Submissions Experiences

PhUSE SDE 18th May, London.

Mr Bhupendra Mistry

Submissions Experiences : The Good, The Bad, The Ugly

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Disclaimer

All opinions are the presenter's own and should not necessarily be considered to be the Roche position or the position of the various steering committees or indeed other sponsors

Agenda

- Reporting and Submission Perceptions
- Current Approach
  - eSubmissions group
  - Overall process
  - Inputs & Outputs
- Challenges faced
- Mitigations
- CDISC Experience
- Future

Reporting & Submissions Perceptions

Reporting Activity

Everybody's happy !

eSubmission Package

Dull & Boring task ?

Reporting & Submissions Perceptions

Dull & Boring task ?

It’s a critical task !

Without packaging it in the required format you could :

- Have **delays** in **Approval**
- Receive more **questions from** the **FDA**
- Ultimately, **not get** your **drug on** to the **market** !

Current Approach : eSubmissions group

- Have a Global eSubmissions group
  - Small team within the Statistical Programming & Analysis (SPA) group
  - To create eSub packages for SPA that meet FDA standards
  - Personnel based in SSF, NJ, Welwyn & Mumbai
  - Support all SPA project teams globally
  - Work with Programming teams to :
    - Obtain input files required in specific format (i.e. specifications & data)
    - provide eSub requirements & awareness training (not tools)
  - Take eSub creation burden away from Programming teams
  - Build eSubmission Expertise on current and future standards
  - Deliver directly to Regulatory

- Follow 1 global eSubmission process
- Work on 2 different systems (Legacy Gne and Roche) but use same set of tools
- Use JIRA as tracking system

Current Approach : Overall process

Objective

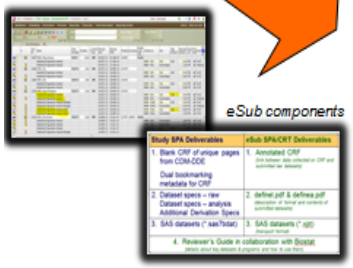
The main objective of the poster is to visually show the end-to-end SPA e-Submission process for non-CDISC filings. End-to-end means, from the point we receive a request to create an e-Sub package to the point it reaches to the FDA (or other regulatory bodies). The mandate date for CDISC filings is in 2016.

1. Initial Request & Scope Assessment

eSub JIRA request

JIRA process is used to initiate the request by creating a ticket. The link to create the JIRA ticket is in the Biometrics Global Process Library (BGPL). All required information must be completed to submit the ticket.

PlanSource

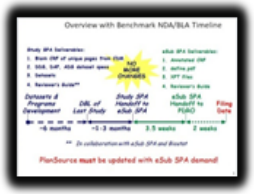


Assess scope of work, resource needs, kick-off meeting

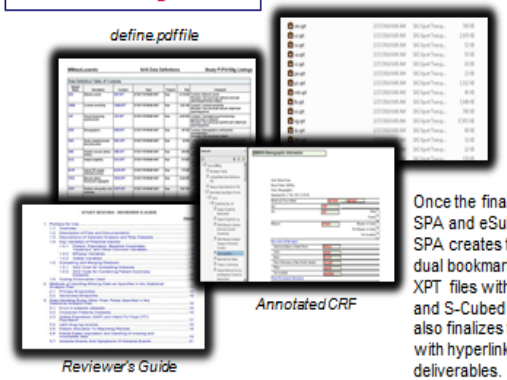
After the assessment of deliverables and their timelines, the managers consult with the Study SPA and the eSub Lead SPA to determine the resources requirements.

Arrange eSub in-time training for the submission teams

eSub SPA and PDRO will need 5.5 weeks before the filing date to complete our deliverables. There is an official handoff between Study SPA and eSub SPA at 5.5 weeks. All the review of Study SPA's deliverables, such as dataset specs and Reviewer's Guide, must be done prior to the handoff.



3. eSub Package Build



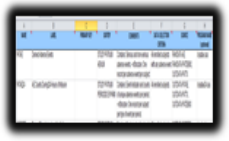
Once the final handoff between Study SPA and eSub SPA is done, eSub SPA creates the annotated CRF with dual bookmarking, define.pdf and SAS XPT files with the help of eSub macros and S-Cubed software. eSub SPA also finalizes the Reviewer's Guide with hyperlinks to navigate to the other deliverables.

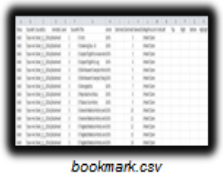
Handover all final/reviewed files to eSub SPA for datasets packaging no later than 5.5 weeks prior to the filing date

2. Contents Review Cycle

Have regular meetings (discuss timelines, deliverables' status & issues)

Regular meetings are held between Study SPA and eSub SPA to discuss any updates in timelines, issues and status of the specifications.

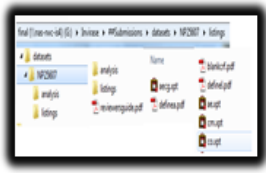

Dataset specifications


bookmark.csv

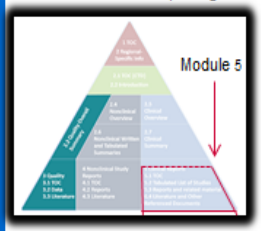
4. Delivery to PDR-O

Deliver to PDR-O (via PDR server)

Regulatory server location

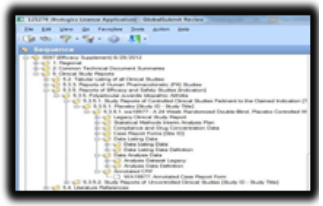


Overall submission package



Once the eSub SPA finalizes the deliverables, these are dropped to Regulatory in their PDR server in the respective study folders for analysis and listings, at least 2 weeks prior to the filing date. From the PDR server, the PDRO team copies the study folders and incorporates them into the overall submission package.

Submission folder structure



eCTD Module 5

5. Submission to FDA

Submit to FDA

All the preparation by Study SPA and eSub SPA for a clear and easy-to-navigate datasets package will enable the FDA reviewer to review the data, to replicate the analyses, and finally to approve the filing.

PDR-O : regulatory operation group

Current Approach : Inputs & Outputs

	SPA Project Team Deliverables (INPUT)	eSub Group Non-CDISC Deliverables (OUTPUT)	
In-house tool →	BlankCRF	eSub-ready annotated CRF *(legacy raw data format annotations)*	← In-house tool
	Raw SAS datasets	SAS XPT files *(raw data in legacy format)*	← In-house programs
In-house template →	Raw data specifications	definel.PDF	← In-house tool
	Analysis SAS datasets	SAS XPT files *(analysis data in legacy format)*	← In-house programs
In-house template →	Analysis data specifications	definea.PDF	← In-house tool
In-house Reporting tool & New programs →	SAS programs	Only <u>if requested by FDA</u> *1st option: Readable* *2nd option: Executable*	← Manual
	Important project documentation	M5 Reviewer's Guide, Additional Derivations Specifications doc, TOC	← In-house template

With all these templates, programs & tools , there should be minimal challenges, right ?

Challenges Faced

- eSub often an after thought
  - Last minute, on-going and late changes (i.e., new datasets, changes to specifications)
  - Changes to files happening in parallel (i.e. data/specs synchronization issue
  - Forgotten deliverables (i.e. popPK)
  - Change in filing strategy

- Impacts
  - Late changes creates re-work, frustration, pressure and stress
  - Quality issues of Input documents
  - Changes in Filing dates
  - Fear of delays in delivery

- Commons issues found :
  - Missing dataset / variable attributes
  - Inconsistency between datasets and specifications (i.e., variables not matching)
  - CRF annotation mismatches, wrong CRF versions, additional annotations
  - Derivation text unclear, meaningless, missing or contains SAS code
  - Wrong templates used, major template modifications, incomplete information
  - Different files formats receive from external sources (i.e. other functions, CROs)

Mitigations

- Provide upfront eSub awareness & guidance to project teams
  - Get involved with projects early
  - Align with Data Standards related groups
- Interactions with Stakeholders (i.e. Filing teams, Regulatory)
  - Make Filing teams aware of eSubmission standards, timelines & impacts
  - Work with Regulatory on responses to FDA on submission format / content
- Conduct early reviews and eSub compliance assessment
  - Conduct a trial eSub package build to highlight issues
  - Will help project teams understand what & why changes are required
- Educate relevant functions on Standards
  - New submission standards (i.e. CDISC)
  - Use of industry templates (i.e. SDRG, ADRG)
  - FDA notices & guidances (i.e. SDTM & ADaM Implemention Guides)

CDISC Submission Experience

- **Successful Submission (Dec 2014)**
  - SDTM, ADaM, Define.XML (v1.0), SDRG, ADR
  - Format Accepted by FDA
  - JUMP START used by FDA

- **Learnings**
  - Ensure team have common understanding of requirements and deliverables *(i.e., requirement of PK data, CMC [Clinical Manufacturing Chemistry] data)*
  - Use the same Model and Implementation Guides & versions
  - Familiarise with validation tools (i.e. OpenCDISC Validator)
  - Educate on use, understanding and interpretation of standards & guides
  - Have clear roles and responsibilities (within & across functions involved)
  - Do multiple test runs and reviews of eSub packages
  - Play the role of an FDA reviewer
  - Many issues due to internal data and not CDISC submission format
  - Adopt standards early (End-to-End), avoid conversions
  - Allow time to learn and implement

Future

- Creating eSubmissions become easier to d
  - Automate creation of key components
- Have flexibility in ADaM standards and not become too rigid
- Eliminate Code delivery
- FDA to make submissions available to other Regulatory Agencies

Easy, Enjoyable & FAST

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