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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 Exchange; Chapter 2: Enhancements to support solid oral dosage form component and composition: multi-layer tablets and capsules; Docket FDA-2023-N-1443-0001

Dear Sir or Madam:

Accumulus Synergy appreciates the opportunity to provide comments on Chapter 2 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 and provide feedback on the new data elements, data model for solid oral dosage forms, and controlled terminologies.

About Accumulus

Accumulus Synergy (Accumulus) is a nonprofit trade association working on behalf of industry to address the global need for digital transformation. To help solve this challenge, 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 information exchange to improve patient safety, help reduce the cost of innovation, and 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.

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1. Comment Overview

Chapter 2 of the Food and Drug Administration's (FDA) Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Exchange document describes specific considerations for structuring product quality data for solid oral dosage forms, focusing on drug product composition and drug product manufacturing process. Accumulus Synergy (Accumulus) recognizes and appreciates FDA's continued dedication to advancing the PQ/CMC initiative, which will have a transformative impact on modernizing and optimizing submission and review of regulatory CMC information.

Accumulus is supportive of the PQ/CMC initiative as the leading Fast Healthcare Interoperability Resources (FHIR) data standard for exchanging CMC regulatory information between biopharmaceutical companies and the FDA; However, we have targeted recommendations for improvement, with the primary goals of easing implementation burdens and supporting global harmonization. Our feedback summarizes general considerations for the PQ/CMC project and describes our recommendations concerning alignment with other data standards and initiatives, the scope of the new data elements, and usage of controlled terminologies.

2. General Comments

2.1 Future Iterations of the PQ/CMC Federal Register Notice and Draft Data Elements Document

Accumulus acknowledges the "living document" approach for communicating newly developed PQ/CMC data elements. We feel that this will allow for increased transparency and more timely updates on the project. However, as a suggestion for future iterations and releases, it would be useful to provide illustrative examples that define the basic logic for all major sections. For example, it would be helpful to see models or examples for drug product manufacturing process (page 102), like what was provided in Appendices A and B (page 179), for ease of understanding.

In addition, Accumulus strongly recommends that HL7 FHIR mappings for the data elements be included where possible in subsequent chapters, as was done for the initial release of Chapter 1. While we recognize that a formal PQ/CMC implementation guide will describe the FHIR representation of the data elements in greater detail, it is helpful and informative for industry to visualize the data elements and FHIR mappings side by side as we are

assessing them. Since the present version of the document does not contain HL7 FHIR mappings, it is presumed that the new fields have been created manually, which may lead to some downstream inconsistencies in how data elements are mapped, defined, and represented. Sharing the FHIR mappings at the earliest possible timepoint aids in familiarizing industry with the FHIR data model, which is needed to assist with change management, given the relative novelty of FHIR in the regulatory domain.

2.2 PQ/CMC Roadmap and Strategic Intent

Accumulus suggests that a roadmap for the future direction of the PQ/CMC project would be beneficial for advancing industry's understanding of FDA's emerging expectations for structured CMC submissions. We recommend that a PQ/CMC roadmap should include additional discussion on other related initiatives on structured data, data standards, and changes to Common Technical Document (CTD) submission requirements.

Specific examples include:

- If and how IDMP concepts will be reflected in the PQ/CMC data elements
- Clarity on how PQ/CMC will be used in the context of eCTD 4.0. Specifically, we believe that eCTD 4.0 will continue the current document-centric submission paradigm, whereas PQ/CMC will introduce a structured, FHIR-based exchange format. Additional information is needed to understand how these might work together.
- Impact of emerging ICH guidelines, including ICH M4Q R2 and ICH SPQS, which are anticipated to significantly change the structure and format of Modules 2.3 and 3. This could impact the eCTD Profiles that will be established under the PQ/CMC FHIR implementation guide.

The availability of a roadmap would provide significant assistance to industry in preparing for the implementation of PQ/CMC, which will require substantial investment and internal system configuration to meet new requirements. Namely, an enterprise-wide data quality and master data management program is needed to ensure that industry can deliver high quality and consistent data as part of each submission. If all data elements are introduced at once without a robust master data management program, this increases the burden on industry and introduces a risk to data integrity. Transparency on the development timelines, release plan, and anticipated implementation requirements will help industry to prepare accordingly for this substantial change in practice.

2.3 Conceptual Alignment with IDMP and Other Emerging Standards and Guidelines

While we acknowledge that PQ/CMC and IDMP have different use cases and intentions, Accumulus strongly recommends that FDA align PQ/CMC with IDMP concepts for data elements where overlap exists to ease adoption and usability of global CMC data standards. Data standardization is needed to reach digital maturity in the regulatory domain, and it will be an ongoing challenge for industry to maintain alignment with multiple international data standards on the same topic areas. Therefore, seeking convergence where possible is necessary to be effective. Managing the same datasets in more than one way due to differing regional requirements creates significant potential for inconsistency.

As mentioned above, PQ/CMC's alignment with other data standards and initiatives is needed for industry to effectively achieve compliance by establishing internal master data systems to manage pharmaceutical product data. Regarding ISO IDMP, we acknowledge that the FDA has recently established a webpage on PQ/CMC and IDMP, which is helpful in addressing some of these concerns. Explanation on the timelines for both initiatives and whether they are intended to run concurrently would help with anticipating future expectations. In addition, we recommend that high-level terms (e.g., unit of measure, dosage form, manufacturing site responsibility, contacts, ingredient roles) align with the definitions in ISO IDMP and EMA's SPOR specification to encourage the possibility of global harmonization.

In addition to conceptual alignment across data standards, we recommend that nomenclature and naming conventions should match where possible. As a specific example, PQ/CMC's "Manufacturing Site Responsibility Subcategory" may map to IDMP's "Manufacturing Activity." This alignment will make the development of ontologies and master data management programs more feasible for industry.

2.4 Controlled Terminologies and Ontologies

As the intent of PQ/CMC is to construct structured data elements that describe CMC concepts, we recommend that codable elements are used wherever possible to enhance the potential for standardization, particularly if data elements are designated as mandatory. Free text fields may encourage the use of unstructured narrative. We believe expanding controlled terminology will provide opportunities to link across ontologies and existing systems containing controlled vocabulary terms (e.g., GSRS, SPOR). With the publication of the additional terminologies included in Chapter 2, we recommend that an ontology extension request should be submitted to EMA and ISO to foster data interoperability across the product life cycle. Rather than mapping between like terms, a unified ontology is needed.

Additionally, as described in greater detail in Section 3.1 below, we have significant concerns with the "product part" approach described throughout Chapter 2 and the accompanying terminologies. To cite a specific example, the lack of granularity of the "Ingredient Function Category" which defines ingredients as active ingredients, adjuvants, or inactive ingredients, will render it difficult to categorize ingredients comprehensively and accurately. Product parts are also not consistently defined throughout regulatory jurisdictions, which will contribute to burdens for sponsors to manage dissimilar terminologies that describe the same product components. For example, "minitablet" is given as a terminology input for Product Part Type on page 123. However, minitablets are not consistently defined in any nomenclature guidelines including USP <1121>. Minitablets are mentioned once in the USP, in USP 711 as a parenthetical under "Inserts." As this is not a defined nomenclature, we recommend against using minitablet as a term. Additionally, if we are working towards global harmonization of submissions, the capsule definition should be expanded to cover the description in the Ph. Eur. for "Granules" which states "For reasons of patient safety and to ensure the correct administration of the medicinal product, this term [granules] may also be used where very small tablets (rather than granules) are presented in a sachet, and where the entire contents of the sachet are intended for oral administration as a single dose."

We also recommend that the FDA clarify whether there would be a process in place to request additional terms or lists of terms to support use cases or activities that are unaccounted for.

3. Discussion on Specific Data Elements and Sections

3.1 General Considerations: Drug Product Composition Data Elements – Solid Oral-Focused

Accumulus recommends that the Agency provide additional rationale on the granularity of the new data elements introduced to support solid oral dosage forms. While the examples presented (e.g., multi-layered tablet, bead-filled capsule, etc.) are helpful for understanding the logic behind specific applications of the PQ/CMC data elements as they apply to dosage forms, we have significant concerns about the level of detail that is introduced by the additional data elements. The dosage form-specific elements introduced in chapter 2 focusing on "product parts" may introduce significant challenges for supporting unique/complex dosage forms and modalities. **We believe that this may limit flexibility and the overall ability to structure product quality information.** The "product part" approach as described is highly specific to a particular type of products or product configurations, which introduces a rigid approach that is difficult to apply to other modalities and may not be scalable. Industry will instead need a common approach for all products rather than one specific approach for each product variant or permutation of variants.

Accumulus suggests that a broader set of data elements may be less specific but can be more readily adapted for use across complex scenarios. This sentiment is also in line with the FHIR approach, which is "to build a base set of resources that, either by themselves or when combined, satisfy the majority of common use cases." Rather than using a product part model, an ingredient approach is recommended, wherein each ingredient has a role and location. A common, ingredient-based data model also more readily supports a transition away from the document-centric approach by allowing reusability and interoperability across a portfolio, whereas the rigidity of the product part approach described in Chapter 2 is more likely to lead industry to create XML versions of PDF documents without receiving the benefits of XML and structured data. Following this path, cost, effort, and complexity are likely to increase rather than decrease over time.

Notably, with the introduction of these new data elements, there is a considerable increase in the volume of structured master data associated with each product, which will be difficult to maintain over a product's lifecycle. While this is true for organizations of all sizes, this is particularly applicable for small biopharmaceutical companies, who may find it prohibitive to maintain these

data elements across parallel filing processes in the US and global marketing regions. In addition to technical limitations, we believe that increasing the scope of product master data to include product parts in advance of a mature industry wide process for managing substance and pharmaceutical product identity will be complex and may increase the likelihood of inconsistently or incorrectly identified data.

With respect to a PQ/CMC development roadmap, as previously discussed, it would be helpful to understand if the Agency intends to engage in a similar product part-based modelling exercise for other modalities (e.g., biologics, vaccines, cell and gene therapies) moving forward, as the potential for continued expansion of highly granular data elements and attributes creates additional concerns.

3.1.1 Itemized List of Recommendations: Drug Product Composition Data Elements –Solid Oral-Focused

Page #	Data Element #	Current Text	Proposed Change	Rationale
85	1, 2	Product Proprietary Name, Product Non-Proprietary Name	Harmonize naming conventions with IDMP (e.g., IDMP uses scientific name, common name, Invented name, generic name, proprietary and non-proprietary name)	Regulators, industry, and ISO should agree on common terms to enable harmonization and interoperability
85	3	Product Co-Packaged Cross Reference	Co-packaging should be addressed via packaging; therefore, a packaging hierarchy can be identified: primary, secondary, tertiary. The packaging can contain reference identifiers to declare what products are contained in which package or package layer. E.g., Package type is a blister. The blister will contain references to two different tablets: tablet A and tablet B. There is no direct relationship between tablet A and tablet B individually. The relationship between them is defined by the blister packaging rather than trying to establish a direct connection between tablet A and tablet B. Industry is therefore given the flexibility to recombine various	Products must be unique entities that can be reconfigured in many ways to support international use. The packaging entity or FHIR packaged product resource joins the products together, not the products themselves. Co-packaging is not a product related concept but instead is a packaging concept. The current approach disrupts the ability to reuse product information across different presentations and creates a US-specific approach that would not be repeated internationally.

Page #	Data Element #	Current Text	Proposed Change	Rationale
			products with different packs without needing to change the product relationships.	
85	4	Product Dosage Form	Clarify that this is the dosage form in the primary packaging to differentiate manufactured vs administrable form of the drug.	This does not seem to be aligned with the proposed IDMP basic dose form concept. Differentiate between manufactured vs administrable form
85	5	Product Route of Administration - Cardinality: 1	Correct cardinality to 1. *	Products can have many routes of administration. This is also noted in the description.
86	12	Product Overall Release Mechanism	Maintain alignment with IDMP's basic dose form approach.	This appears to break from the proposed ISO IDMP basic dose form approach which describes the release mechanism.
87	13-16	Product Coating Indicator, Product Tablet Layer Count, Product Tablet Bead Type Count, Product Capsule Constituent Count	Ingredients should be listed individually. The ingredients can then be grouped according to their role via a user-defined application layer.	We recommend against the product part approach because it will create the need for dedicated data elements and a specific standard for every type of product variant or permutation of variant.
87	17	Product Schematic Cardinality: 1.	Correct cardinality to 0. *	For IR dosage forms, this information is not necessary.
88, 89	19-24	Product Total Weight Numeric Numerator, Product Total Weight Numeric Denominator, Product Total Weight Textual, Product Total Weight Operator	Revert to the ingredient first, role second approach that is described above.	We do not believe the product part approach is sustainable or scalable across a portfolio. The product part weighting appears incomplete and difficult to implement on a scale. As a result, this is too specific and complex to scale up across a portfolio.
90	26	Product Part Identifier	Revert to the ingredient first, role second approach that is described above.	There is unclear value in having text-based identifiers for product parts as these are likely to be unique to one product and not reusable across products. This is likely to break interoperability and reusability which increases the effort needed to maintain granular data at this level at scale.

Page #	Data Element #	Current Text	Proposed Change	Rationale
90	27	Product Part Identifier Reference	Revert to the ingredient first role second approach that is described above. Adopt a more flexible approach that does not impose only an FDA specific way of managing the data. Adopt a more flexible approach that allows other stakeholders to benefit from structured data.	Product part business rules are highly specific to an FDA reviewer's use case rather than the industry use case needed to produce, manage, maintain the data, and convert the data into submittable documents.
91	31	Tablet Product Part Function Description	Example should include "Delivers API" instead of "Push, Target"	"Delivers API" is more descriptive and accurate. Additionally, a codable list may be achievable for this element vs free text.
92	38	Product Part Content Percent	Remove since this is unnecessary and can be calculated based on the provided composition using internal tools/application layer.	This approach expands the scope of work and effort for industry to manage at scale in a sustainable manner
93-98	40-58	Product Part Ingredient Name […], Product Part Ingredient Content Percent	Revert to the ingredient first role second approach that is described above.	Refer to comments above about ingredient first approach. These data elements are unnecessary with ingredient first approach.
99	66	Product Impurity UNII	Add the requirement to use the UNII in the description and rename the attribute to 'code'	Recommend using 'code' instead of UNII
100	69	Impurity Structure Graphic	Remove need for images where possible	This data element is not needed when we have the structured version captured in #68 (Chemical Structure Data File)
101	71	Analysis Graphic	Acceptable data formats need to be independent of eCTD. Avoid requiring industry to adopt a PDF constrained version of FHIR.	This standard should be future focused and should align with FHIR's acceptable file formats rather than eCTD file formats. eCTD, as a legacy standard, places unnecessary constraints on the

Page #	Data Element #	Current Text	Proposed Change	Rationale
				management of structured data using FHIR. This would require industry to expend cost and effort to implement a constrained form FHIR. Those constraints would prevent industry from gaining a full return on investment since it: 1. Requires extra burden, in terms of cost, time and effort, to support a constrained form of FHIR (i.e., XML version of the PDF) rather than its full form. 2. Restricts industry to work in a document/PDF paradigm and eliminates the ability to gain benefits like content reuse and interoperability.

3.2 General Considerations: Drug Product Manufacturing Data Elements – Solid Oral-Focused

Accumulus recommends that the Agency clarify expectations on the inclusion of GMP information and other details that are outside of the scope of current regulations in the newly defined data elements. In addition to specific considerations on solid oral dosage forms, Chapter 2 includes a new section containing data elements to describe the drug product manufacturing process. We agree that the drug product manufacturing process sections of the CTD (e.g., 3.2.P.3.3 – Description of Manufacturing Process and Process Controls) are suitable for structured data exchange and representation, including descriptions of manufacturing processes and parameters, unit operations, and equipment. We are encouraged to see the development of new data elements from "Phase 2" of the PQ/CMC project.

Accumulus has concerns about the level of granularity in the Drug Product Composition – Solid Oral Dosage Form section. Specifically, the GMP information that is outside of the current scope of what is required in regulatory applications. Site-based GMP information is not typically included in regulatory submissions. Equipment information, sampling information, and IPC procedures are examples of content that is beyond current regulations for reporting, which may contribute unnecessary regulatory burden to maintain. Contract manufacturing organizations may not always provide the level of detail described by the new PQ/CMC data elements. Additionally, specific details such as equipment model numbers may differ across facilities, but this may not confer any meaningful insight into the manufacturing process. Therefore, it may be incorrectly determined that there are inconsistencies in the data or risk associated with the process, which could delay post-approval change management and reviewing processes, thereby contributing to potential supply chain risks and delays for patients in need of therapeutics.

The Data Exchange Industry – Pharmaceutical Quality (dx-PQ) HL7 FHIR implementation guide that is currently being co-developed by industry and Accumulus participants will aim to address this issue, among others. The dx-PQ standard may be a more appropriate use case for the exchange of GMP data across systems and facilities involved in the product manufacturing process (e.g.

contract manufacturing organizations). Further collaboration and discussions are needed to determine how the dx-PQ and PQ/CMC projects can work synergistically to ensure that the appropriate level of detail is captured to describe the manufacturing process, depending on the business need of each specific dataset.

The relationship between the new manufacturing process structured data elements and Form FDA 356h should also be defined. The benefit of providing information such as manufacturing site contact person and contact details is also unclear, as this information appears in Form FDA 356h and is not typically repeated in Module 3. If there are planned synergies between Form FDA 356h and the PQ/CMC elements (e.g., if PQ/CMC elements are used to populate the form), we recommend that the data element nomenclature and controlled terminologies are consistent. For example, we recommend the creation of a new data element to describe “manufacturing establishment status.” This is in line with Form FDA 356h, which contains a codable element with the following input options: pending, active, inactive, and withdrawn.

As part of the suggested mapping efforts discussed above, we recommend including drug substance manufacturing to understand the timescale at which these elements might become available, as well as the Agency’s priority level for this domain. If the drug product manufacturing data elements are also extensible to drug substance manufacturing, we recommend that this should be clearly articulated.

3.2.1 Itemized List of Recommendations: Drug Product Manufacturing Data Elements – Solid Oral-Focused

Page #	Data Element #	Current Text	Proposed Change	Rationale
103	5	Manufacturing Site Contact Person	Remove requirement for personal contact information in Module 3	Unclear business justification for providing these details in Module 3. This is provided on Form 356h.
107	30	Unit Operation Critical Indicator	Remove to remain within the scope of existing regulatory requirements	Beyond the scope of requirements per the current guidance.
108	31	Unit Operation Hold Time	Cardinality: 0.1	Hold time is not relevant for every unit operation
108	32	Unit Operation Hold Time UOM	Add “Mandatory when Unit Operation Hold Time” is provided	“Unit Operation Hold Time” will always need units of measure
108-109	33-39	Equipment Manufacturer Name, Equipment Model Number, Equipment Identifier […], Equipment Utilization Percent	Remove to remain within the existing scope of regulatory requirements	Significant detailed information about equipment is not currently required and would be difficult to maintain at scale and across the lifecycle.
109	40-42	Unit Operation Equipment Process Parameter Name, UOM, and Criticality Cardinality: 1	Cardinality should be 0.1	Process parameters may not need to be defined for every unit operation, such as packaging
110	51	IPC Reference to Analytical Procedure	Remove to remain within the existing scope of regulatory requirements	Providing the actual file of the analytical procedure for the IPC for a typical manufacturing process is beyond the scope of requirements in current guidance and constitutes an unnecessary regulatory burden.
111	56-58	Acceptance Criteria Usage, Interpretation Code, Acceptance Criteria Additional Information	Remain within the existing scope of regulatory requirements using a more simplified and flexible approach.	This seems incomplete, and industry could not use this format to describe a complete manufacturing process.

111-112	59-63	Sampling/Timing Frequency, Sampling Location, Sampling Quantity, Sampling Quantity Unit of Measure, IPC Batch Usage	Remain within the existing scope of regulatory requirements using a more simplified and flexible approach.	This seems incomplete, and industry could not use this format to describe a complete manufacturing process.

4. Conclusions

Accumulus Synergy is thankful for the opportunity to provide comments on Chapter 2 of the FDA's PQ/CMC Data Exchange document and FRN. Accumulus Synergy looks forward to supporting the implementation of structured CMC data and enabling PQ/CMC data exchange with the development of its cloud-based platform. Accumulus Synergy thanks the FDA for their consideration of our comments and welcomes any opportunities for additional discussion or clarification.