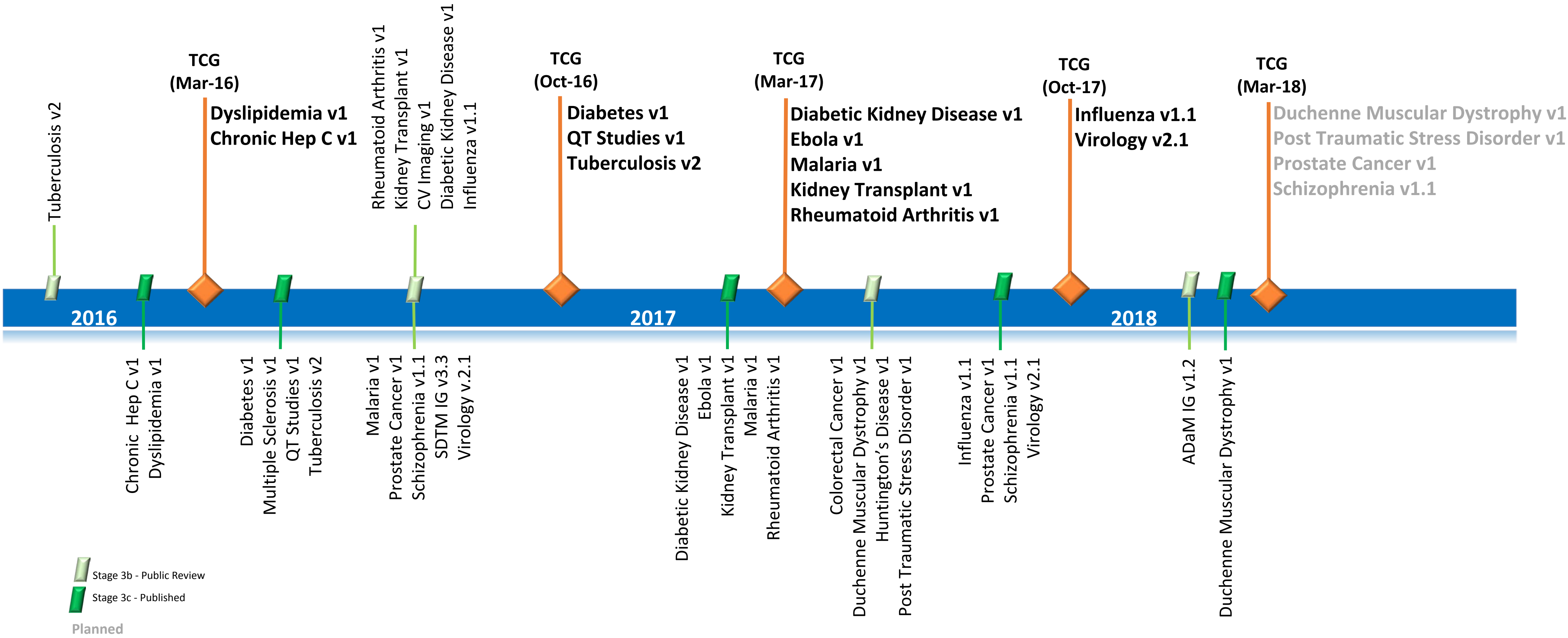


FDA Assessment and Acceptance Process of TA-specific Clinical Data Extensions to CDISC Foundational Standards

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As part of PDUFA V, the FDA published a project plan outlining the priority therapeutic areas (TA) for which development of clinical terminologies and data standards are important. During PDUFA V FDA updated this Therapeutic Area Standards Initiative Project Plan on a regular basis. CFAST, including CDISC and TransCelerate BioPharma (TCB) used the list of priority therapeutic areas to determine the schedule for the development of Therapeutic Area User Guides (TAUG). The Study Data Standards (SDS) Working Group evaluates the standards and manage the process. This diverse group is comprised of regular members with more technical backgrounds, as well as subject matter experts who contribute on an ad hoc basis to their therapeutic areas of expertise. Assessment of the TAUGs is conducted during CDISC 3b and 3c stages to evaluate the impact of the new standard’s extension on FDA medical science review. The testing process includes review of the TAUG, determination of whether there are any unfulfilled FDA recommendations specific for the TA, and submission of comments to CDISC. The decision on adopting a TA standard for use in electronic study data submissions is listed in the Technical Conformance Guide (TCG) that is published biannually. The results of the assessment are provided as input to standards development projects as FDA recommendations. The approach we have taken to develop FDA TA recommendations includes a description of the impact on tools, processes, and information technology, as well as future-state benefits.

Timeline of the TAUGs Assessments and Acceptance by FDA

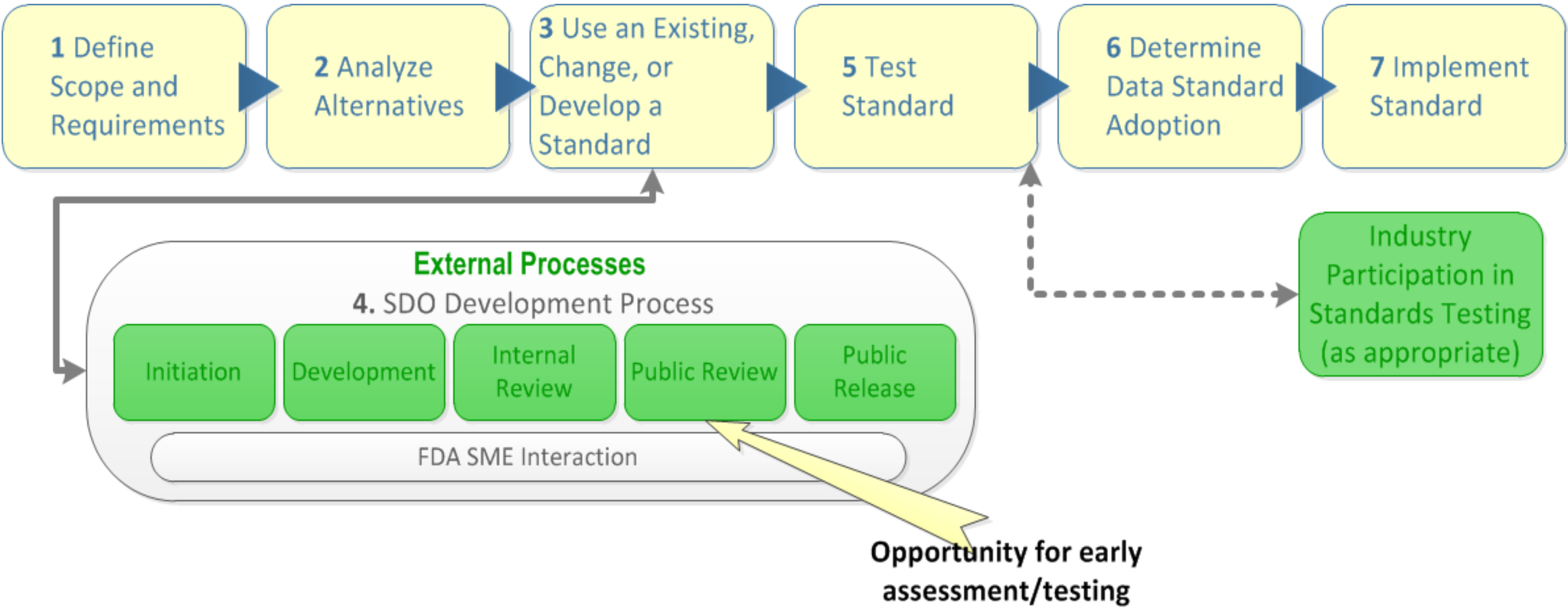


5.	THERAPEUTIC AREA STANDARDS.....
5.1	GENERAL.....
5.2	SUPPORTED THERAPEUTIC AREAS.....
5.2.1	Chronic Hepatitis C.....
5.2.2	Dyslipidemia.....
5.2.3	Diabetes.....
5.2.4	Diabetic Kidney Disease.....
5.2.5	Ebola.....
5.2.6	Influenza.....
5.2.7	Kidney Transplant.....
5.2.8	Malaria.....
5.2.9	QT Studies.....
5.2.10	Rheumatoid Arthritis.....
5.2.11	Tuberculosis.....
5.2.12	Virology.....

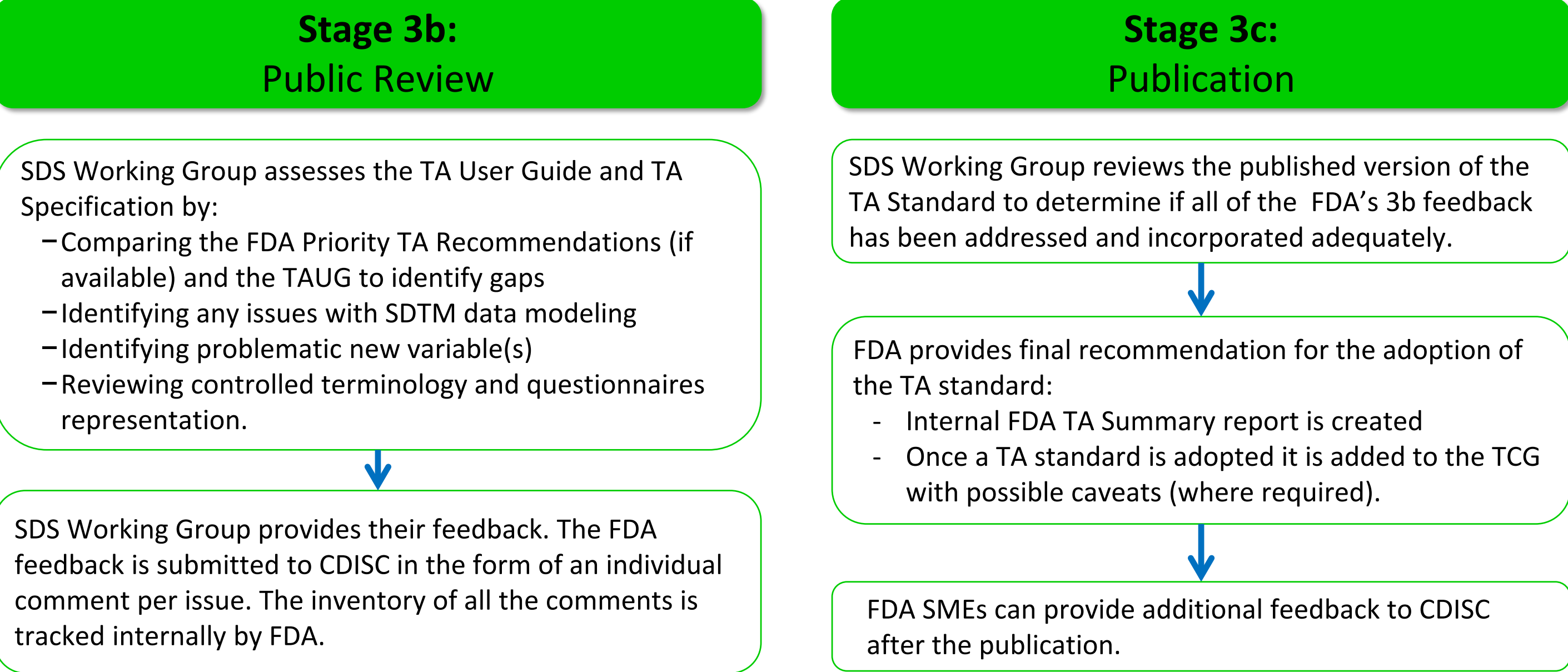
5.2.10 Rheumatoid Arthritis
Standardization for Radiologic Score variables is not available in the Rheumatoid Arthritis TAUG. Sponsors should refer to Radiographic Scoring methods as outcome measures in Rheumatoid Arthritis for additional guidance. Additionally, while the Controlled Terminology for the HAQ-DI Questionnaire is being tracked by CDISC, sponsors should refer to the Standard HAQ-DI instrument. It is advised to consult with the review division for further guidance regarding a specific study.

Technical Conformance Guide (TCG) provides technical recommendations to sponsors for the submission of animal and human study data and related information in a standardized electronic format in INDs, NDAs, ANDAs, and BLAs. The Guide is intended to complement and promote interactions between sponsors and FDA review divisions. However, it is **not intended to replace the need for sponsors to communicate directly with review divisions** regarding implementation approaches or issues relating to data standards. Sponsors may use **new TA extensions of a CDISC standard**, but are **not required to until the extensions have been incorporated into a SDTMIG version supported by FDA** (the supported SDTMIGs are listed in the Catalog). Sponsors should explain the rationale in the Study Data Reviewer Guide for clinical studies (cSDRG) for using TA extensions that are not currently listed in the Guide.

Data Standards Program Process Framework



How TA Standard is evaluated at FDA



CDISC Dispositions of FDA Comments

CDISC Disposition	CDISC Disposition Purpose	Number of FDA Comments per CDISC disposition
Question answered	Use this disposition if the comment is a question that has been answered. Note that some comments phrased as questions are actually suggestions for change. Use this disposition only if the question is not one that would be better dealt with by clarifying the text of the standard.	49
Persuasive	Use this disposition if the change requested in the comment is accepted and the change will be made as proposed in the comment.	34
Considered – no action required	Use this disposition if the comment was considered but nothing is required as a result of the comment. An example of this type of comment would be a compliment for a job well-done. There is no action being requested.	29
Considered for future	Use this disposition if the comment will be considered for a future release, but not the release associated with this review.	24
Persuasive with modification	Use this disposition if the comment is accepted but the change made is different from the proposed solution.	14
Not persuasive	Use this disposition if the comment is not convincing or is unclear. If possible, an unclear comment should be clarified with the reviewer before resorting to this disposition.	10
Out of scope	Use this disposition if the comment is considered not related to the document under review. If a comment is out of scope for the version being reviewed, but relevant for a future version, the disposition should be "Considered for future."	2
Not persuasive with modification	Use this disposition if the comment is not convincing but changes were made based on the content of the comment.	1

The numbers are based on the TA standards where 3b FDA SMEs' comments were submitted and tracked by CDISC during the 3c stage.

Status of FDA Review of TAUGs

TA Standard Name	Stage 3b - Public Review	Stage 3c - Publication	TAUG publicly available version	FDA Recommendation Document available	Number of FDA Submitted Comments
Chronic Hep-C Virus		X	1.0	No	
Colorectal Cancer	X		In progress (1.0)	Yes	
Cardiovascular Imaging	X		In progress (1.0)	No	
Diabetes		X	1.0	Yes	
Diabetic Kidney Disease	X	X	1.0	Yes	11
Duchenne Muscular Dystrophy	X	X	In progress (1.0)	Yes	
Dyslipidemia		X	1.0	No	
Ebola	X	X	1.0	No	13
Huntington's Disease	X		In progress (1.0)	No	
Influenza	X	X	1.1	No	15
Kidney Transplant	X	X	1.0	Yes	13
Malaria	X	X	1.0	No	30
Multiple Sclerosis		X	1.0	No	
Post Traumatic Stress Disorder	X		In progress (1.0)	No	
Prostate Cancer	X	X	1.0	Yes	14
QT Studies		X	1.0	No	
Rheumatoid Arthritis	X	X	1.0	Yes	9
Schizophrenia	X	X	1.1	No	36
Tuberculosis	X	X	2.0	No	
Virology	X	X	2.1	No	22

The FDA SDS Working Group is responsible for testing the foundational standards and TA extensions, not the actual submission data. The assessment has a definable process that is repeatable across all TA standards. Ultimately, if the FDA decides to adopt a TA extension of the foundational standard, it is included in the TCG.

During the TA standards’ evaluations several challenges and opportunities for future development have been identified:

- There is no tracking history for the PDF versions which creates difficulties in identifying changes (e.g. in domains, variables, narrative) from one release to the next.
- Data examples in the wiki can be very long and require to scroll horizontally. It would be helpful to have a feature to hide columns and improve the formatting in the copy and paste feature.
- Some of the FDA comments apply to multiple TAs. However, currently there is no process or a place to address the impact of such comments.
- It would be beneficial for FDA SMEs to have the ability to review and track the linkage between relevant domains, variables, and controlled terminology across TAs.