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CDISC UK Network 5th July 2018

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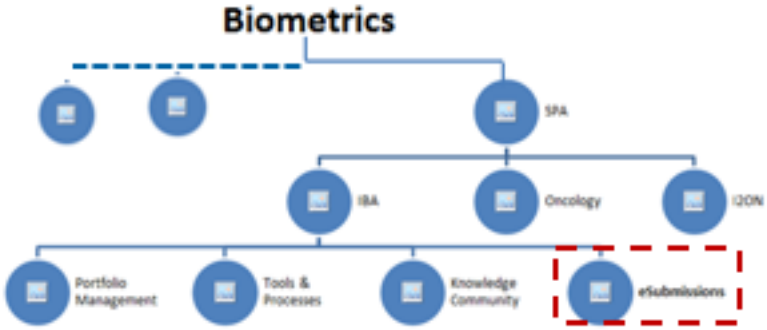


Infrastructure and Business Alignment

Agenda

- Global Biometrics eSubmissions Team
- Legacy (non-CDISC) and CDISC deliverables
- Common Challenges
- Some Submissions considerations
- Take Away

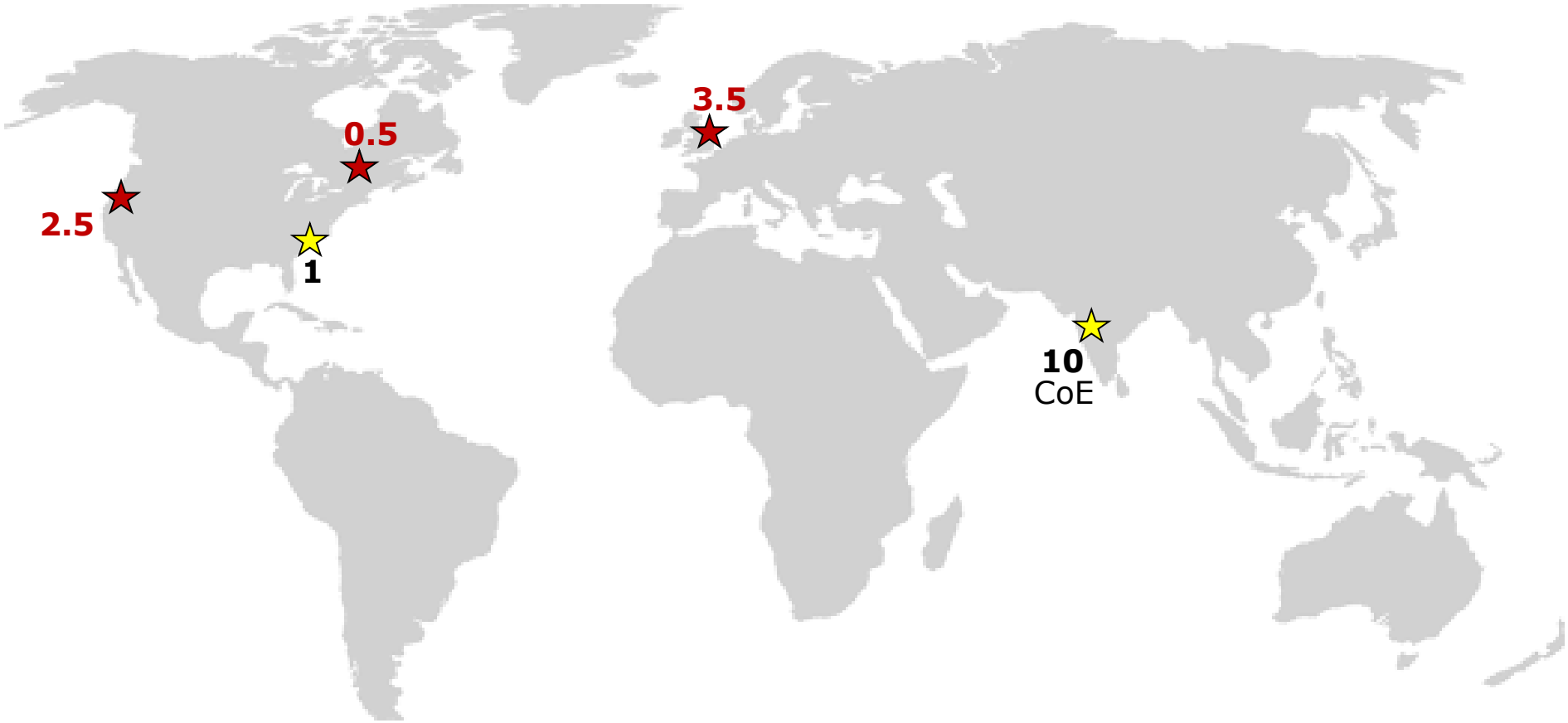
Take Away Message

- **If you take away anything from this presentation, let it be**

- **There's more to submissions than just creating SDTM / ADaM datasets**

- **Prepare Early**

Global Biometrics eSubmissions Team

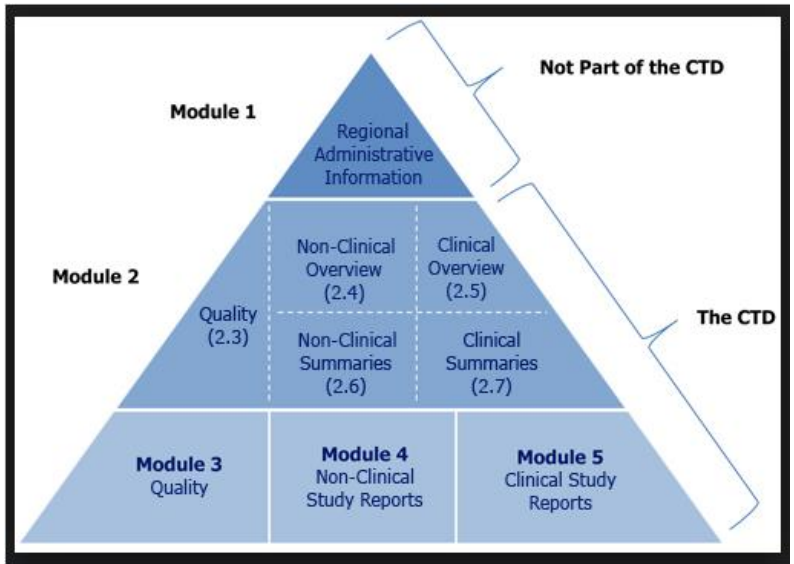


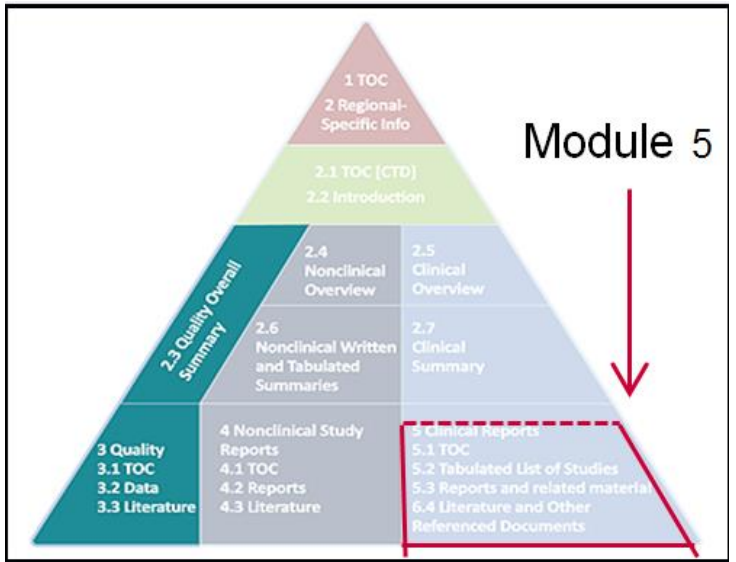
Permanent FTE (full & partial time)

FSP FTE (Centre of Excellence)

Global Biometrics eSubmissions Team

- Global Biometrics eSubmission is a dedicated team.
- FTE & FSP Resources from Clinical Programming and Statistical Programming groups for Raw & Analysis related eSub Dataset Packages
- Create Legacy (non-CDISC) and CDISC SDTM/ADaM format eSub Dataset Packages
- EU and NA Leads PoC's for projects from those regions across TA's
- Filings primarily to FDA but also Canada, South Korea, Australia and PMDA(Japan)



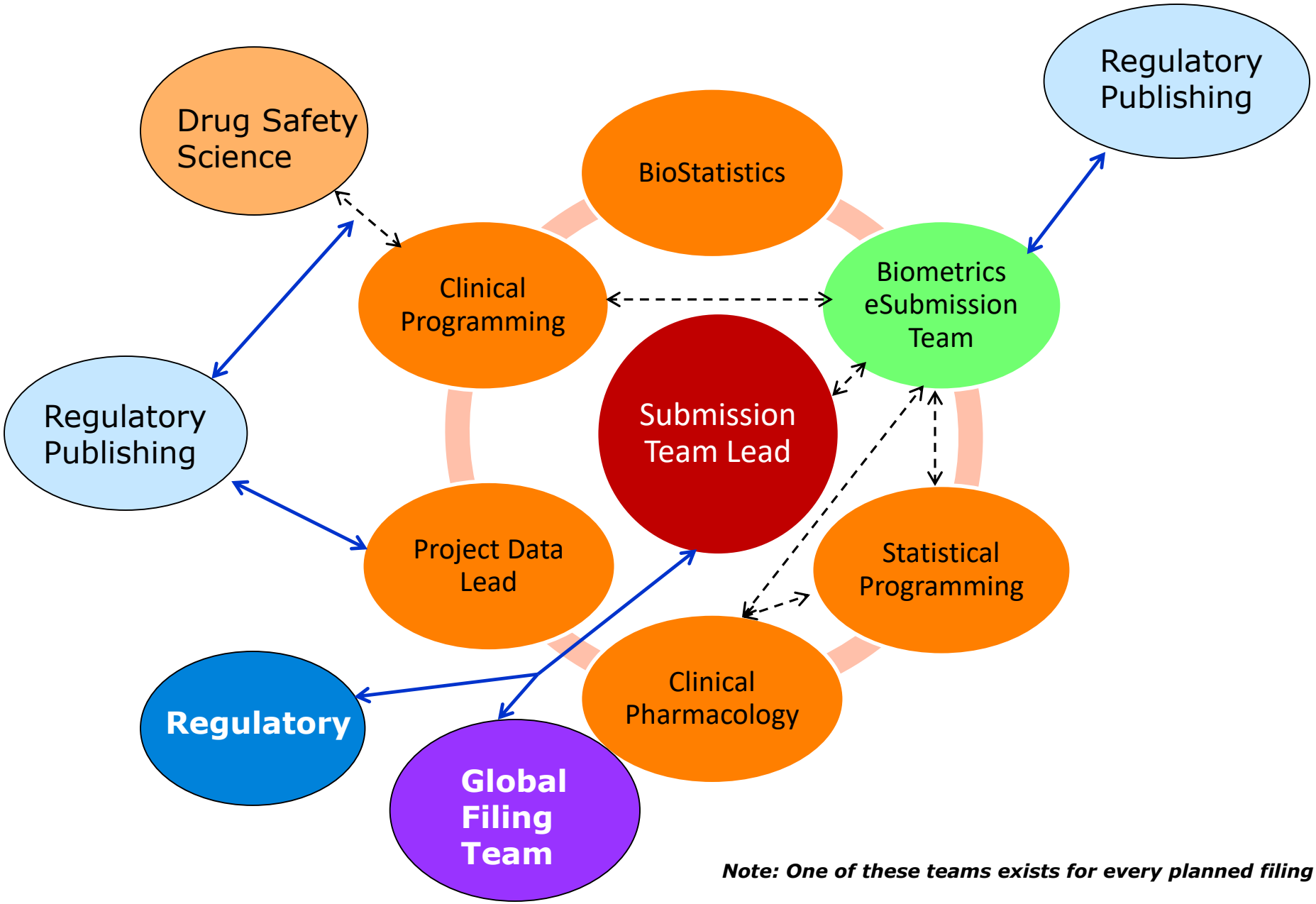


Global Biometrics eSubmissions Team

- Provide eSubmission expertise
- Educate molecule teams on submission requirements (content & format)
- Support all Planned Submissions* and adhoc Health Authority (HA) requests *
  - HA request : turn around anything from 1→ 2 → ≥5 days
- Review & input into content of submission Pre-Meeting Package (PMP)
  - ensure correct terminology (CDISC , Legacy, non-CDISC)
- Provide training & education to
  - relevant programming groups on submission package build requirements
  - Other stakeholders (Regulatory, BioStatistics, Global Filing Teams)
- Consultancy service during filing planning

** 2017 : ~30 Planned Submissions, 25+ HA requests*

Biometrics eSub Team Interactions

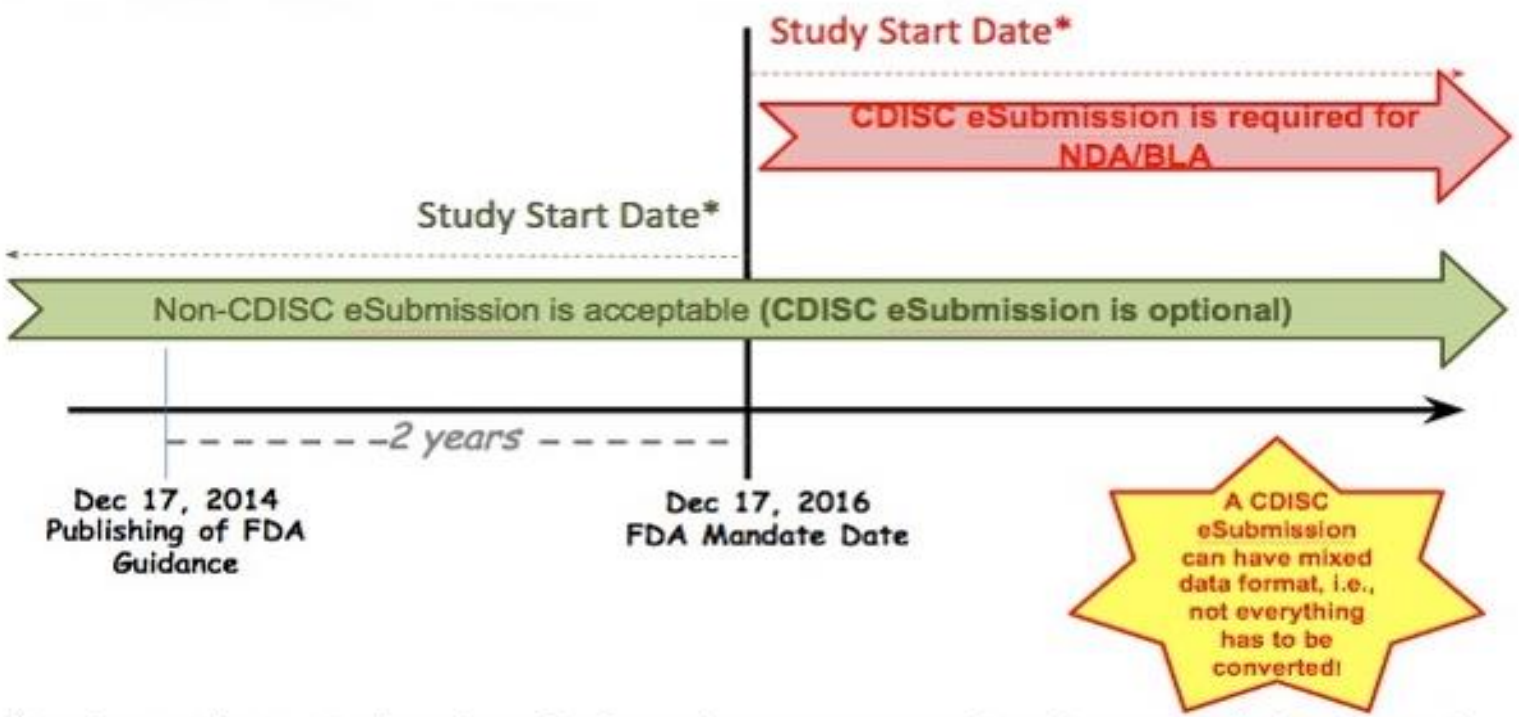


Note: One of these teams exists for every planned filing

CDISC eSubmissions mandate

FDA Mandate for CDISC eSubmissions

FDA final guidance on "Providing Regulatory Submissions In Electronic Format — Standardized Study Data" requires all studies starting after December 17, 2016 to have CDISC data standards.



**Study start date = Earliest date of informed consent among the subjects enrolled in the study*

CDISC eSubmissions mandate

- Electronic format of the overall eSubmission of data with at least 1 study following CDISC SDTM and ADaM compliance
- It does NOT mean all the studies (in the submission) have to follow CDISC standards. Only those that started after the CDISC mandate **must** follow CDISC standards
- CDISC submissions can contain a mixture of different Submission formats of the dataset packages
  - Full CDISC compliant studies only (if started >17-Dec-2016)
  - Mix of CDISC compliant AND Legacy (non-CDISC) studies
- There is no requirement to convert a legacy study to comply with CDISC standards
- No clear standards regarding the format of eSubmission dataset package for Pooled Analysis

Legacy (Non-CDISC) & CDISC Deliverables

Roche

Submission Deliverables	Non-CDISC Deliverables (Type A or Type B)	CDISC-A Deliverables	CDISC Deliverables
Annotated CRFs	Non-CDISC annotations [i.e. **SDTMv, GDM**]	CDISC annotations [i.e. **SDTM**]	
Raw / Tabulation datasets	SAS XPT files [i.e. **SDTMv, GDM**]	SAS XPT files [i.e. **SDTM**]	
Raw / Tabulation data definition file	define**.PDF**	define**.XML**	
Analysis datasets	SAS XPT files [i.e. **VADs**]	SAS XPT files [i.e. **ADaM-ADSL+VADs**]	SAS XPT files [i.e. **ADaM**]
Analysis data definition file	define**a.PDF**	define**.XML**	define**.XML**
SAS programs	**Only if requested by FDA** 1st option: Readable 2nd option: Executable (& supporting program TOC)	**Only if requested by FDA** 1st option: Readable 2nd option: Executable (& supporting program TOC)	**Readable SAS Programs are Required** 2nd option: Executable
Important project documentation	M5 Reviewer's Guide (internal template)	**SDTM** M5 Reviewer's Guide, **ADaM** M5 Reviewer's Guide, M1 Reviewer's Guide	**SDTM** M5 Reviewer's Guide, **ADaM** M5 Reviewer's Guide, M1 Reviewer's Guide

eCTD Module 5 Folder Structure for Data Packages

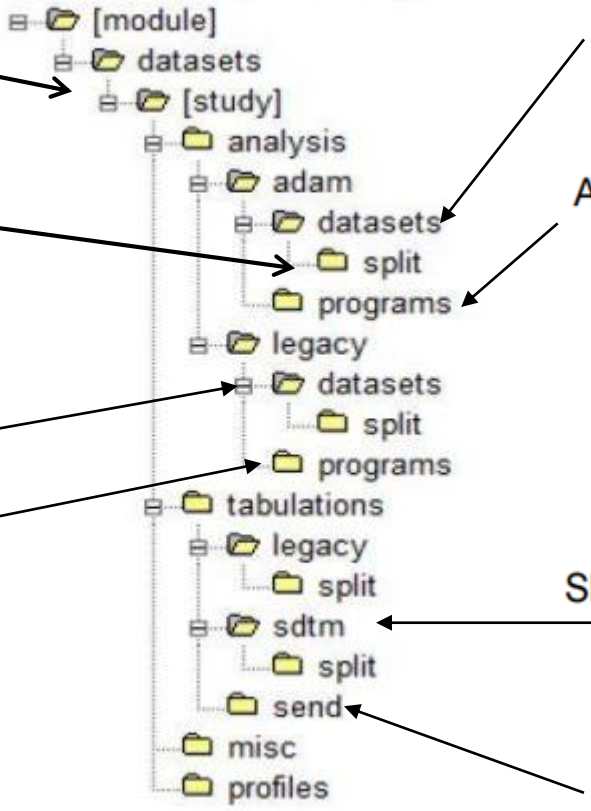
Study number or Pooled (ISS/ISE) or poppk/ER/CQT

Current Understanding :
Split only if dataset >5GB.
Deliver split datasets AND complete dataset

Legacy xpt datasets

Legacy SAS programs, TFL SAS programs

Figure 1: Folder Structure for Study Datasets



ADaM xpt datasets, Define.xml, ADRG

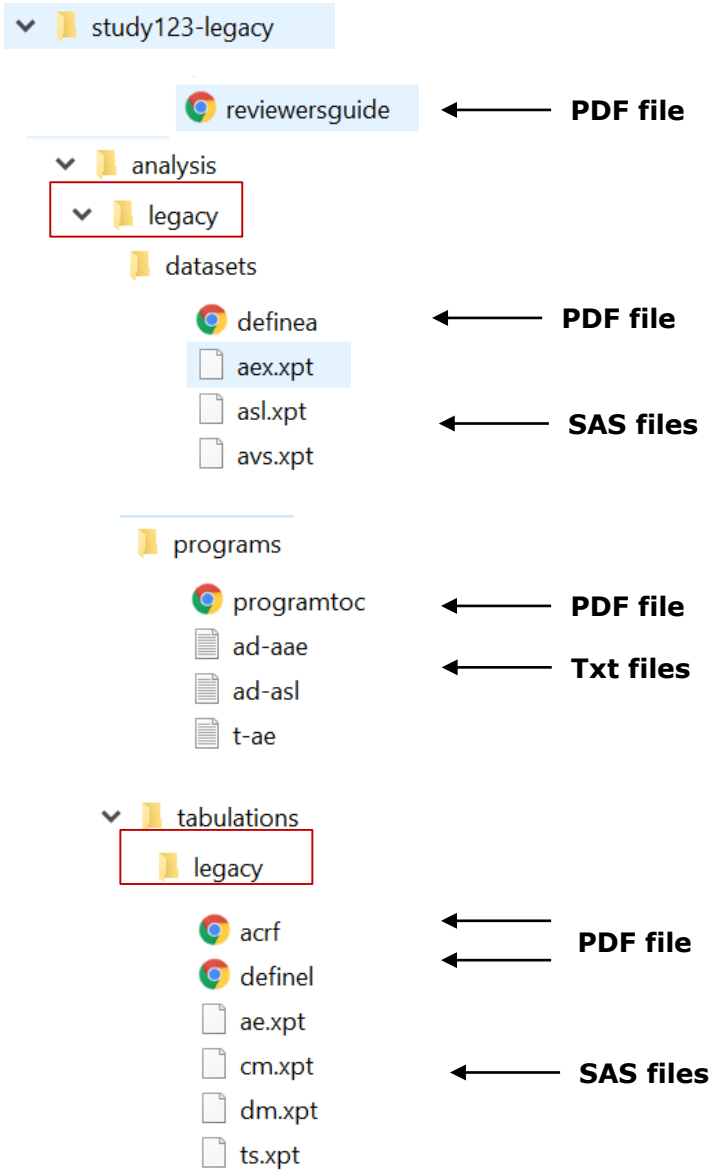
ADaM SAS programs, TFL SAS programs

SDTM xpt datasets, Define.xml, SDTM annotated blank CRF, cSDRG

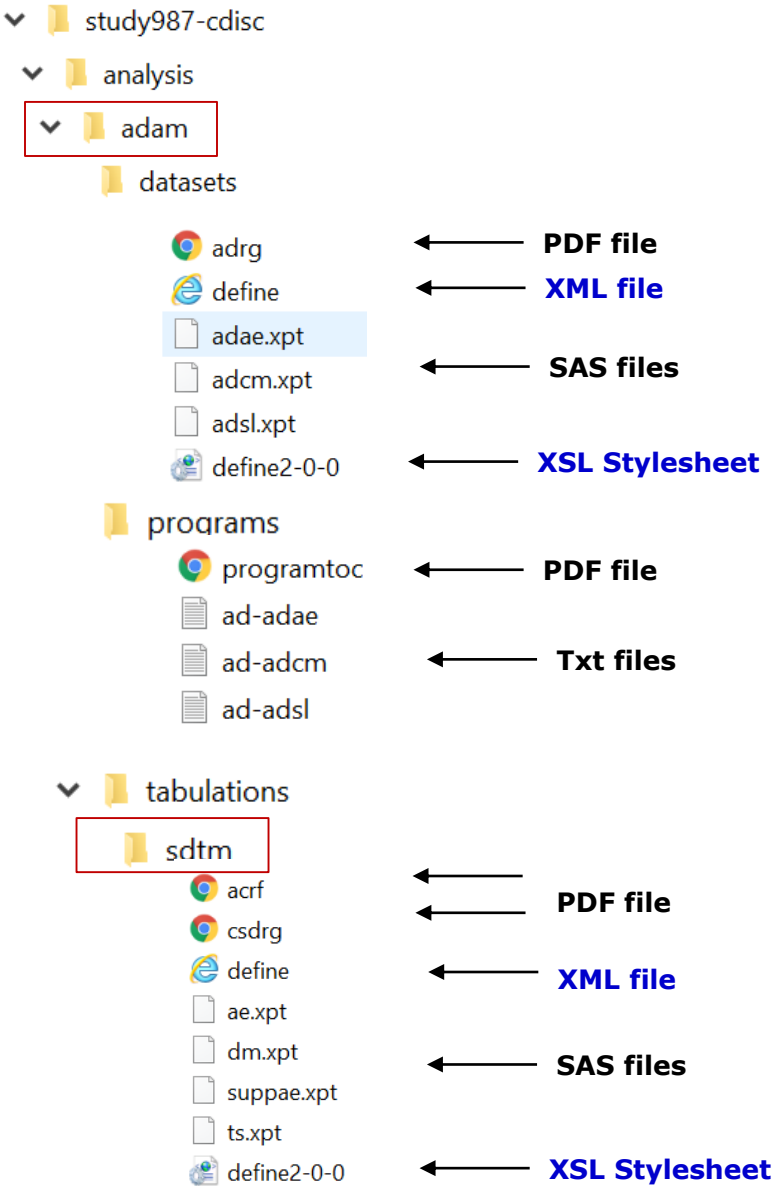
SEND xpt datasets, Define.xml, non Clinical SDRG

eCTD Module 5 Folder Structure for Data Packages : Example

Legacy Package



CDISC Package



5 Most Common Challenges

when creating eSub datasets packages for submission to Health Authorities.

- Inconsistencies (no 1:1 match) between the SAS Datasets and the actual Dataset specifications, e.g.
  - The number/names of variables in the dataset do not match those listed in the dataset specifications
- Incomplete variable specifications, e.g.
  - Incorrect variables (raw and/or analysis) listed in derivations and incorrect naming convention used
- Dataset Specifications template not usable by our tools, e.g.
  - Wrong columns populated or incorrect information in the columns
- Mis-use of the word CDISC & it's implication on submission requirements
- eSubmissions not considered early enough / insufficient time allowed

Health Authority (HA) Requests Examples

- Examples can be very general, for example, '**Send all programs**'
  - Requires negotiation on executable or readable code as FDA guidance does not specifically state if the code must be readable or executable.
  - More work involved in executable code.
  - Negotiate to primary and secondary endpoints outputs.

- Can be very specific, for example, **requesting new datasets of pooled study safety data**.
  - In this case the team need to look at the timelines suggested by the FDA as there is negotiation required when having to pool large amounts of data with a lot of complexity.
  - Many teams once the initial submission has been sent to the FDA actively prepare dataset packages they are aware are likely to be requested after the initial FDA review.
  - These questions can come back as early as a few weeks after submission!

- Short notice, for example, "**require this by tomorrow**"
  - teams need to look at the scope/timelines and negotiate if necessary

Are Dataset Specifications important ?

Are Reviewers Guides important ?

Why ?

Are dataset specifications & Reviewer Guides important

- The Health Authority (HA) use and **rely on them** to replicate our analysis
- If the HA cannot replicate your analysis, it will lead to more questions, longer review times, and ultimately non-approval
- The impact of teams not producing eSubmission compliant data and specifications causes additional work, e.g.
  - Unnecessary back & forth discussions between the eSub team and the project team to resolve issues
  - Creates re-work due to repeated occurrences of the same issues and last minute panic, time and resource constraints
  - Adds to the overall time taken to complete the eSub work
- Teams need to do this from study start and on an on-going basis during the study lifecycle.

Some CDISC Submissions considerations

- Remember, CDISC requirements are stricter than legacy format
- **Must adhere to the Technical Rejection Criteria**.
- Greater focus on conformance checking CDISC SDTM and ADaM
  - Run validation checks
- FDA require more detail documentation for reproducibility.
  - Define.XML content
  - Use ADRG and SDRG template for more details
- Software programs are required
  - No FDA standard to follow, must be readable & interpretable
  - Beware : Some FDA Reviewers may request executable code
- PMDA (Japan) mandate and CDISC variations

Office of Scientific Investigations (OSI)

- The FDA's Office of Scientific Investigations has responsibility to select sites for on-site inspection as part of it's Bioresearch Monitoring (**BIMO**) program and needs each sponsor's help in order to perform this selection quickly and efficiently.

Parts	Details
Part I	Request for general study related information and comprehensive clinical investigator information (If items are provided elsewhere in submission, describes location or provide link to requested information). Includes annotated CRF, tables of subjects screened, randomized and who prematurely discontinued by site. (Mandatory)
Part II	Request for Subject Level Data Listings by Site (Mandatory)
Part III	Request for Site Level Dataset (Voluntary)

Take Away Message

- If you take away anything from this presentation, let it be

- There's more to submissions than just creating SDTM / ADaM datasets

- PREPARE EARLY

- This avo lays in filings and ensures data an ready!

Doing now what patients need next


QUESTIONS

Doing now what patients need next