Then and Now

FDA's Changing Expectations about Data and Documentation

Disclaimers

- The views expressed are those of the presenter and *not necessarily of the FDA*

- With the FDA, as with the stock market, past performance is no guarantee of future direction…

Especially now.

The Evolution of Submission Standards

- A new kind of regulation
- The official timeline
- Changes at FDA driving new *de facto* requirements
- In the old days we could assume…
- New kinds of recurring requests from FDA
- The cost of noncompliance
- New risks call for new strategies
- What the future may bring

A New Kind of Regulation

- Congress has given the FDA the authority to write *one* guidance with the force of law.

  Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

- This is an umbrella Guidance that references additional Guidances and specifications, which renders them binding as well.
- It is still draft, now in its third revision.

Key Points of the Guidances and Specs

1. There is a requirement to submit electronically.
2. Electronic submissions must conform to FDA Guidances and specifications, as updated from time to time.
3. Specifications specify:
   - SDTM and CDISC Controlled Terminology
   - Define.xml and Study Data Reviewer's Guide
   - ADaM datasets for analysis
   - Define.xml and Analysis Data Reviewer's Guide

The Official Timeline

- The Standardized Study Data Guidance says that:

  following final publication of the Guidance, all studies with a start date (earliest date of informed consent) twenty-four months after the Federal Register notice must use the appropriate FDA-supported standards, formats, and terminologies specified in the Data Standards Catalog

- But there's more to the story than this…

Changes at FDA

- Changes at the FDA are creating new *de facto* requirements today
- Reviewers now have powerful desktop tools that lighten their workload and enable them to meet PDUFA timelines
- These tools work best (some *only*) on SDTM standard data
- Reviewers "get it" now. They want SDTM data and have ways to persuade us.

In the Old Days We Could Assume…

- The FDA has only ever specified two valid formats for tabulations data: SDTM and "Item 11" data (named for Item 11 of the 1999 Guidance on Electronic Submissions)
- Until 2012 we could assume that a mixed SDTM and Item 11 submission would be acceptable to the Review Division
- Then things started to change.

The Old Decision Matrix

- Phase III/Pivotal? SDTM.
- Phase II supporting label claims? SDTM.
- Early Phase II? Maybe Item 11.
- Recent Phase I? Could go either way.
- Old Phase 1, healthy volunteers? Item 11.
- Contributes to ISS? SDTM if you can, otherwise complications ensue.
- You'd make the plan, start the work, and ask the Review Division for forgiveness, not permission. Mostly they would agree.

New Recurring Requests from FDA

- The sea has changed. In the past two years we have seen new kinds of recurring requests from different Review Divisions.
- SDTM-enabled desktop tools give reviewers a powerful lever. Slowing down the reviewer puts *your* PDUFA date at risk.
- In multiple submissions we've seen safety reviewers ask for SDTM in situations that surprised even other FDA people at the table.

New Scenarios 1

- Old Phase I studies, a handful of healthy volunteers, treated once.
- Reviewer said to include them in the ISS database (what?!)
- Wanted to scan for possible early onset TEAEs
- The negotiated settlement was to provide limited SDTM data (4–5 domains) with the studies *in addition to* complete Item 11 data.

New Scenarios 2

- Old Phase I studies and studies from other indications and dose formulations/regimens.
- Reviewer wanted complete SDTM
- The negotiated settlement was to add limited SDTM data (4-5 domains) to the ISS database.
- This saved production of a lot of documentation.

Emerging Patterns

- We're seeing more and more submissions in which Item 11 studies have SDTM submitted as well.
- For now, a limited SDTM conversion seems to suffice.
- The desktop tools also raise the bar for conformance and usability of the SDTM. Providing data the tools can't work with defeats the purpose.

The Cost of Noncompliance

- Refusal to File (RTF) is a slow-moving bullet and easy to dodge with ordinary diligence. This is *not* your worst scenario.
- If a reviewer wants SDTM and you don't provide it, the review period may bring a fire hose of data requests that look a lot like SDTM specs, or requests for new tables that the reviewers could have done themselves with SDTM data.
- This can get expensive and delay your review by months.

New Risks Call for New Strategies

- Go to the Review Division with a data plan as early as possible. (Such plans will be required under the new Guidances.) The Divisions are increasingly eager to have these dialogues while plans can still be changed.
- Make a reasonable proposal but don't assume agreement. Work out your fallback positions ahead of time to come away with a firm deal.
- *Get your agreement in writing.*

What the Future May Bring

- The uptake of SDTM by the FDA has created its own wind that's easier to sail with than against.
- More standardized tools at FDA will invite broader uses of standardized data, and broader requests for it.
- The tools will impose usability requirements on data that go far beyond strict conformance to standards. This trend has already begun.

What the Future May Bring

- Uses of ADaM at FDA are currently lagging SDTM. As this gap narrows we may see pressure to change the standard, as we did with SDTM a few years ago.
- Beyond data, we should also expect tighter requirements for documentation. Guidance already references templates on the PhUSE Wiki for the Study Data Reviewer's Guide and the Analysis Data Reviewer's Guide.

What the Future May Bring

- When standardized data becomes compulsory, how will the Agency enforce it?
- Refusal to File will probably not be the mechanism for enforcement, but rather *Refusal to Receive*. This authority has already been created in a new guidance.
- "FDA considers a technically deficient electronic submission to be ***not received*** (i.e., not present at FDA and not under review) until all technical deficiencies are resolved and the submission is in a format that we can process, review, and archive."

Thank you!

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Links to Related FDA Guidances and Specifications

FDA's *Study Data Standards Resources* web page is at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Guidance for industry, *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* is at
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf

Guidance for industry, *Providing Regulatory Submissions in Electronic Format –Standardized Study Data* is at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf

Study Data Technical Conformance Guide (incorporated by reference into the above Guidance) is at
http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Guidance for industry, *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* is at
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384686.pdf

Data Exchange Standards Catalog v3.1 2014-09-17 (an Excel spreadsheet) is at
http://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm340684.xls

Guidance for industry, *Providing Regulatory Submissions in Electronic Format — Receipt Dates* is at
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072385.pdf

The Study Data Reviewer's Guide and Analysis Data Reviewer's Guide templates, guidelines and examples are on the PhUSE Wiki at
http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer's_Guide and
http://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer's_Guide

You should use the most recent versions as they are posted. If you've already downloaded them, check again just before you use them to make sure you have the most recent version. They are currently being updated to improve clarity and usability. The URLs may change when PhUSE makes its work products accessible from a central location.