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September 26, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Comments from Cross-Industry Quality Metrics Collaboration Group regarding Docket FDA-2016-D-1594: Quality Metrics Technical Conformance Guide-Technical Specifications Document.

The undersigned trade and technical organizations, representing a broad informal group across the pharmaceutical industry, stand together collectively as the Cross Industry Quality Metrics Collaboration Group (the “Collaboration Group”) to provide consolidated feedback on FDA’s draft Quality Metrics Technical Conformance Guide (“Conformance Guide”). These comments should be considered in addition to comments submitted by each individual organization.

Our organizations all value patient safety and understand the Agency’s goals behind the proposed quality metrics program. To ensure clear expectations for industry we have comments and requests for clarification concerning some areas of the Conformance Guide. Our organizations continue to support the points made in our November 25, 2015 letter to the docket on FDA’s Draft Guidance Request for Quality Metrics (“Draft Guidance”), including our request that FDA adopt a phased-in approach for quality metrics in an effort to maximize learning, minimize burden on both industry and FDA, and enhance the chances of a successful implementation.

We welcome the opportunity to continue our collaboration as stated in the Federal Register notice including dialogue prior to and following the anticipated release of the revised Draft Guidance in 2016.

To demonstrate our commitment, following the Draft Guidance in 2015, Industry continued

working to better understand FDA's proposals and optimize our internal metrics programs. It should be noted that a number of industry activities have been conducted since last November. We would like to acknowledge the work of ISPE's Wave 2 and its results, PDA's Quality Culture Assessment Pilot, and other efforts by industry to better understand Quality Metrics and its impact on resources, quality culture and preventing unintended consequences.

Technical Challenges and Learning Curve

There will be a significant learning curve associated with XML file transfer for the technical quality personnel and additional operations staff to ensure these quality metrics submissions are in electronic submission format in accordance with FDA requirements. At many companies, the quality unit is not the group that performs electronic submissions to the FDA.

Consequently, the FDA's Conformance Guide does not provide all the necessary detail for companies to report quality metrics data. While the Draft Guidance (section 1.4) refers to the FDA document entitled "Study Data Standard Resources," that document provides a plethora of information on the standards related to submission of clinical and nonclinical information, adverse event information, therapeutic-specific information, as well as electronic submission details. None of the electronic submission guidance documents issued by FDA indicate they are applicable to quality metrics data. Hence, this leaves a significant gap at the moment for industry to understand which guidances to follow to ensure compliance with the electronic submission requirements for quality metrics.

Formatting and aggregating the data as FDA specifies in its Conformance Guide will be a significant undertaking for companies with existing quality metrics information systems. FDA-specific definitions will require manual intervention in the data even with electronic systems. For companies using largely manual data collection, the challenge is even higher. For all of these reasons, industry requests that FDA provide at least a year after issuance of the final quality metrics guidance and Conformance Guide before industry is required to begin data collection (a total of 2 years before metrics submission is required).

Additional considerations of note include the following:

- The current draft Conformance Guide does not specify the type of submission the quality metrics will constitute (e.g., is it lifecycle eCTD, analogous to NDA Annual Report, or some other type).
- How will manufacturers be required to address amendments and/or any modifications in information to their submissions?
- From a review and approval perspective, will these documents have a timeframe for which FDA will review the quality metrics submission and what kind of response will FDA provide to industry and in what timeframe?
- Are any fees associated with these submissions?

Industry also has concerns about the data format and conversion rules including assurance that there will be no data loss or inconsistency during file conversion, storage, analysis or transmission. Key concerns identified by industry that are unclear in the Conformance Guide include: XML readability, conversion of XML data to other formats and ensuring no loss of data, as well as how will FDA ensure security for the data obtained in the quality metrics submissions

via these procedures. Industry requests greater transparency in the manner in which data will be assessed, and how outcomes and conclusions will be determined and communicated.

Pharmaceutical manufacturers consider metrics data to be Confidential Commercial Information per 21 CFR 20.61(b) and would expect FDA to follow existing protections for this category of information as well as implement reasonable protections against electronic theft or unauthorized access. We feel strongly that data security is paramount to the success of this program. Data security should be prominently addressed in FDA's Conformance Guide, along with assurances for how data security will be maintained.

Given that FDA has specified a file format designed for data sharing, industry requests more details about how FDA intends to use the data, clarity about FDA's procedures to ensure data confidentiality/security and whether FDA intends to share any industry data outside of the FDA. We would particularly ask that the agency specifically state whether, when, and how it will share quality metrics data with its foreign counterparts.

Data Submission Format

The 2015 Draft Guidance Request for Quality Metrics allows for a comment field. The option for a manufacturer to provide context around specific data and metrics was a frequently discussed need from industry in advance of that draft being issued. We note that there appears to be no technical accommodation for a comment field in this technical document either for each data element or for a general comment field for the entire submission. If all comments are submitted in a separate section of the report, then a link to each data element type or reference to specific data entry is needed. For ease of submission and to minimize potential for errors, industry recommends the allowance for a comment field be included for each data element. Industry feedback during the Draft Guidance comment period was strongly in support of the providing the means to submit comments with the data.

We ask that FDA specify in its Conformance Guide the mechanism for providing comments on individual data points in order to put the data in its proper context. Along with this, we ask FDA to implement processes internally to read and consider each submitted comment and to communicate said comments along with any data shared with its investigators.

The Collaboration Group also recommends that FDA provide a sample format to ensure consistency of submitted data including samples for API data and for drug product data. Consideration should be given to the ICH Data Elements outlined in the E2B(R3) document package guidance.¹

Additional Technical Comments

Beta Testing

There does not seem to be a provision for beta testing of the system before companies submit live data. Industry respectfully requests FDA to include a period of beta testing where manufacturers could test submissions which would increase the confidence of manufacturers that

¹ ICH E2B(R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm274966.htm>

their data is correctly transmitted. Industry suggests FDA create a “sandbox” type environment for companies to play in with sample requests to which industry could respond and receive FDA feedback on whether the response meets expectations of format, structure, and verification. Additionally, we recommend that FDA have ongoing support (e.g., a Help Desk) so that manufacturers may have a resource to direct ongoing electronic submission questions to regarding the quality metrics submissions.

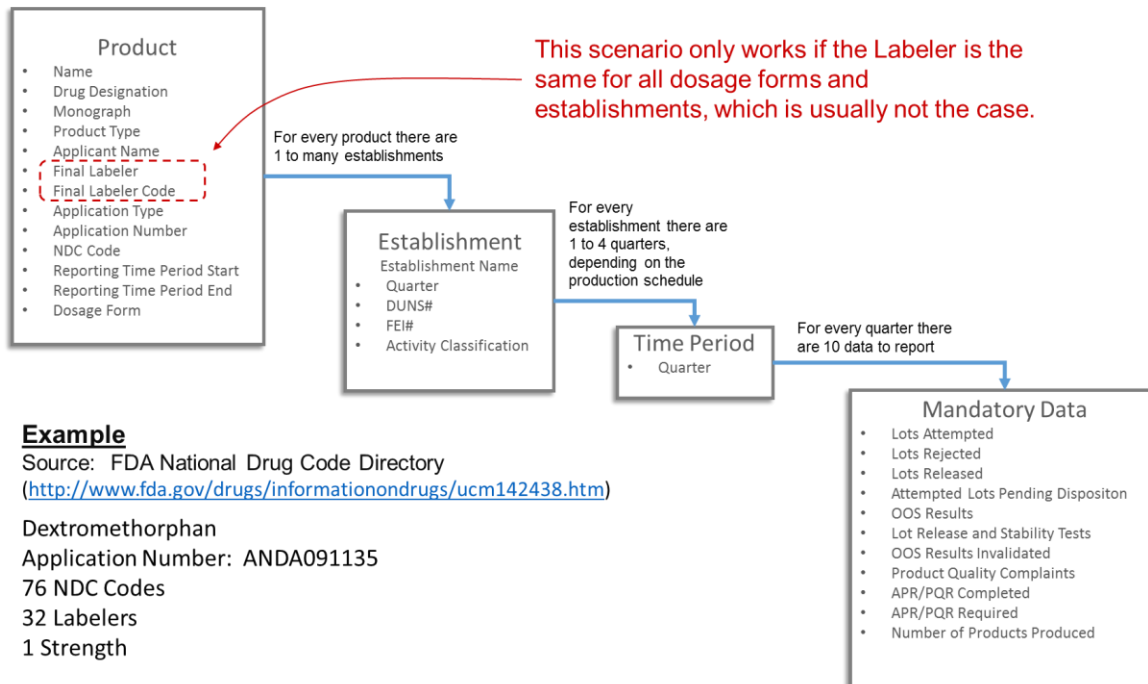
Data Aggregation

The Conformance Guide, as written, seems to indicate that data aggregation for the submissions will be well beyond what is specified in the Draft Guidance; that is, by product, by establishment, by quarter. The Conformance Guide indicates that aggregation will be by product, by establishment, by quarter, and also by labeler, dosage form, formulation, strength, package type and package size.

In order to fully understand data submissions the Collaboration Group compiled a few examples below, while not covering all scenarios, these may serve as illustrations to obtain further clarity.

Looking at FDA’s Draft Guidance and Conformance Guide, it appears that the XML file is intended to be structured as diagrammed in the figure below as Scenario 1.

SCENARIO 1: How the Draft Guidance Seems to be Structuring the Data Submission



Example

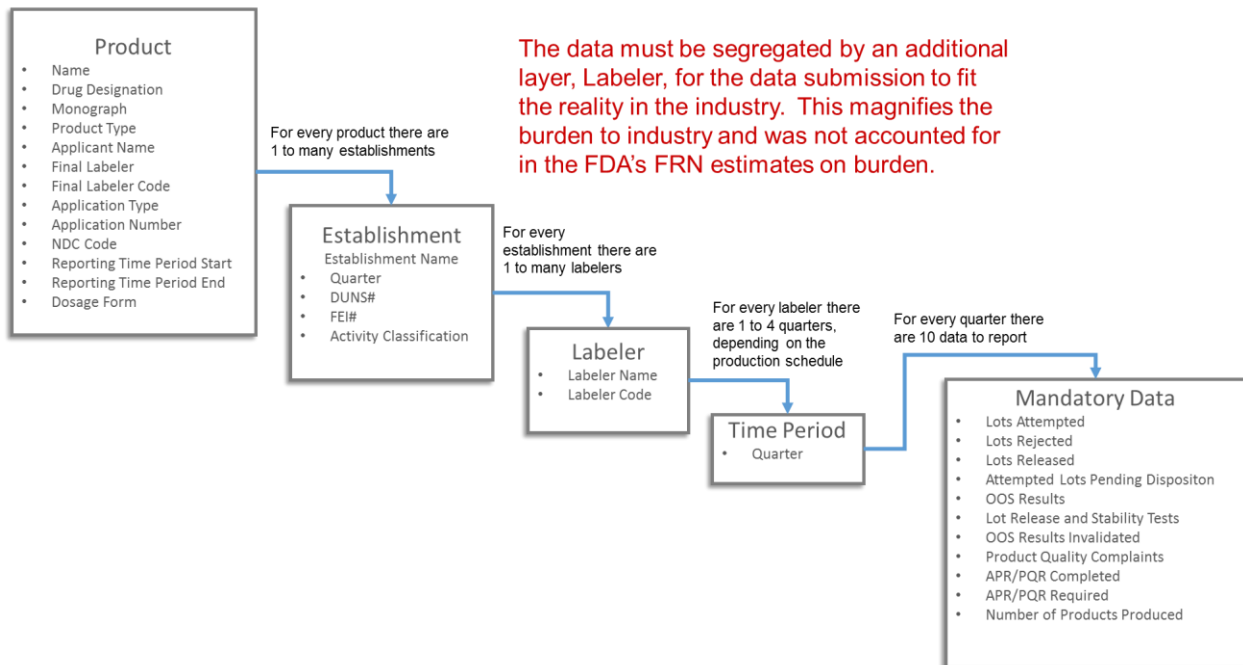
Source: FDA National Drug Code Directory
<http://www.fda.gov/drugs/informationondrugs/ucm142438.htm>

Dextromethorphan
 Application Number: ANDA091135
 76 NDC Codes
 32 Labelers
 1 Strength

The Final Labeler name and code are included in the Product Information table, as shown on page 25 of FDA’s Draft Guidance, and include only 1 row for Final Labeler. This assumes that there is only one labeler per application, which is not always the case. Looking at FDA’s National Drug Code Directory, there are a multitude of applications that have many labelers. An example of this is Dextromethorphan. Application ANDA091135 has 32 Labelers associated with it.

Given that in many cases there will be more than one Labeler per application or product, and then it seems that the XML file would need to be structured more like what is diagrammed below as Scenario 2.

SCENARIO 2: Corrected to Account for the Labeler Being Different for Different Establishments and Dosage Forms



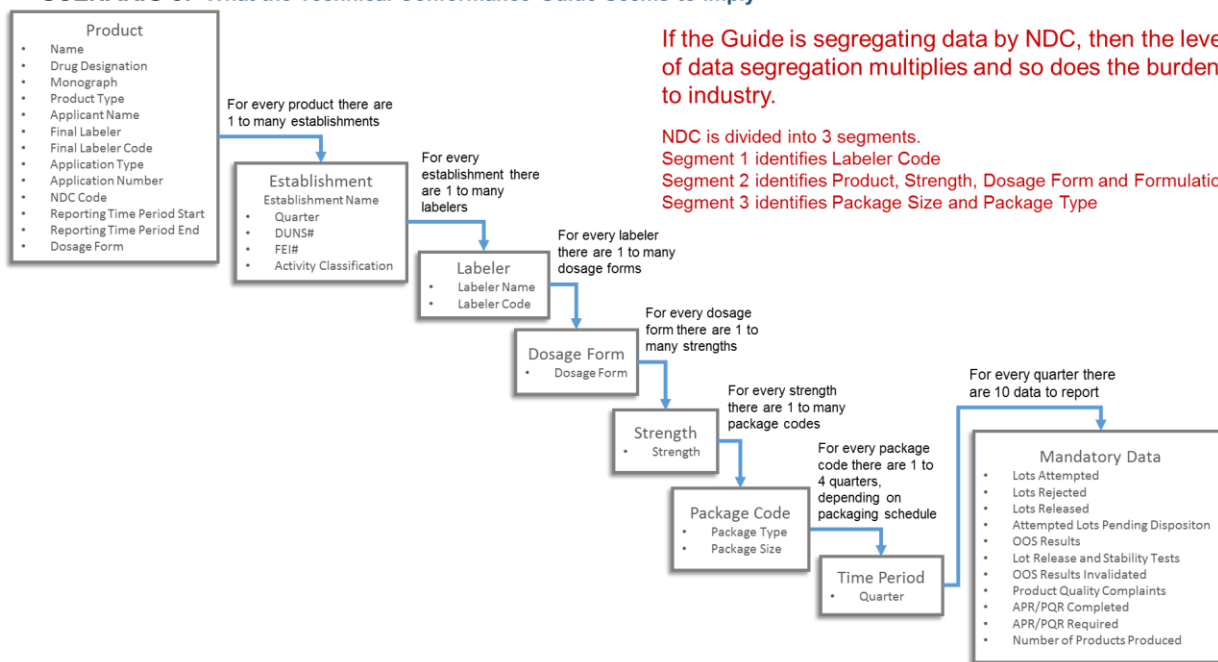
FDA’s Draft Guidance and Conformance Guide both request NDC Product Code be reported with the Product Information. The NDC Product Code is divided into three segments:

- Segment 1 identifies the Labeler Code
- Segment 2 identifies the Product Code, which is specific to product, strength, dosage form and formulation
- Segment 3 identifies the Package Code, which is specific to package type and package size.

FDA, in its example data submission table on page 25 of its Draft Guidance, shows a single NDC Product Code for each product. However, like Labeler, typically there are many NDC Product Codes associated with a single application or product. Going back to the aforementioned Dextromethorphan ANDA example, application ANDA091135 has 76 NDC Product Codes associated with it. For the data element, 4.2.2 Drug Designation, the Conformance Guide specifies only one designation per product, but a product can be both Rx and OTC, especially depending on strengths. By restricting the Drug Designation to one or the other, but not both, it implies that the metrics must be submitted segregated, not only by product, but also strength.

Given this and the fact that there will be many NDC Product Codes per application or product, in most cases, then it seems that the XML file would need to be structured more like what is diagrammed below as Scenario 3.

SCENARIO 3: What the Technical Conformance Guide Seems to Imply



If Scenario 3 is an accurate depiction of how the XML file would need to be structured, then the data reporting burden to industry multiplies significantly.

It is possible that FDA is not intending to aggregate the data for reporting as shown in Scenarios 2 and 3. Either way, it is unclear and needs to be diagrammed in detail by the FDA in its Conformance Guide. We ask that the FDA clarify its Conformance Guide and Draft Guidance to show exactly how the XML file would be structured. Without this, a full understanding of the feasibility and burden associated with reporting cannot be obtained. If, as the Conformance Guide indicates, data are to be aggregated by the additional attributes of labeler and product code, then the burden will be greatly multiplied over and above the FDA estimates given in its Federal Register Notice.

If it is the case that FDA is requesting data reported at a product application level only, such as diagrammed in Scenario 1 above, then the need for a list of Labeler Names/Codes and all NDC Codes is not apparent. We ask that FDA to clarify why it needs Labeler and NDC codes for product application-level reporting. The aforementioned example of Dextromethorphan had a total of 98 codes to gather and verify. Such reporting will add a significant burden, and it is unclear what additional benefit is added by labeler or NDC codes in the context of product level reporting.

Errors and Omissions

There were a number errors or missing information in the Conformance Guide. These are outlined below:

- Table of contents is missing 4.2.12, 4.2.15 and 4.4.2
- In Table 1, FDA states the maximum number of characters for a variable name is 8 characters. However, DOSAGEFORMS and APRAPPVDY both exceed 8 characters. Is “Variable Name” the same as a “Data Element Name”? If so then they exceed the stated limit.

- The Draft Guidance requires reporting of the Total Number of Products Produced at each establishment during each quarter. This is the denominator for APR/PQRs Completed Within 30 Days; however, Total Number of Products Produced metric is not defined nor mentioned in the Conformance Guide. Total Number of Product Produced needs to be defined in the draft guidance, as the current version does not define it, and it needs to be included as a data element in the Conformance Guide.
- On 4.2.7 Labeler Codes, the description asks for the name of the labeler for validation of the text entered as “final labeler name”. However, the title of this data element is Final Labeler Codes. Code is a 4-5 digit assigned by the FDA. FDA needs to clarify if it means name or code for 4.2.7 and make the necessary corrections.
- The Data Element Descriptions in Table 2 should exactly match those included in the Draft Guidance for each Quality data point. For example, LOTRELTST is described in the Conformance Guide as “number of lot release tests conducted for commercial use”. According to the Draft Guidance, this data element is “number of lot release and stability tests conducted for the product”
- TIMEPRD is listed as the code for both Time Period Stat and Time Period End. It cannot be both. We assume this is a typographical error.
- APRWIDD is listed as the code for Attempted Lots and APR/PQR Completed. It cannot be both. We assume this is a typographical error.

Validation Rules

FDA states in its Conformance Guide that validation rules will be posted to the FDA web page once the Request for Quality Metrics guidance is published in final form. While we recognize that determining the validation rules in advance will have its challenges, we do not support having said rules set after the Conformance Guide is final without any industry prior review and comment period provided. We do support FDA engaging with industry in a collaborative dialog on developing appropriate and accurate validation rules.

Validation rules, as stated by FDA in its Conformance Guide, companies should validate (using validation rules) their metric data before submission using the posted validation rules and correct any validation errors. Without upfront collaboration with industry on said rules, FDA risks creating inaccurate validation rules, which will result in false positive validation errors due to a lack of understanding for the nuances of metrics data inclusions and exclusions.

The validation rules need to be written and publically published in draft form for industry comment prior to making them final.

Additionally, the Conformance Guide does not address an avenue for clarifications of data submitted, specifically typos or other administrative errors that should be amended. Please clarify how FDA plans to allow submission of corrections for such errors.

Specific Data Elements

- Industry should not be required to submit duplicate information, for example both FEI and DUNS numbers.
- Drug Designation: products can be Rx and OTC, particularly if different strengths.

- The following metrics should be defined in the Conformance Guide along with a list of standard options (e.g. drop-down menus utilizing consistently defined terms) to prevent varying classifications for the same type of activity and to allow easier reconciliation upon submission receipt
 - Establishment Activity Classification (e.g. manufacturer, repackager, relabeler)
 - MONOGRAPH
 - DOSAGEFORMS
 - ACTIVITY
- Trigger for CAPA is a numeric value, but will have no meaning without knowing for what PC or PP index the value corresponds. The numeric value by itself has no meaning unless the unit of measure goes with it. If FDA feels they must request this metric, it must also request what PC or PP indicator is being used or the Trigger for CAPA metric will have no value.
- CAIRTP is a numeric field reporting a percentage. We ask FDA to clarify the format of the value to be entered in this field. If the metric to report is 10.7%, then do we report 10.7 or 0.107?

Attempted Lots Pending Disposition

FDA has clarified its definition for “Attempted Lots Pending Disposition” to be only those lots still pending disposition past 30 days as of the last time point of the time period; for example, 11:59 pm on the last day of the quarter. Although this definition may seem simple in concept, it is complicated to execute in electronic systems in that it would require a query to reference a specific time; that is a snapshot, which would likely require manual data manipulation for reporting. Depending on the configuration of the electronic system, it may be simpler and less burdensome to simply query on any cycle times for disposition exceeding 30-day duration during the reporting period.

Product Quality Complaints

Structure around the data included in product quality complaints should be carefully considered. It is quite common for the complaint submitter to not know the product code, lot or to not still possess the package information. If FDA keeps the definition to a specific product, then such complaints will be either double reported across multiple products in a product family or omitted because they cannot be linked to a specific product.

In addition, FDA clarified its definition in 4.2.19 to include product complaints “received for product distributed in the United States...” different from the Draft Guidance. The Conformance Guide and Draft Guidance should be consistent in all definitions.

For Consideration in Future Guidance

Prior to finalization of Quality Metric Guidance and Conformance Guide, we request clarification of roles and responsibilities for metrics data reporting in regards to contract manufacturer organizations (CMO) and active pharmaceutical ingredient (API) organizations under contract agreements with license holders. For example, CMO and API manufacturers may

supply the same product to many pharmaceutical companies for multiple markets. It is unclear how the metric data should be attributed per contract giver.

Conclusion

In closing, this group appreciates the additional technical guidance and asks FDA to consider the challenges and issues in implementing this guidance raised above. While specific comments will be submitted by individual organizations, including technical questions and requests for clarification, there is consensus that several aspects of the Conformance Guide need to be clarified and would benefit from additional dialogue between industry and FDA. We appreciate the opportunity to provide our input on this program and aspire to continue the communication with the Agency.

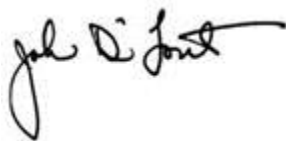
Sincerely,



Luisa Paulo
Compliance Senior Director
Hovione
Vice-chair of the Active Pharmaceutical Ingredients Committee Quality Working Group



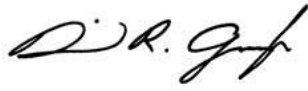
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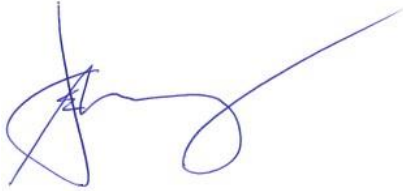
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