapeutic protein product using transdermal drug delivery device
7.1 – Injection Delivered Volume	7.1.1	A measure of the volumetric accuracy of the product which is delivered from the drug delivery device (e.g., dose accuracy, delivered volume)
7.1 – Injection Injection Time	7.1.2	A measure of the time to inject the dose
7.1 – Injection Injection Forces	7.1.3	Measures of force relating to the use of the injection device to administer the dose (e.g., activation force, break loose force)
7.1 – Injection Injection depth	7.1.4	Measures relating to the depth of injection using the drug delivery device
7.2 – Inhalation and Nasal	7.2.1	A measure of the dose delivered or

Delivered Dose		emitted from the drug delivery device (e.g., pump delivery, emitted dose)
7.2 – Inhalation and Nasal Dose uniformity	7.2.2	Measures relating to particle size distribution, spray pattern, droplet size distribution
7.2 – Inhalation and Nasal Dose delivery forces	7.2.3	Measures of force relating to the use of the inhalation or nasal device to administer the dose (activation force, actuation force)
7.3 Transdermal and Topical Adhesion	7.3.1	Measures the quality of the adhesion of the transdermal or topical delivery system (e.g., peel adhesion, release liner peel, tack, shear)
7.3 Transdermal and Topical Drug release	7.3.2	Measures the dose release profile of the delivery system

Recommendation: Promote Subcategory to Main Taxonomical Category: Safety Assurance

We recommend the Agency consider promoting 4.4 Microbial or Adventitious as a separate taxonomical category (Safety Assurance) to better harmonize and standardize microbial safety and virus safety for easier implementation.



About Accumulus

Accumulus Synergy is a nonprofit trade association working on behalf of industry to address the global need for digital transformation. To help solve for this need, Accumulus is developing a transformative data exchange platform to enable enhanced collaboration and efficiency between life sciences organizations and health authorities worldwide. The Accumulus Platform aims to improve efficiencies in the regulatory process by leveraging advanced technology, including data science and AI, as well as tools for secure data exchange to improve patient safety, help reduce the cost of innovation, and ultimately bring patients safe and effective medicines faster. Accumulus is working with key stakeholders in the life sciences - health authority ecosystem to build and sustain a platform that aims to meet regulatory, cybersecurity, and privacy requirements spanning clinical, safety, chemistry and manufacturing, and regulatory exchanges and submissions.