Plasma Protein Therapeutics Association

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

SUBJECT: Draft Standardization of Pharmaceutical Quality/Chemistry Manufacturing and Control (PQ/CMC); Docket No. FDA-2017-N-2166

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) thanks FDA for the opportunity to comment on FDA's draft standardized PQ/CMC data elements and terminologies for the electronic submission of PQ/CMC data. PPTA will provide comments on the accuracy, suitability, and appropriateness of these data elements and terminologies for submission of PQ/CMC data.

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies. Plasma protein therapies are used mostly in the treatment of several rare diseases. These diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. These therapies include clotting therapies for individuals with bleeding disorders, immunoglobulins (IG) to treat a complex of diseases in persons with severe autoimmune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult-onset emphysema and substantially limits life expectancy, and albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings, shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

Introduction

PPTA recognizes that the establishment of standardized pharmaceutical quality data elements and terminologies will provide opportunities for FDA and industry to transform PQ/CMC submission data into a readily useable electronic format and that, as a result, these established data elements and terminologies will improve the efficiency and quality of the drug review process.

147 Old Solomons Island Road · Suite 100 · Annapolis, MD 21401 USA
tel: 202.789.3100 · 410.263.8296 · fax: 410.263.2298 · e-mail: ppta@pptaglobal.org · www.pptaglobal.org
PPTA Offices in Washington · Annapolis · Brussels · Tokyo

General Comments

Comments	Rationale
FDA should clarify a system in which sponsors/license holders can add new data elements and/or acronyms/terms when developing submissions in the instance they have a product or need that has not been contemplated before and that those issues can be addressed in a timely manner.	Not every possible nuance of a product can be captured in a set of terms, especially with respect to "Controlled Terminology/Vocabulary." This will be true of existing products and of future technologies. In order to ensure submissions can be published and received at FDA in a timely manner and not create bottle necks or delays in reviews, it would be prudent to provide direction to industry on how to ensure all the terms/data elements/definitions they need to complete their submissions can be created as needed.
FDA should clarify how sponsors/license holders can address existing CTDs that do not necessarily reflect FDA's current proposal.	In line with comments above, to avoid bottle necks or delays in reviews, FDA should provide direction on how to implement changes to existing CTDs that are already life-cycled.
The FDA should define the requirements vs. recommendations for each data element.	Depending on the history for any given application, and prior agreements with the Agency for that application, a given data element may not apply. The application holder should be permitted to maintain the extent of data elements currently expected by the Agency. Otherwise, edits to CTD sections to meet the requirements could lead to undue burden on industry and the Agency. For example, in order to report data elements via SPL that are not currently included in the application and currently reflected in the manufacturing documentation, there could be undue burden placed on the overall quality system(s) with industry to align, or create terminologies not currently existing in the documentation. If FDA makes all the data elements a requirement, then some BLA sections may need to be created or significantly edited to accommodate the new guidance; if they make them suggestions/guidelines/recommendations, then this can potentially be avoided, especially for older CTDs.
FDA should provide an implementation plan in order to ensure that Controlled Vocabularies do not create validation conflicts with existing metadata.	For an existing product, FDA should ensure that any update to existing metadata fields maintains the life-cycling of each submission node and that the introduction of new metadata does not create technical validation conflicts.
In the implementation plan for this controlled vocabulary, FDA should ensure flexibility in their use.	As per the proposed data elements there are proposals for terms and definitions that may not currently be applied to existing CTD sections for certain products. While most data elements are likely currently captured in

	majority of existing licenses/applications, there are many that are not historically required to be documented or maintained within the application. The following list provides examples of data elements that should not be required within the application in order to avoid undue burden. Specification version Specification status date Stage name, for a test Stage sequence number, for a test Testing site name, batch analysis Retest date Batch utilization Specification version, during batch analysis Test date Release date, batch analysis Substance structure graphic Chemical structure data file Drug substance method type Analysis graphic Analytical instrument data file Overage justification Diluent information Drug excipient component supplier name, manufacturer Source organism country of origin Drug substance impurities, all elements Drug product impurities, all elements In line with the comment above, the implementation plan should clarify which elements can be considered options vs. requirements. At a minimum, it should be clarified that if an element is not used it should be understood that it is considered not applicable and therefore not included.
The FDA should harmonize the data elements and controlled vocabulary with other jurisdictions, in particular ICH jurisdictions or future requirements.	An assessment of how these data elements align with the requirements or future requirements of other jurisdictions and with ICH expectations would be helpful. For example, if applicants are forced to use specific data elements that are not harmonized with other jurisdictional requirements, then an applicant may be unreasonably burdened by having to maintain two

	different sets of data elements and controlled vocabularies.
It is positive to see standardization of data elements in the document. In general, it is noted that the terminologies proposed are more commonly used terms and aligned with small molecule pharmaceuticals. There is no mention of biologics-specific requirements, such as cell banks and methods. FDA should confirm that biologics and products approved via unique mechanisms (e.g. Animal Rule products) should be captured. There are several comments below around this.	--

Specific Comments

Page	Location in Document	Current Text	Proposed Change	Rationale
6	Section 2 Test, row #4 Test Category	No code for Excipients under the codes table item #22 Section 2B Table	Add Excipients code to Section 2B table.	Excipients measured for finished product release; does not seem to have a category already captured under codes
9	Section 3 Acceptance Criteria, row #2 Value unit	No percentage % code identified under item #26 Section 2A Table and not under FDA Data Standards-Unit of Measure	Add a code for %.	Several of substance/product release acceptance criteria for specifications are presented in percentage.
9	Section 3 Acceptance Criteria, row #2 Value unit	No code for value units that are presented per another unit (e.g. mg/mL, units/vial, etc.)	Add a code with more flexibility.	Several of substance/product release acceptance criteria for specifications are presented in units/vial etc.
9	Section 3 Acceptance Criteria, row #4	No codes for capturing range of results under	Add a code for a range of results.	Several of substance/product

	Interpretation Code	item #13 Section 2A Table		release acceptance criteria for specifications are presented in a range (e.g. 30-80 mg/mL).
11	Section 4 Batch or Lot Information	Row #3 Manufacturing Site Name Row #4 Manufacturing Site Unique	Although the site may be unique, there may be several buildings listed in the same FEI/DUNS registration. What type of system will be put into place to ensure the manufacturer is using the correct location? There needs to be another check.	If the FEI/DUNS is listed incorrectly with relation to the function of the facility, then this can cause confusion, especially when it comes to paying annual establishment fees.
13	Section 4 Batch or Lot Information	Row #11 Batch Size	The scale of the batch should be specified. How would the reviewer know if the batch is the approved smaller scale, commercial scale, or scaled up quantities?	If a smaller batch size is used then scaled up, where will this be captured?
13	Section 4 Batch or Lot Information, row # 12 Batch Size Unit	No code for Batch Size in “vials” under item #26 Section 2A Table and not under FDA Data Standards-Unit of Measure	Add a code for “vials.”	The Batch Size for the drug filled product is in vials.
15	Section 4 Batch or Lot Information, row # 22 Batch Utilization	No code to capture “Nonclinical” use under item #1 Section 2A Table	Add a code for “Nonclinical” use.	Lots were used in nonclinical studies supporting efficacy for products approved under the “Animal Rule.”

27	Section 9 Description and Composition of Drug Product, row #4 Strength	The content of an active ingredient expressed quantitatively per dosage unit, etc.	Propose the number field to be flexible to include more than one number and text (e.g. per the label claim: serotype A > 4500, serotype B > 3300, serotype C > 3000 units per vial, etc).	The potency of some biologic products may be made up of potencies of several different monovalent lots in one vial.
27 & 29	Section 9 Description and Composition of Drug Product, row #5 Strength Unit of Measure and row #13 Amount per unit	No current code for vial #26 Section 2A Table and not under FDA Data Standards-Unit of Measure	Propose to add the term "vial" to the code per the strength presented on the label.	For each fill, each vial contains a minimum of the same potency for each of the different serotypes (i.e. serotype A >4500 units/vial, serotype B >3300 units/vial, etc.), however the final fill volume is not consistent among fill lots. The final fill volume depends on the potency of each of the 7 serotype bulk lots among lots being blended, which is only known after the blending of the bulk lots.
29	Section 9 Description and Composition of Drug Product, row #15 Content (%)	No current field	Make the field more flexible or add a "Not applicable" field for ingredients where the percentage units are not easily applied.	Active ingredients are presented on the label in Units/vial; see point above for more explanation.
35	Section 11 Drug Substance – Control of Materials, row # 3	The current FDA regulatory status of the specification. Examples:	Propose to add "Released," "Not Released," etc. to the	The current text is confusing as usually raw material, reagents, and

	Specification Status, and Section 12 Drug Product – Control of Excipient, row # 3 Specification Status	Approved, not approved, etc.	code field under Section 2A Table item # 18.	excipients used in the manufacture of a drug product are internally released for use and at that stage are not approved by FDA; the product manufactured using them and submitted as BLA, PAS, CBE30, AR, etc. will be approved or not.

Page	**Section**	**Comment**
58	17 Source type	Which is the category for recombinant proteins manufactured in CHO cells? According to the definitions/examples, neither “Chemical,” “Animal,” “Microbial,” “Plant,” “Insect,” or “Human” applies. The best choice would be “Animal-derived indirectly,” but the examples do not fit. Is there a possibility to add another value, like “Biotech”?
63	26 Unit of measure	Da/kDa (Dalton) is not in the list of FDA Data Standards-Unit of Measure. In addition, there are tests with special acceptance criteria, e.g. SDS-PAGE with text requirement: *Band pattern does not contain additional protein bands in comparison to the control sample, main band in the area of 150 to 250 kDA.* Is this still acceptable?

Conclusion

PPTA appreciates the opportunity to comment on the draft standardized PQ/CMC data elements and terminologies for the electronic submission of PQ/CMC data and looks forward to continuing to provide the perspective of the plasma protein therapeutics industry. PPTA welcomes from FDA any questions regarding these comments. Thank you for your consideration.

Respectfully submitted,

Mary Gustafson
Vice President, Global Regulatory Policy
Plasma Protein Therapeutics Association