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Harmonization of CDISC standards for Regulatory submissions

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Abstract:*Harmonization plays a key role in the modern world due to its impact on resourcing and budgeting. When submitting the dossier to regulatory agencies the requirements differ hence, there should be guidelines for companies to set the differences right. The drug development process submissions should be done in an integrated way to regulatory agencies although there are major differences between them. We should prioritize our requirement for easy implementation and determination. Since it causes double work to be done to regulatory agencies, we need to identify the gap and the requirement of implementation of the model and the need for standardization of regulations globally. Has time finally come to harmonize regulatory agency requirements across the world? if not now, can it be done in due course of time? The major challenges to have this implemented include globalization, approval time shortening, enhancing safety measures and accelerated review process. Until then, the drug development submission process should be done in an integrated way considering the differences. There is a need for inter organisational harmonisation process and companies must reconsider in the study package during the initial trial phase. This paper will outline the requirement of regulatory harmonization across globe and the need for inter-organisational harmonisation model. This helps in providing an overview of implementation of one model of harmonization approach and strategies for effective planning and harmonization of company specific implementation standards.*

Keywords:*Harmonisation; CDISC; Regulatory harmonisation; Inter-organisational harmonisation model; One model; SDTM; ADaM; Controlled terminology; Scope; Implementation; Unified approach; Organisation benefit;*

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I. Introduction

The end goal of clinical research is the submission of dossiers to regulatory authorities.Submission dossiers include electronic data submission to regulatory agency per required standard. Clinical Data Interchange Standard Consortium (CDISC) standards are now widely used as this standard for submission of data. CDISC is an open non-profit organization that has established standards to support the acquisition, exchange, submission and archival (1). CDISC's vision is to enlighten patient care and safety through higher class of medical research. CDISC's mission is to improve medical research and healthcarerelated areas (2).The major goal of CDISC is traceability from collection of data till analysis. This aids in efficient and fast review of data by regulatory authorities, resulting in faster approval and reducing the time-to-market for drugs. However, the integration of CDISC standards requires a lot of time, efforts, resources and budget from pharmaceutical companies.

This identifies the need for standardization of processes and inter-organisational harmonisation.Ithelps to identify the changes required for the submission model of FDA and PMDA, which are not aligned across organisations. This model would avoid the possibility of errors and havea consistent and unified approach across all organisations. Itwill benefit the organisationsinthe long run as it will help to cut down the budget for new studies.Having standardised processes will also lead to faster review of trials which in turnnot only helps in reducing the study set-up time; it also improves the end to end traceability and enhanced interoperations across organisations.This helps in change in system and processes thereby reduce the cost, resource utilization and standardization.The rules from different regulatories are bit stringent since regulatory agencies don't want too many generics and the fact that they have emphasize more on safety and efficacy. In case of differences across built in or metabolism, considering the efficacy analysis, japanese people built in is different than americans which is making investigations more different and regulatory submissions stringent. These differences can be handled in an easier way if more data is collected and by performing specific tests for specific group of people for analysis. As, regulatory agencies don't want submissions for studies to be different with different sponsors with different standards hence they would like to have a unified approach of tool set based on unified standard and support review of data (8).

It is always good to keep in mind the end process in clinical research. The companies must revise the approach they use for regulatory submissions by developing a common model. This requires identification of differences between regulations and alignment of Study Data Tabulation Model (SDTM), Analysis Data Model (ADaM) and controlled terminologies (3).CDISC Controlled Terminology is a set of CDISC-developed standard expressions (values) used with data items within CDISC-defined datasets (4). It takes a lot of time in standardizing the

systems considering the violation checks, standard non-conformity issues, data issues and SDTM implementation guide (IG) issues. Why we need to investigate and know the characteristic differences between FDA and PMDA? It is interesting to study the differences between the Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA). CDISC standards have been mandated across globe but still FDA and PMDA, which had worked closely with CDISC since its inception (5). It has major differences in submission requirements. The submission to regulatory agencies includes different documents like statistical analysis report and resolutions of blind review, which are unique.Hence, to make the submission process easier there is a requirement for harmonized regulatory submissions. The harmonisation process helps in aligning the requirements, standardization of processes and systems globally (6).

Submission of dossier to regulatory agencies

When pharmaceutical companies submit a dossier to regulatory authorities, they need to consider the submission requirements from these authorities.Unfortunately, different authorities have different submission requirements. This can be due to several factors. Example. Local regulatory guidances, laws etc., As a result, pharmaceutical companies need to create different dossiers, which requires additional resources. For this paper, submission requirements from the FDA and PMDA are taken into consideration. Other regulatory authorities are CFDA (Chinese food and drug administration), EMEA (European medicines evaluation agency). These authorities, however, are similar to either FDA or PMDA. Therefore, the biggest differences are between the regulatory authorities FDA and PMDA, which are further discussed in this paper.

Characteristic differences between FDA and PMDA

The major characteristics differences between FDA and PMDA are tabulated in figure 2. Comparing the FDA and PMDA requirements, the key differences identified are ARM for PMDA, clinical pharmacology study submission differences, communication or interaction across the regulatory team, legacy (previously locked trials) data conversion and CDISC compliance check. The regulatory differences play a major challenging role for the companies to have unified approach for submissions.

DIFFERENT CHARACTERISTICS	FDA	PMDA
Electronic data submission	Studies which start after Dec 2016	Studies for NDA* submission after Oct 2016
CDISC Compliance Pinnacle 21 check	SDTM SEND	SDTM, ADaM, Define.xml with Reject criteria
Communication	Sponsor Meetings for FDA/Sharing best practices/ End to End discussions	Data format of electronic study submissions
ARM	Not required	Define XML should preferably have ARM
SI UNIT	Therapeutic and Lab tests	Tests with applicable SI unit
CLINICAL PHARMACOLOGY STUDIES	Not specific per Study data technical conformance guide	Specific documentation-Electronic study documents
Legacy data	If study falls between Dec 2016 its mandated	Non CDISC not accepted

Table 1 Characteristic Differences Between FDA/PMDA (2) (3)

***NDA- New drug application**

Despite of the differences and issues, if we have a unified harmonized regulatory submission requirement it will help all the companies to use in a standardized manner and unified approach. But not everything needs to be done at once. We need to prioritize what is needed first and what can be easily implemented. If regulatory bodies sit together and streamline the guidance, it will benefit the organisations to have unified approach.Even if not implemented immediately and taken up slowly over due course of time this would have a huge impact on the process of clinical trial submissions.

Why is there a need for harmonisation of regulatory submissions?

There is a requirement for effective clinical trial submissions to regulatory agencies focussing on the safety and efficacy of the trial data. Currently the companies are handling both FDA and PMDA CDISC requirements (15). The dossier submissions are different due to the differences across regulatory submissions and making it more stringent.Both FDA and PMDA has different dossier submissions.

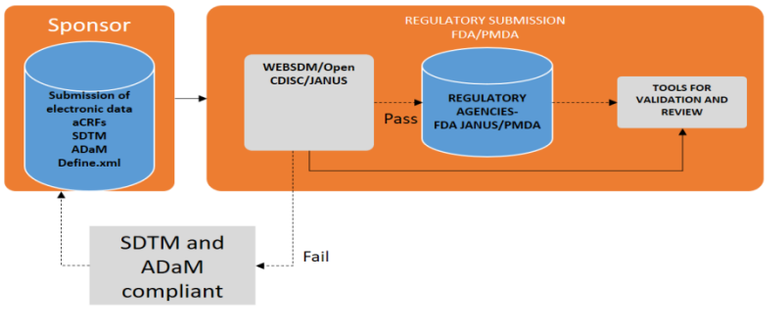

Fig.1 Harmonization Of Regulatory Submissions FDA/PMDA (4) (29)

**aCRF-annotated case report form, CDISC-Clinical data interchange standard consortium, FDA-Food and drug administration, PMDA-Pharmaceuticals and Medical devices agency, SDTM- Study data tabulation model, ADaM-Analysis data model, JANUS- Clinical trial repository, WEBSDM-Web submission data manager*

FDA submission includes adobe portable document format (pdf), SAS institute transport file format (xpt), extensible mark-up language (xml) (6)or SAS transport file for submissions. Submissions to PMDA includes annotated case report form (aCRF) (31), define-xml (7) for SDTM and ADaM dataset, Analysis Results Metadata (ARM),primary and secondary efficacy analysis, safety analysis and analysis for AE datasets, SAS® programs for generating ADaM dataset and analyses, Study Data Reviewer's Guide (SDRG), Analysis Data Reviewer's Guide (ADRG).Until then, companies need to have a single model to have effective submission readiness. Companies need to prepare one submission package for each regulatory authority, considering the different requirements for submissions to FDA and PMDA. Companies need to identify the data issues, validation specific issues and correct the reject issues in the report before the submission. This can be done with the help of pinnacle 21 enterprise and community reports (23). Pinnacle 21 report extracts the issue summary and classifies the severity as reject/ error or warning. It helps to identify the data validation issues and major differences between the reviewer's guides including Study data reviewers guide (SDRG) and Analysis data reviewers guide (ADRG). P21 report provides data issues including dataset and issue summaries. It helps to achieve CDISC compliant datasets (9) maintaining industry standards, and to submit data per regulatory requirement.Using single model inter-organisational harmonisationapproach will make it easier and simpler for companies to prepare regulatory submission packages.

Scope of inter-organisational harmonisation

The scope of harmonization of this model is to identify the differences between the standards and regulatory requirements and to have unified process. This one model approach will help in organisational harmonization internally and helps in ease of submissions. It is not the same approach followed by all the companies for the submission package to FDA and PMDA. If we do not have one model approach it makes the submission packages more difficult. Having unified approach will ease the process of data collection and analysis. When we have a process in place, harmonizing submission standards will be made easy.

A good way to start inter-organizational harmonization model is with data standards. This can be implemented by strategical planning and integration of CDISC processes (10) (Fig 3). Common grounds must be identified which will be a good start.Effective planning and implementation of harmonized CDISC standards will help companies to generate more standardized and useful data. That is why, companies need to focus on what is needed and what can be easily implemented. We need to have a team of governanceinternally across organisation for the implementation of standards for ongoing (21) and new trials.

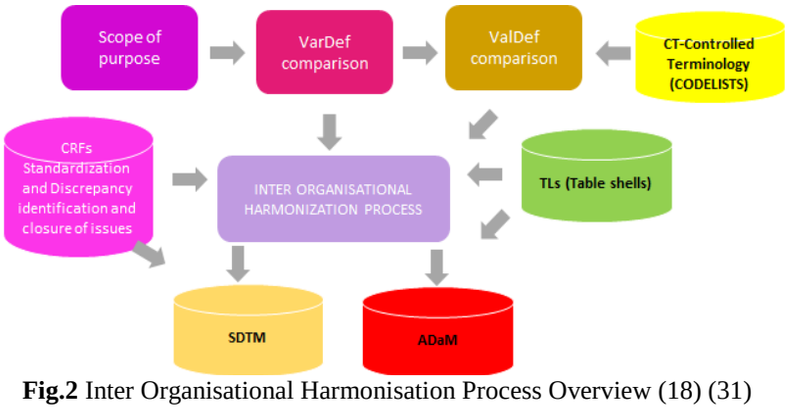

Fig.2 Inter Organisational Harmonisation Process Overview (18) (31)

**CRF- Case report form, SDTM-Study Data Tabulation Model, ADaM- Analysis Data Model, TLs- table shells or templates to specify outputs for statistical display, VarDef- Variable definition, ValDef- Value level definition*

Also, we need to have lessons learned sessions, sharing best practices between standard teams, trial specific teams and documentthe findings. The internal standards team must organize with study team meetings during study closeout to capture the results or findings from implementation. This aids in understanding the differences arising during the execution stage. For legacy or locked trials, meta-analysis (quantitative systematic statistical analysis of research) must be performed considering the submission requirement and cost. This should be an added value for a standard database as mapping has been complex for completed trials. In the case of ongoing studies, there are scenarios where metadata and CDISC guidelines varies during development. Hence, we need to have target SDTM approach (unified collection of data as metadata repository)elected by companies for reporting and analysis.Synchronized standards will save time and helps in cost effectiveness and additional findings on validation issues which can also be documented during the implementation process to data structure and controlled terminology (6).In addition, we need to emphasize regulatory submissions to be done via dataset-xml (format for transferring the contents of a dataset). This is a suggestion to companies for submissions as currently not all the companies submit to FDA by dataset-xml, which has been used as a replacement for SAS V5 XPORT.SAS version 5 (V5) transport file format is an open standard developed by SAS to support data transfers between systems, especially those running across different operating systems. (1). This helps in implementation of synchronized standards on higher level (15).

Harmonization of SDTM metadata, ADaM and controlled terminology

A rational place to initiate harmonization is with data standard methods having unified one model across the organisation. To achieve our one model, we need to harmonize SDTM Metadata, ADaM and controlled terminology.

SDTM

SDTM **(**Study Data Tabulation Model**)** is the standard for submitting data to regulatory agencies (4). This was developed by CDISC with the help of small to midlevel service providers regularly by email communications, quarterly face to face meetings and teleconferences. It is built based on domain models and real data examples, assumptions and interpretation, trial design domains or table, relationship across datasets for submission.

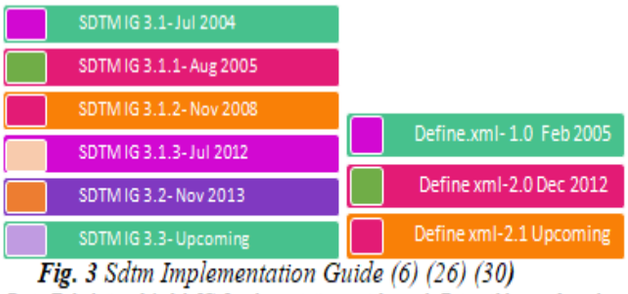

***Fig. 3** Sdtm Implementation Guide (6) (26) (30)*

**SDTM- Study Data Tabulation Model, IG-Implementation guide, xml- Extensible mark-up language*

ADaM

It is for documenting analysis results. It makes traceability of data easy. It identifies columns included for analysis data results. It includes ADaM data in SAS transport format (xpt files), Analysis Data Reviewer's Guide (ADRG) and result metadata including define.xml (18). The major differences between SDRG and ADRG includes validation level, SI unit conversion, conformance issues, unexpected specification. SDRG will update the reviewer about the standards being used, traceability, datasets being submitted and data validation.

Controlled Terminology

CDISC controlled terminology is a set of standard value lists which are used throughout the clinical research process from data collection through analysis and submission.

The various steps involved in the harmonization process are the following:

1. Extraction of SDTM metadata in machine readable format
2. Comparison of variable level metadata,
3. Value level harmonization and this helps in ADaM variables and supplemental domains of SDTM (7).

We need to extract the SDTM metadata in machine readable format thereby comparing the variable level metadata and we need to have value level harmonization. SDTM variable level harmonization is highly important to establish ADaM datasets and to have consistency across the value level-controlled terminologies.Sharing issues of conformance, version upgrade issues, unexpected specification issues during the validation need to be checked before the submissions to both FDA and PMDA (16). Considering the ADaM model, then all terminology harmonization will occur in ADaM datasets. This process in analysis datasets is very similar to the SDTM process, but the case report forms no longer need to be considered. Instead, supplementary SDTM variables need to be included in the ADaM datasets for traceability. If more than one study has SDTM variable with varying terminology, then SDTM variable

needs to be comprised in the ADaM dataset, and new analysis version of the variable with harmonized terminology need to be derived (27).Hence, submission goals are met in a faster manner with the harmonized standards with implementation of SDTM IG and with harmonisation of SDTM, ADaM and controlled terminology. This can support other emerging study data exchange standards (19). This helps in having one model approach across pharmaceutical companies.

Challenges on harmonization of SDTM metadata, ADAM and controlled terminology

The major challenges putting harmonization in practice include electronic study data preparation and submission of dossier to regulatory per required format. This includes compiled list of checks, Janus checks (FDA validation check), failure warning severity and usage of software tools (28). The legacy trials data conversion has major submission challenges as studies has been conducted prior and currently studied. The major challenges include lack of consistency across studies, different methods of data collection, lack of electronic datasets and lack of reconciliation. Hence, data can be converted to SDTM and then to ADaM by preparing the aCRF, define xml, data reviewers guide and SAS programs for TLFs (table shells or templates to specify outputs for statistical display) (24).Clinical pharmacology trial challenges include getting the details and involving the clinical pharmacologist for electronic study preparation. The other challenges include the need for the team of technical expertise as all studies require CDSIC compliant format for submission on or after April 2020. The gap analysis need to be identified during the implementation of the process with the help of steering committee of the organisation and must take prospective decisions. It includes,

1.Itemisation and evaluation of files to support migration activities,
2.Validation of sample CRFs against the source data,
3.Reconciliation of sample CRFs against the source data,
4.Comparison of protocol (4) amendments and identifying the differences in data collection formats (25).

Also, the internal study team must share their technical expertise across platforms.Companies need to set optimistic timelines and organisations must focus on the deliverables. Analysis teams needs to hold meetings and simplify decision-making process and document the next steps. In most of the cases, the case report forms will guide resolutions for differences in the SDTM model. We need to ensure the challenges are identified and addressed in an early stage and ensure traceability for clinical study report (20).

Implementation of inter-organisational harmonisation

As soon as the roadmap is prepared, the next step includes planning and implementation of harmonization. We need to identify common differences between standards and it will serve as a good starting point. Hence, to implement the inter-organisational model,we need to have organisation specific policies and guidances to update the process. The organisations should have internal goal setting and the standardization and study team should work towards the goal. We need to have process improvement initiatives and this helps in smoother execution of implementation process. After every successful implementation, internal team of every company should also assess the impact of the implementation issues and take necessary measures to overcome.

Below is a high-level outline of various steps involved in the harmonization process:

1. Extraction of all the metadata components in a machine-readable format. For example, excel files converted into SAS datasets, it allows programming comparison.
2.Comparison of variable level metadata like role, name, label, core, type, derivation, format and codelist for common variables.
3. The flag records to indicate the differences across.
4. Harmonizingthe value-level information if within scope.
5. Saving this report in a user friendly portable format such as excel.
6. Manually review the report to document reasons for differences. This especially applies to sponsor defined ADaM variables and supplemental SDTM domain.This standardization would help global harmonization of regulatory differences despite of local regulatory requirements (15). Although there are differences in local regulatory requirements, this model will be accepted as the local standards will usually include variable level content and is fully supported with CDISC models. Local interpretation is related to collection forms and table shells. Existing standards must be respected as it has large downstream effect. Thus, the major impact of implementation of inter-organisational harmonisation model includes cost effectiveness, man power and time saving. As in clinical research we need always start keeping the end in mind (17).

Adoption of harmonized submission standards

This model is ideal for most of the companies to adopt, however,companies having adjudication on the differences must rethink on this one model approach for harmonisation process. It is possible that some companies will not be able to adopt this model because of an already existing system in place, sothose companies witha group of experts should sit together and devise a unified approach to benefit the organization and to ease the process of regulatory submissions. Adopting a unified modelwill not only be cost and time effective for the companies but also

will help them to utilize their resources in a better way.This includes teamwork and collaboration between both global and japanese counterparts by holding preliminary meetings on data format consultation for preclinical and clinical trials (22).

II. Conclusion

Inter organisational harmonisation will help in development of harmonized standards across companies which will in turn increase work efficiency.As this will eradicate the study data variation, promote more efficient and faster reporting of data to the regulatory authorities. At present FDA and PMDA requests pharmaceutical companies to comply to CDISC for submissions, but there are few differences between the requirements. It's time for regulatory submissions to get harmonized. Harmonization across regulatory authorities will help sponsors to have a unified and efficient approach. Either the pharmaceutical companies would have to adapt a single, unified inter-harmonization model or regulatory authorities needs to come up with unified regulations to make the submission process easier and more efficient. If alternative model has been adapted it will result in different dossier preparation and increases the cost, utilisation of resources and time for submissions to regulatories. Hence, adoption of harmonised standards will eradicate study data variation and enable efficient pooling and speeder submission process to regulatory agencies.

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