Therapeutic Area Standards Initiative Summary Report

for the

Prescription Drug User Fee Act (PDUFA) FY2013 - FY2017

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1 Introduction

Study data standards for medical product analysis and reporting provide new opportunities to transform the massive amount of data from submissions in specific diseases into more useful information that could potentially speed the delivery of new therapies to patients. Standardized data elements, terminologies, and data structures enable automation of important analyses of study data to support more efficient and effective regulatory decision-making.

In 2011, in response to the need to further standardize study data terminologies and concepts for efficacy analysis, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) compiled a prioritized list of disease and therapeutic areas (TAs) where additional data standardization was needed, and made the list available on the FDA website.[1] Several factors were considered in the identification and prioritization of these areas, including: (1) number and type of active investigational new drug applications (INDs), (2) existing standardization projects underway, and (3) industry input on drug development pipeline activity. The list has been updated periodically to reflect progress and changes in prioritization by stakeholders.

2 Regulatory Framework

In October 2012, the FDA Safety and Innovation Act (FDASIA) reauthorized the fifth Prescription Drug User Fee Act (PDUFA). FDASIA added section 745A(a) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) and provided FDA with the authority to specify, in guidance, the required electronic format for submitting new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs) and investigational new drug applications (INDs).[2]

Under the PDUFA V performance goals, FDA agreed to publish a project plan for the development of standardized clinical terminologies in distinct therapeutic areas (TAs) and to publish it using a public process that allowed for stakeholder input[3].

In November 2012, the FDA issued a *Federal Register* (FR) notice to inform the public of its intent to prioritize and develop clinical terminology standards for distinct TAs, and to request public comment on the TA priority roadmap.[4] In addition, the notice requested

[1] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297093.pdf

[2] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[3] https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

[4] https://www.federalregister.gov/documents/2012/11/20/2012-28197/development-of-prioritized-therapeutic-area-data-standards-request-for-comments

recommendations on how the effort could be accomplished most efficiently. The public comment informed FDA's project plan and approach to the development of clinical terminologies for the various therapeutic areas. In October 2013 FDA published a FR notice, for public comment, announcing the availability of the Therapeutic Area Standards Initiative Project Plan.[5] Over fiscal years 2012-2017, FDA collaborated with stakeholders to prioritize, develop and implement standard therapeutic area standards for use in regulatory submissions.

This report summarizes the results of the Therapeutic Area Standards Initiative. The report describes the (1) goals and objectives, (2) governance, (3) collaborative development approach, (4) progress-to-date, (5) metrics and (6) long-term sustainability of therapeutic area standards.

3 Goals and Objectives

The scope of this initiative included the development and implementation of distinct TAs to support the regulatory review process for drugs and biologics. FDA emphasized that the value of TA standards extends well beyond the regulatory drug review process, and that the standards are essential to the consistent delivery of quality health care. As such, FDA embraced several core operating principles in the execution of this initiative:

- Ensure engagement and input of key authoritative clinical and medical professional societies in TA projects
- Adopt or adapt existing standards where possible
- Harmonize with nationally recognized healthcare standards and controlled terminologies wherever possible
- Use a well-defined data standards governance function
- Scope projects to develop standards incrementally such that progress can be achieved within a relatively short time, with additional value added iteratively.

The TA project plan guided all major aspects of this multi-year initiative and provided the overall management framework for addressing and accomplishing the PDUFA V goals to develop/adopt clinical terminology standards for therapeutic areas. The plan was not intended to provide a detailed timeline for the development, adoption and support of each TA standard, but rather to provide the overall goals and framework for the development and implementation. The Data Standards Strategy-Action Plan[6] and the Table of Priority Therapeutic Area

[5] https://www.federalregister.gov/documents/2013/10/24/2013-24909/therapeutic-area-standards-initiative-project-plan-availability

[6] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm249979.htm.

Standards[7] will continue to provide the list and status of projects addressing each therapeutic area standard.

The goals and objectives for this PDUFA V initiative were:

Goal 1: Make significant progress in developing and implementing clinical terminology standards for distinct therapeutic areas.

Objective: ***Establish and implement standards that support FDA's recommendations***

FDA implemented a process to engage the FDA subject matter experts on the prioritized TAs and to provide recommendations on efficacy data elements to Standards Development Organizations (SDOs) to inform in project scoping and standards development.

Goal 2: Implement binding guidance for study data standards with a consistent and predictable approach.

Objective*: *Implement in Guidance

As noted above, FDA issued final guidance on December 17, 2014 (with an effective date of December 17, 2016) which required the use of study data standards listed in the FDA Data Standards Catalog. FDA will continue to announce support for new data standards and version updates to current data standards in the *Federal Register*.

Goal 3: Establish a consistent process that supports continued TA development.

Objective: Use an open and transparent process

Effective collaboration with open, consensus-based SDOs is important to the success of this initiative. In addition, collaboration with stakeholder organizations that have domain knowledge and common interests is essential.

FDA continues to engage with stakeholders involved in standards development such as SDOs, collaborative consortia, and the public through *Federal Register* notices. The Communications Plan[8] further describes the collaboration efforts.

[7] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm287408.htm

[8] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm508192.htm

Goal 4: Define a forward-looking model and timeline for study data standards to ensure sustainability and flexibility over time.

Objective: Support the development of information models

FDA recognizes the continued advancements in medical science and information technology and the need to ensure that standards and terminologies are sustainable without undue burden to stakeholders. FDA continues to collaborate with SDO working groups in the development of the information models shared across the regulated clinical research and health care.

Goal 5: Promote interoperability with healthcare data standards.

Objective: Express TA recommendations in sustainable standards

In this initiative, TA clinical terminology standards are being developed through the Coalition for Accelerating Standards and Therapies (CFAST) initiative using Clinical Data Interchange Standards Consortium (CDISC) standards[9]. TA standards are extensions of the CDISC foundational standards (e.g., SDTM and ADaM) and are developed to represent data that pertain to specific disease areas. Where possible, TA development projects adopt / adapt existing data elements and terminologies that are fit for their purposes. FDA envisions a semantically interoperable and sustainable submission environment that serves both regulated clinical research and health care.

FDA recognizes the continuous progress in medical science and information technology, therefore, an effort to identify the best future direction is important to ensure that standards and terminologies are sustainable without undue burden to stakeholders. The efforts to support interoperability include participation in the development of the information models shared across the regulated clinical research and health care, support of tools to enable greater usability of the present CDISC standards, and exploration of the new technologies capable of enabling reuse of the content developed across the biomedical community.

4 FDA Governance for Therapeutic Area Standards

To meet this initiative's goals and objectives and those of other data standardization efforts ongoing in the Centers, a comprehensive FDA therapeutic area standards operating structure was established to provide leadership and management.

[9] https://www.cdisc.org/partnerships/cfast

FDA used its established data standards governance, the CDER Data Standards Program Board (DSPB)[10] which is comprised of representatives from each CDER office involved with data standards, CBER, and the Center for Devices and Radiological Health (CDRH), as well subject-matter experts (SMEs) and project managers to conduct the internal activities of the TA standards initiative.

The implementation approach for data standards, in general, and specifically for clinical terminologies for TAs involved collaboration with stakeholders to define the business case, any potential alternatives, development, review and public release.

5 Collaborative Development Approach

FDA recognized that in order to accomplish the resource-intensive process to develop and implement multiple therapeutic area standards, it had to collaborate with internal and key external stakeholders. In order to ensure the availability of adequate resources to address the prioritized TAs, as well as to ensure the developed TA supported the regulatory review process for drugs and biologics, FDA used a multidimensional approach to the development, testing and acceptance, and implementation of TA standards.

The development approach included collaboration with:

- External medical / scientific organizations to develop clinical data elements using the FDA grants program
- FDA review division subject-matter experts to develop clinical data element recommendations for specific TAs
- Coalition for Accelerating Standards and Therapies (CFAST) (see section 5.3)

The implementation of the therapeutic area data standards for FDA included a testing and acceptance process using the CDISC Therapeutic Area User Guide (TAUG) and TA specifications to ensure that the FDA recommendations were incorporated and that the TA could support regulatory review. The FDA-supported TAs are listed in the Study Data Technical Conformance Guide (TCG)[11].

5.1 FDA TA Recommendations Supporting Efficacy Data Standards

Table 1 presents the 21 internal projects initiated with FDA review divisions in order to capture recommendations for supporting efficacy data standardization for human clinical trials for

[10] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM250306.pdf

[11] https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm384744.pdf

specific TAs[12]. The recommendations report for each project was provided to CFAST as input to the development of the specific disease area and the publication of the TAUG.

Table 1. Internal TA FDA Recommendations Reports

1. Acne
2. Anticoagulants for Atrial Fibrillation
3. Anticonvulsants
4. Attention Deficit Hyperactivity Disorder
5. Brain Cancer
6. Breast Cancer
7. Clostridium Difficile associated with Diarrhea
8. Colorectal Cancer
9. Complicated Intra-abdominal Infections
10. Complicated Skin and Skin Structure Infections
11. Complicated Urinary Tract Infections
12. Diabetic Kidney
13. Irritable Bowel Syndrome
14. Kidney Transplant
15. Lung Cancer
16. Muscular Dystrophy
17. Prevention of Pregnancy
18. Prostate Cancer
19. Rheumatoid Arthritis
20. Treatment of Overactive Bladder
21. Treatment of Postmenopausal Osteoporosis

*Status as of September 2017

The focused effort to establish these recommendations has resulted in a consistent process that can continue to be used as new priority therapeutic areas are identified for further standardization.

5.2 FDA Funded TA Development

FDA established and continues to manage a grant program to fund selected medical / scientific organizations to develop disease/domain-specific standards. FDA has awarded grants, cooperative agreements, and contracts to external organizations for development of clinical data elements in the TA areas listed in Table 2. The data elements for each of these TAs were developed with participation of the FDA SMEs and then submitted to the CFAST to further develop and to publish the associated TAUG.

12 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297093.pdf

Table 2. TA Development Funded by FDA*

1. Bipolar Disorder
2. Cardiovascular Endpoints
3. Cardiovascular Imaging
4. Clostridium Difficile associated Diarrhea
5. Colorectal Cancer
6. Diabetic Kidney Disease
7. Diabetes
8. Dyslipidemia
9. Generalized Anxiety Disorder
10. Hepatitis C
11. Influenza
12. Kidney Transplant
13. Lung Cancer
14. Major Depressive Disorder
15. Prostate Cancer, Diabetes
16. QT Studies
17. Rheumatoid Arthritis
18. Schizophrenia
19. Treatment of HIV
20. Virology

*Status as of September 2017

5.3 Coalition for Accelerating Standards and Therapies

In 2012, CDISC formed a partnership with C-Path to establish the Coalition for Accelerating Standards and Therapies (CFAST), an initiative to accelerate clinical research and medical product development by creating and maintaining data standards. In addition to the CDISC, C-Path and FDA, CFAST includes: (1) TransCelerate BioPharma, (2) National Cancer Institute / Enterprise Vocabulary Service, (3) Association of Clinical Research Organizations and the (4) European Innovative Medicine Initiative, among others.[13] FDA's role in its collaboration with CFAST included:

- Participation on the CFAST Steering and Scientific Committees
- Review Divisions consult / review proposed scope of TA projects
- Periodic review of data element concepts
- Review of draft and final TA User Guides

[13] http://www.cdisc.org/cfast-0

The output from a CFAST TA project is the release of a TAUG that describes how to use CDISC standards (i.e., CDASH, SDTM, ADaM) to represent data pertaining to a particular disease. Table 3 presents the status of released TAUGs over the 2012 -2017 time period.

Table 3: TA Standards Released by CDISC*

1. Alzheimer's v1, v2
2. Asthma
3. Breast Cancer
4. Cardiovascular
5. Chronic Hepatitis C
6. Colorectal Cancer
7. COPD
8. Diabetes
9. Diabetic Kidney Disease
10. Dyslipidemia
11. Ebola
12. Influenza
13. Kidney Transplant
14. Major Depressive Disorder
15. Malaria
16. Multiple Sclerosis
17. Pain v1, 1.1
18. Parkinson's Disease
19. Polycystic Kidney Disease
20. Prostate Cancer
21. QT Studies
22. Rheumatoid Arthritis
23. Schizophrenia v1, v1.1
24. Traumatic Brain Injury
25. Tuberculosis
26. Virology v1, v2

*Status as of September 2017

5.4 Testing and Acceptance of TA Standards

Generally, when a data standard is released by a SDO for public use, it is not supported by FDA until it undergoes a testing and acceptance process and is announced in the *Federal Register*. Testing and acceptance is conducted to assess the consistency and usability of the standards in FDA medical science review and the impact of new standards on FDA review tools.

Therapeutic area standards are not CDISC foundational study data standards, but rather extend the foundational standards (e.g., SDTM and ADaM) to represent data that pertain to specific therapeutic or disease areas. CDISC publishes a TAUG for each therapeutic area which includes the SDTM and ADaM extensions as disease-specific metadata, examples, disease characteristics, and recommendations for use. The TAUGs are important references but should not be interpreted as FDA guidance.

6 Progress and Reporting

As noted above, the FDA initiated, in earnest, the development of therapeutic area standards at the commencement of PDUFA V. The FDA's Therapeutic Area (Disease/Domain) Data Standards Prioritization List[14] lists 54 areas that were identified as key areas in need of standardization. On a regular basis FDA reviews and updates the prioritization list.

FDA, with its internal and external stakeholders, has initiated or completed work on 44 out of 54 (81%) listed TAs.[15] The outstanding ten TAs will be discussed with the respective review divisions to asses current and future need for standardization.

On a biannual basis, the TCG publishes the TAs that are supported by FDA for use in electronic submissions of study data. Table 4 presents the TAs that are supported by FDA and Table 5 presents the list of TAs that will undergo testing acceptance in 2017.

14 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297093.pdf

15 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297093.pdf

Table 4. FDA Supported Therapeutic Areas*

1. Chronic Hepatitis C
2. Diabetes
3. Diabetic Kidney Disease
4. Dyslipidemia
5. Ebola
6. Kidney Transplant
7. Malaria
8. QT Studies
9. Rheumatoid Arthritis
10. Tuberculosis

*Status as of September 2017

Table 5: TAs in Testing & Acceptance: 2017*

1. Asthma
2. Breast Cancer
3. Cardiovascular
4. Colorectal Cancer
5. Duchenne Muscular Dystrophy
6. Influenza
7. Prostate Cancer
8. Schizophrenia
9. Vaccines
10. Virology

*Status as of September 2017

7 Metrics

FDA committed to assessing the impact of electronic submissions and data standards on the human drug review process. In FY2016, FDA performed an assessment to identify gaps and recommend an actionable path forward for improvement. In June 2017, FDA posted the results of the assessment entitled " Assessment of Impact of Electronic submissions and Data Standards on the Efficiency and Other Performance Attributes of the Human Drug Review Process."[16] The assessment indicated that primary clinical reviewers strongly agree or agree that standardized data makes a difference in different aspects of their review activities. The

[16] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm144373.htm

reviewers believed that standardized data makes it easier to complete standard analyses, perform analyses more efficiently, decreases time spent preparing data, and allows more time to conduct additional non-standard analyses. FDA will continue its efforts to provide metrics on submissions that are in conformance with FDA-supported study data standards.

8 Long-Term Sustainability

PDUFA VI Performance Goals state that FDA will collaborate with SDOs and other stakeholders to ensure long-term sustainability of supported data standards.[17] Concurrent with advancing TA standards as described above, we are taking steps to ensure that standards remain viable over time to enable automation of important analyses of clinical study data to support more efficient and effective regulatory decision-making. FDA will continue to assess options based on a number of considerations critical to increasing the efficiency and effectiveness of the TA content development process, including:

- Support for a widely-accepted, open technology to maintain the TA standards
- Ability to support evolving models that are implemented and shared by multiple stakeholders and systems, including maximized re-use and built-in business validation
- Availability of reliable tools and infrastructure promoting data discovery, re-use, pooling, and harmonization
- Potential to enable development of standards that can be harmonized, as needed
- Ability to achieve conceptual alignment through computable semantic interoperability, by reducing or eliminating the impact of differences in implementation technologies and transport protocols
- Having a significant base of current clinical research and life sciences standards and terminologies already captured and available for being referenced from TA models

The development and maintenance of data standards for medical product reporting provide new opportunities to transform the massive amount of data from submissions in specific diseases into more useful information that could potentially speed the delivery of new therapies to patients. FDA is committed to the continued development, update and the long-term sustainability of study data standards.

[17] https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm446608.htm

Appendix: Acronym List

ADaM	CDISC: Analysis Data Model
ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDASH	CDISC: Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CFAST	Coalition for Accelerating Standards and Therapies
C-Path	Critical Path Institute
DSAB	FDA Data Standards Advisory Board
DSPB	CDER Data Standards Program Board
FDASIA	FDA Safety and Innovation Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FRN	Federal Register Notice
IND	Investigational New Drug Application
NDA	New Drug Application
NCI/EVS	National Cancer Institute / Enterprise Vocabulary Service
PDUFA	Prescription Drug User Fee Act
SDO	Standards Development Organization
SDTM	CDISC: Study Data Tabulation Model
TA	Therapeutic Area
TAS	Therapeutic Area Standards
TAUG	Therapeutic Area User Guide
TCG	Study Data Technical Conformance Guide