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A Framework for Implementing [Conflicting] FDA Guidance

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ABSTRACT

On July 21, 2004 the US Food and Drug Administration (FDA) announced a format, called the Study Data Tabulation Model (SDTM) that sponsors *can* use to submit data to the agency. Twelve years later (on December 17, 2016) the FDA began enforcing the requirement of standardized electronic data submissions in SDTM format and now, in addition to SDTM, there are multiple sources (and versions) of data Standards which impact data supporting applications to the FDA: the FDA Data Standards Catalog (primary list and source of standards) AND the Study Data Standardization Plan, the SDTM model (Version 1.4), the SDTM Implementation Guide (SDTMIG – Version 3.2), the Analysis Data Model (ADaM) - Version 2.1, the ADaM Implementation Guide (Version 1.1), the FDA Guidance for Industry (April, 2017[1]), the Study Data Technical Conformance Guide (October, 2017[2]) and the Prescription Drug User Fee Act (PADUFA), Version V for fiscal Years 2013-2017 (and VI for fiscal years 2018 – 2022). At times these documents, guidance's and laws can be contradictory and it's up to the Sponsor (when appropriate) to engage with the FDA to determine which 'standard' (of the standards) to adapt, which version(s) to use and when to update versions.

INTRODUCTION

The purpose of this paper is to clearly articulate the definitive source of clinical data standards, what versions of the standards are acceptable and active, and which standards (and guidance/documents) supersede when there are contradictions.

THE EMERGENCE OF ELECTRONIC CLINICAL DATA SUBMISSIONS

Beginning in the 1980s and coinciding with the proliferation of business, academic and personal computing the FDA began to accept data (ASCII files generated by computer software) in formats that would facilitate faster reviews for applications. In the late 1990s the FDA supported submission of actual SAS XPT files. Laws followed (e.g., PADUFA V), which mandated clinical data standards and resulted in Clinical Data Interchange Standards Consortium (CDISC) submissions being the uniform and sole method to submit data application to the FDA as of December 17, 2016. The history and path to electronic standardized data was illustrated concisely in a slide presented (Slack and Martin, 2015) at a February 9, 2015 FDA webinar, below:

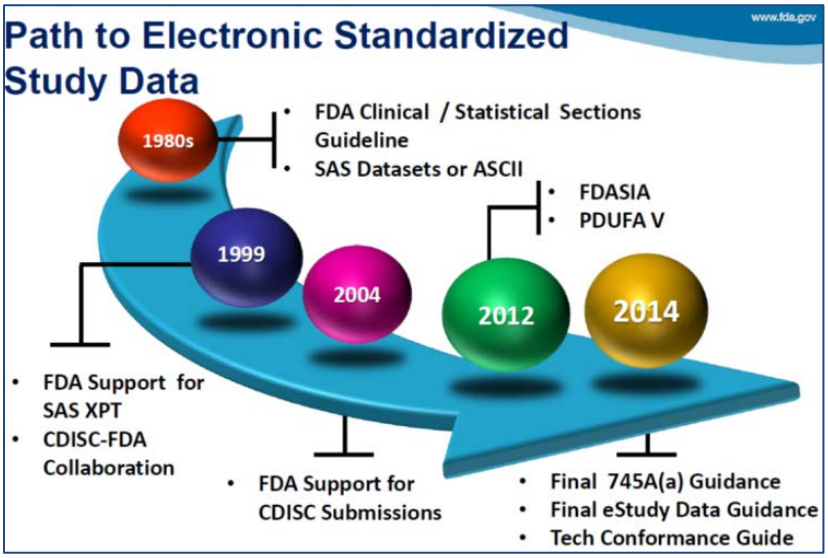

Figure 1: Path to Electronic Standardized Study Data[1]

THE EMERGENCE (AND PLETHORA) OF LAWS, STANDARDS AND GUIDANCE

When the FDA issued its December 2014 FDA Guidance for Industry (this was revolutionary in that it was binding as opposed to the 'recommendations' that FDA usually made) this mandated that all applications (e.g., (s)NDA, (s)BLA, ANDA) be submitted in SDTM format within 24 months (December 17, 2016). Along with that mandate came more clarity around what standards should be used (and also more standards), technical requirements and laws that all would ensure more compliance. Since the purpose of this paper is to navigate the reader through the slew of information regarding standards 'out there' the paper presents standards in the three relevant categories:

1. Law(s): Prescription Drug User Fee Act Reauthorization (V): 2013-2017, and (VI) 2018-2022
2. FDA/Regulatory Sponsored Standards and Requirements
3. Other Guidance

LAW(S) – PADUFA V and VI

The first category, Laws, primarily relates to the Prescription Drug User Fee Acts (PADUFA's), primarily V and VI.

PADUFA V was a reauthorization (covering 2013-2017) of a law that regulates how the FDA collects fees from drug manufacturers (i.e., sponsors) to fund the new drug approval process. This particular reauthorization included a 5-year plan for achieving specific Information Technology (IT) goals:

1. Supporting Regulatory Operations—describing the approach to strengthening the Electronic Submissions Gateway to support the long-term exchange and review of drug and biologics applications.
2. Electronic Regulatory Submissions—providing a consistent approach to the creation and review of regulatory submissions.
3. Data Standards—defining and implementing standards supporting drug efficacy, drug safety, manufacturing, product identification, and other areas.
4. Metrics and Measures—tracking progress and assessing implementation of goals.
5. Communications and Technical Interactions—disseminating information to stakeholders to help improve the program.

PADUFA VI was a continuation in many ways of the IT goals outlined in PADUFA V, with the following new overarching aim of Enhancing Capacity to Support Analysis Data Standards for Product Development and Review, as follows:

1. FDA will develop the staff capacity to efficiently review and provide feedback to sponsors on the readiness of submitted analysis data sets and programs for statistical review.
    a. This staff will support pre- and post-submission discussion of standardized datasets and programs, and maintain the knowledge of and engage in collaborations about standards models used in the design, analysis and review of clinical and non-clinical studies. Examples of these standards models could include the Standard for Exchange of Nonclinical Data (SEND), Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM).
2. In parallel, FDA will improve staff capacity to assist with FDA development and updating of therapeutic area user guides (TAUGs) to include the appropriate content for the analysis data standards used in submission and review.
3. By end of FY 2019, FDA will convene a public workshop to advance the development and application of analysis data standards.
4. FDA will collaborate with external stakeholders and participate in public workshops held by third parties such as standards development organizations, on development of data standards, processes, documentation and continuous improvement of clinical trials and regulatory science.
5. By end of FY 2020, FDA will develop or revise, as appropriate, relevant guidance, MAPPs, SOPPs and training associated with submission and utilization of standardized analysis datasets and programs used in review, and on the processes, procedures, and responsibilities related to the receipt, handling, and documentation of submitted analysis data and programs.

FDA/Regulatory Sponsored Standards and Requirements

The second category, FDA/Regulatory Sponsored Standards and Requirements, consists of many established and new (e.g., the October, 2017 Technical Conformance Guide) documents. This category is much more detailed and numerous documents exist on the FDA Website to explain these standards. For example, in addition to documents that spell out the standards (the ADaM and SDTM Models), there are Implementation Guides for both (this is not new) as well as Define.xml, the eCTD (for the entire submission), Subject Data Standards, Study Participation Standards, the Statistical Software Clarifying Statement, Position on Use of SI Units for Lab Tests, Technical Rejection Criteria for Study Data, etc. This is where it gets more confusing and it's not always clear where to look, particularly if you find what appears to be an inconsistency among the documents. In response to that, the FDA has made significant updates (as recently as July 18, 2016) to the FDA Data Standards Catalog – which is a single location for stakeholders to identify all data and data exchange standards that the FDA supports. The main point here is that this document needs to be looked at first, discussed within the sponsor team (including regulatory) and, if possible, discussed with a reviewer prior to submission so that everyone is on the same page about the standards that will be used, which version of those standards, which associated IG, what Controlled Terminology, and whether it will require the new eCTD format. Please see a screenshot of the most recent guidance just on eCTD, in Figure 2, below:

Screenshot of eCTD Guidance as of 05Mar2018

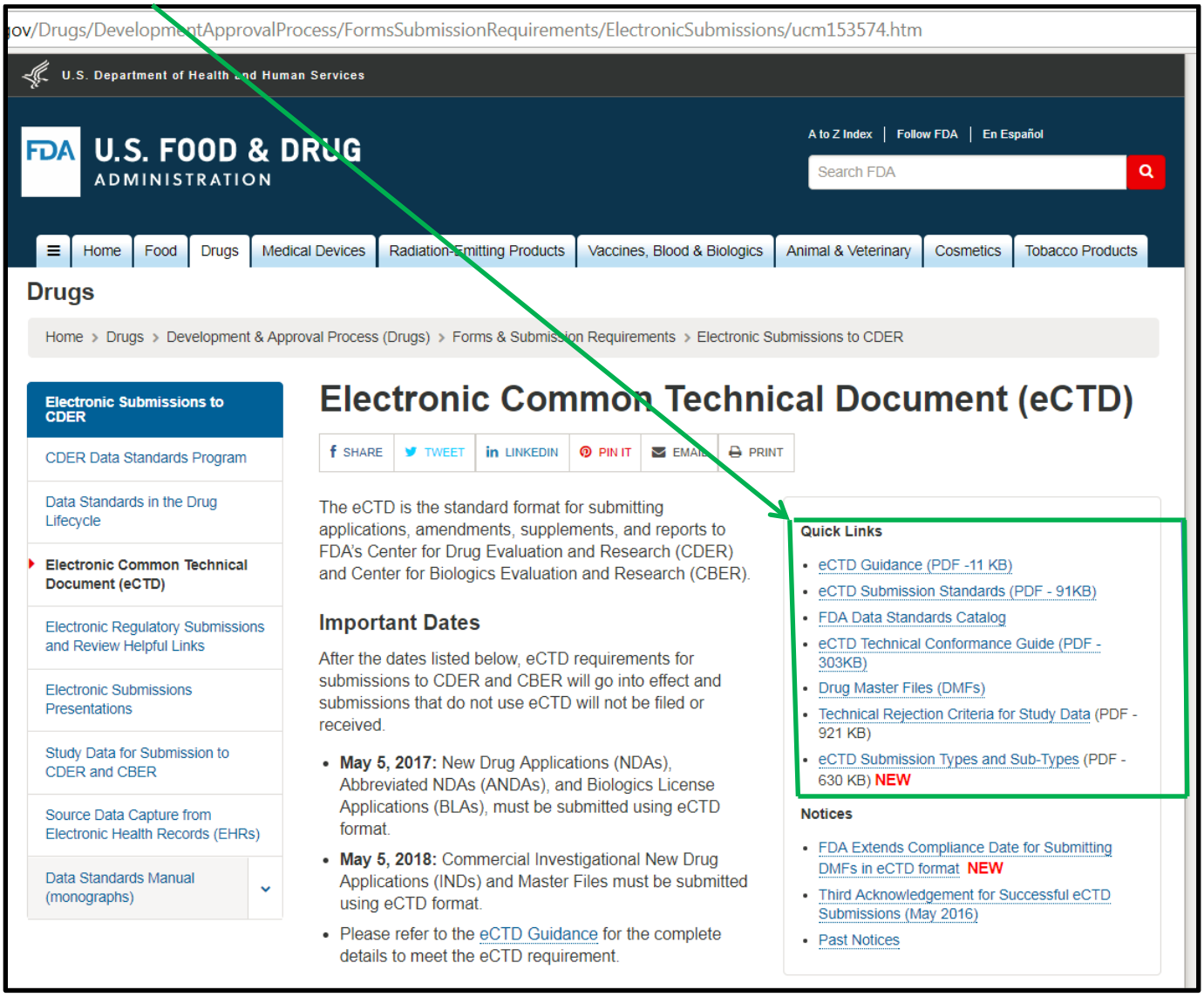

Figure 2: eCTD Guidance as of 05Mar2018, source: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Other Guidance

The third category, Other Guidance, primarily relates to White Papers and presentations given at industry-sponsored events, such as Pharmaceutical Users Software Exchange (PhUSE) Conferences and [PhUSE] Working Groups (which have FDA representation) to software sponsored events such as PharmaSUG and SAS Global Forum. One example of a very useful paper in this category is *Best Practices - Assigning VISITNUM to Unscheduled Visits and Assigning EPOCH to Observations*[1] which is not something that is covered in detail in either the SDTM Model document or the [SDTM] Implementation Guide.

'GRAY' AREAS

Arguably the biggest challenge of data standards is the delicate balance between remaining consistent within a drug program/company/industry and when and how to adopt always evolving standards. And even within a single standard (e.g., SDTM) there are often questions about how to program variables, some examples include:

- **Populating unscheduled visits**
- **Populating EPOCH**
- **Mapping Screen Failures**
- **Populating actual treatment**
- **Mapping 'Not Done' records**
- **Adding VISIT Structure (VISIT, VISITNUM, VISITDY) to SDTM domains (e.g., EX) where Visit is Scheduled**
    - **Example: home-based exposure was collected**

Please note the examples above focus primarily on general approaches to populating SDTM variables. There are other challenges as well, including whether or not the data was collected (e.g., how were 'not done' data fields mapped, partial vs complete dates, etc.), how it was collected (scheduled vs. unscheduled, etc.), which Electronic Data Capture (EDC) vendor was used and/or how paper CRFs were created to capture the data, etc.

STEPS TO ADDRESS GRAY AREAS

This is perhaps the most challenging implementation strategy of 'standards' - how to populate variables where the values are not always explicitly defined in the IG(s) or perhaps depend on conventions or historical precedents set in your company. The following steps are recommended:

Step 1: Start with the FDA Data Standards Catalog

What's the use of this object (e.g., clinical study data)? What is the Data Exchange Standard (e.g., SDTM)? What is the Exchange Format (e.g., XPT)? What's the Standards Development Organization (e.g., CDISC)? What is the supported version (e.g., 1.4)? What is the Implementation Guide version (e.., 3.2)? What's the Regulatory Body Review Division (e.g., CBER, CDER)? The FDA Data Standards Catalog will help you organize these questions so your project team can address them.

Step 2: Determine which model it impacts (SDTM/ADaM) and what question or area is 'Gray'

When assigning EPOCH values to all observations, there could be many scenarios where it may be acceptable to assign EPOCH but it may not be clear how (e.g., if the observation has a partial date, if an observation falls during a period of time which is not a planned element in the trial, etc.). In this case it's clearly an SDTM question but it may not be addressed specifically in the IG. It certainly is not mandated by a law (PDDUFA V) so what is left? The 'Other

[1] *http://www.phuse.eu/download.aspx?type=cms&docID=7043*

Guidance'. This specific example can be found on the PhUSE wiki site, *Best Practices - Assigning VISITNUM to Unscheduled Visits and Assigning EPOCH to Observations* (cited earlier and in the References section).

Step 3: Review the IG to determine if more detail is included

The IG provides examples for many scenarios. If you have an example in your data that is not covered by the IG it's best to try and retain the spirit of the IG when mapping.

Step 4: Review in detail company conventions and try to be consistent when possible

This is especially important in situations that are not covered in the IG and/or for rare diseases where the data hasn't been collected before or for studies which have been ongoing for years and haven't been previously mapped. Either way, you want to strike the right balance between using the standards (MUST be compliant) but also doing it in such a way that benefits (or provides the least amount of impact) to your organization.

Step 5: Refer to the Technical Conformance Guide for issues related to format (e.g., file size).

Remember – the Study Data Technical Guide (October, 2017 version) is intended to complement and promote interactions between sponsors and FDA review divisions. However, it is not intended to replace the need for sponsors to communicate directly with review divisions regarding implementation approaches or issues relating to data standards. However, this document currently supersedes all other FDA documents in terms of submitting electronic data to the FDA.

Step 6: Contact Regulatory to try and discuss with FDA

By the pre-IND meeting, sponsors should use the established regulatory process to discuss with the relevant review division the key data necessary to support a submission, the data elements that should be included in each dataset, and the organization of the data within the datasets.

ELECTRONIC REGULATORY SUBMISSION AND REVIEW

If, after exhausting the Steps above, there are still questions about you NDA, ANDA, IND, BLA the FDA does have an email address specifically designed to answer specific submission questions that cannot be found in any other guidance document (or that require further clarification). The email address to send these questions to is edata@fda.hhs.gov and more information about this can be found on the following website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm .

CONCLUSION

The purpose of this paper is to help the reader navigate through the ever-increasing list of laws, standards, guidance documents, etc. that define clinical data standards and how to submit your clinical data in the way that the regulatory agency you send it to will be able to review in the acceptable and most comprehensive way. These are (in no particular order): know the company conventions and study design of your drug, know what the standards documents are and what versions are appropriate, know what document(s) supersede others, know the difference between regulatory requirements and industry best practice documents (e.g., PhUSE), ensure there has been an agreement about what type of standards and in what format they will be submitted with the regulatory agency *prior to submission* and understand all the files/documents which are required and in what formats they are expected/required. If there are still questions about submission-related activities which have not been adequately addressed in other documents the FDA, again, will respond to questions addressed to the following email address: edata@fda.hhs.gov.

ACKNOWLEDGMENTS

I'd like to acknowledge all my colleagues and management at Vertex Pharmaceuticals for their dedication to standards and quality.

REFERENCES

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- eCTD FDA Page: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

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