Response to a request for comments "***Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls Data Elements and Terminologies***" Draft Guidance or Consultation Document Docket No. FDA–2023–N–1443

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT (optional)
PQ/CMC Data requirements should not exceed the level of detail required in the current version of ICH M4Q (R1) and should be consistent with the revision, ICH M4Q(R2). A significant amount of the information required in Chapter 2 Section 2 is considered to be GMP or more frequently associated with a site master file and is not currently normally provided in NDAs, ANDAs, SNDAs, BLAs, and MFs.
Equipment information and sampling information are examples of content that is beyond current regulations for reporting, that is going to cause unnecessary regulatory burdens to maintain, and will increase the burden of activities to support continual improvement. Some examples but not all are given in specific comments below. The level of detail stated within this draft document could be difficult to maintain in countries without the lifecycle management infrastructure of the U.S.
ISPE recommends that the requirements state what information must be maintained over the lifecycle.
ICH's desire published in the M4Q(R2) Concept Paper[1] to "*facilitate leveraging advances in digital tools, data management and standardization, and analytics to enhance efficiencies and effectiveness of regulatory submissions and assessments"* is not referenced anywhere in the documentation relative to the potential of SPQS to link with M4Q (R2) and how SPQS may assist in resolving divergence. Managing all the new terminology as structured master data, without global commitment would lead to significant industry challenges to submit consistent, accurate, or complete data.

[1] Concept Paper M4Q(R2) Common Technical Document on Quality Guideline. (Nov. 2021). ICH_M4Q-R2_ConceptPaper_Endorsed_2021_1115.pdf

ISPE recommends aligning the high-level terms (e.g., Unit of Measure, Dosage form, Manufacturing Site Responsibility, contacts, and ingredient roles) with the definitions in ISO, EMA Implementation guides, etc. With the publication of these enhancements, an ontology extension request should be submitted to EMA/ISO to foster interoperability of these data across the Product/CMC lifecycle.
We recommend that if the information is designated as mandatory, then code type is preferred versus text whenever possible. We believe that this will provide opportunities to link across ontologies and to existing systems that contain controlled vocabulary terms (e.g., Global Substance Registration System (GSRS), and Identification of Medical Products (IDMP).
The example use cases presented (e.g., multi-layered tablet, bead-filled capsule, etc.) are helpful for understanding specific applications of the PQ/CMC data elements as they apply to particular dosage forms. It would be helpful to understand if the Agency intends to engage in a similar exercise for other modalities (e.g., biologics, vaccines, cell and gene therapies) moving forward.
The additional granularity introduced in chapter 2 may introduce challenges (and expand the potential for needing more data elements) to support unique/complex dosage forms and modalities. We believe that granularity may ultimately decrease flexibility. 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 Fast Healthcare Interoperability Resources (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."[2]
We recommend the creation of a new data element to support Drug Product Manufacturing Data Elements "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.
Listing examples for "manufacturing processes" in Chapter 2 would be helpful for a better understanding of expectations, just as examples were listed for Drug Product in the Introduction to Chapter 2.

2 HL7's FHIR (Fast Healthcare Interoperability Resources) Specification, https://build.fhir.org/overview.html

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Page 87, item #17 Product Schematic	The pictorial representation of the drug product.	Data element 17 should be deleted, please.	For IR dosage forms, this information is not currently required and is considered unnecessary.
Page 88, Data Element #19	Product Total Weight Numeric Numerator	We recommend providing an example of a case where this field is not mandatory to make it clearer or making this data element mandatory.	It is not clear when it is not mandatory to provide the "Product Total Weight Numeric Numerator." Since the "Product Part Total Weight Numeric Numerator" (#34) is mandatory, it seems to follow that the "Product Total Weight Numeric Numerator" is also mandatory.
Page 89, Data Element #21	Product Total Weight Numeric Denominator	We recommend providing an example of a case where this field is not mandatory or make this data element mandatory.	It is not clear when it is not mandatory to provide the "Product Total Weight Numeric Denominator."
Page 91, Data Element #28	In Business Rule/Comments column: "When part does not include an API then Part Release Profile='Not Applicable'"	We recommend rephrasing to state "Cannot be Not Applicable when part includes an API."	"When part does not include an API then Part Release Profile='Not Applicable'" may not always be true. For example, on page 184, 3. Tablet with two coatings, "Product Parts" table item 3, "Product Part Release Profile" for "Coat 1" is "DR" (delayed-release), not "Not Applicable," although Coat 1 does not include an API.
Page 91, Data Element #31	In Business Rule/Comments column: "Mandatory when Dosage Form = 'Tablet' and Part Type is not 'Coating,' otherwise null"	ISPE recommends rephrasing to state: "Mandatory when Dosage Form = 'Tablet' and Part Type is not 'Coating,' or when Dosage Type = 'Capsule' and part type is 'Tablet' or 'Beads."	"Mandatory when Dosage Form = 'Tablet' and Part Type is not 'Coating,' otherwise null" may not always be true. For example, on page 182, Titled: ***Capsule Filled with 2 Constituents***

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
		The Business Rule could be expanded to include all cases that may require an entry.	Reference the first item in table 1: the Dosage Form = Capsule, and following the Business Rule on page 91 #31 in the table "Tablet Product Part Function Description" states: Mandatory when Dosage Form = 'Tablet' and Part Type is not 'Coating', otherwise null However, in the "Product Parts Function" table 3 , for both "Tablet" and "Beads" states : "delivers API," and is, therefore, not "null."
Page 91, item #31 Tablet Product Part Function Description	The main purpose for the part in the solid oral tablet. [Source: SME Defined] Example: Push, Target	The example should include "delivers API" instead of "~~Push,Target~~"	"Push" and 'Target' are not usual words to describe drug release mechanisms. 'Delivers API' is used elsewhere in the document.
Page 107 item #30 Unit Operation Critical Indicator	A property that identifies whether the unit operation is considered critical in the drug manufacturing process. [Source: SME Defined]	Data element should be deleted, please.	Data element 30 is not in the scope of requirements in current guidance
Page 108 item # 31 Unit Operation Hold Time	Cardinality, 1	In the Cardinality column, please start numbering at zero.	Cardinality should be "0..1" as hold time is not relevant and included for every unit operation, for example, for many unit operations for solid oral dose products.
Page 108 item #32 Unit	The business Rule (BR)/Comments field is currently blank	Business Rule (BR)/Comments – add "Mandatory when Unit Operation Hold Time is provided"	If a hold time is given, units of measurement are required.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Operation Hold Time UOM			
Page 108 Items # 34-38	Data Elements: 34 Unit Operation Equipment Manufacturer Name 35 Equipment Model Number 36 Equipment Identifier 37Equipment Size 38 Equipment Working Capacity	Even though they are not listed as "mandatory," ISPE recommends removing these PQ/CMC Data Elements that have been newly added.	This information is beyond the scope of requirements in current guidance and constitutes an unnecessary regulatory burden. Overly committing to specifics in equipment descriptions limits the ability to make a "like for like" change in a pharmaceutical quality system based, for example on a justification using critical process parameters.
Page 109 item# 39 Equipment Utilization Percent	The percent used or proposed is based on the equipment's working capacity for this manufacturing step.	Even though not listed as "mandatory," ISPE recommends removing this PQ/CMC Data Element	This is beyond the scope of requirements in current guidance and constitutes an unnecessary regulatory burden
Page 109 Items #40, #41, & #42	40 Unit Operation Equipment Process Parameter Name 41 Unit Operation Equipment Process Parameter Name 42 Critical Process Parameter Indicator Data Type Numeric, Cardinality, 1	In the Cardinality column, please start numbering at zero.	Cardinality should be 0..1, as process parameters may not need to be defined for every unit operation such as some packaging operations.
Page 111 Item# 59	59: Sampling Timing/Frequency "The occurrence indicating how often material from the lot (sample(s) of the lot) are extracted for testing during the manufacturing step. FDA recommends that Industry use applicable guidance and best practices based on the appropriate unit operation when providing the sampling frequency"	Data element should be deleted, please.	These data elements are beyond the scope of requirements in current guidance and constitute an unnecessary regulatory burden related to change and continual improvement.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Page 111 Item# 60	60:Sampling Location The place or the spot in the manufacturing equipment or the immediate environment (e.g., air in the room) from where the material from the lot (sample of the lot) was extracted for testing during a manufacturing step. FDA recommends that Industry use applicable guidance and best practices based on the appropriate unit operation when providing the location information	Data element should be deleted, please.	These data elements are beyond the scope of requirements in current guidance and constitute an unnecessary regulatory burden related to change and continual improvement.
Page 112 Item 61	61: Sampling Quantity The amount of material taken from the lot to be inspected to determine if the entire lot will be accepted or rejected based on the quality of the sample size. Examples: 10, 200	Data element should be deleted, please.	This data element is beyond the scope of requirements in current guidance and constitutes an unnecessary regulatory burden related to change and continual improvement.
Page 112 Item 63	IPC Batch Usage Acategorization of the batch that identifies its usage. Examples: commercial, development. This is the same as Batch Utilization published in the previous Chapter document, but is in the context of IPC.	Data element should be deleted, please.	This data element is beyond the scope of requirements in current guidance and constitutes an unnecessary regulatory burden related to change and continual improvement.
Page 121 item 15	Product Part Ingredient Name Type.	Based on the description, it is not clear how will the data elements be applied. If just one item needs to be selected, such as CAS or USP/NF, it may be acceptable. However, if a new drug substance is part of the DP, supplying of multiple pieces of information such as CAS, INN, IUPAC, and USAN is repetitive since it is already supplied on the drug substance. Further clarity and examples are requested, please.	Some further clarification is requested please on what is required, particularly if information is provided in the drug substance part.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Page 123 item#17	Product Part Type- Minitablet: A constituent composed of small tablets that are filled into capsules.	It is recommended that the term 'mini-tablet" is removed from the list of dosage forms (valid values) and the granule definition should be expanded.	Rationale: minitablets are not mentioned in USP <1121> nomenclature, thus are not defined. Minitablets are mentioned once in the USP, in USP 711 as a parenthesis under Inserts. As it is not a defined nomenclature, at this time, it should not be added. As the goal is global harmonization of submissions, the capsule definition should be expanded to cover the mention in the European Pharmacopeia 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."
Page 179 Appendixes	Appendix A and Appendix B	It would be helpful to add examples to illustrate the use of structured data elements for drug product manufacturing for solid oral dosage forms (SODF).	It would be helpful to applicants to have an example of the use of structured data elements applied to drug product processing, for example, solid oral dosage form in a similar manner given in Appendices A, Product Weight Representation, and B, Drug Product Composition.