TRIALS AND TRIBULATIONS: EXPERIENCES USING DATA STANDARDS AND ASSISTING STAFF IN REVIEWING SUBMISSIONS

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Disclaimer

- **The opinions expressed in this presentation are the presenter's and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA).**

- **Additional disclaimer: I have not conducted any clinical reviewers myself, but I have conducted clinical pharmacology reviews as part of multi-disciplinary review teams**

Important Dates for Data Standards

- "Sponsors whose studies start after **Dec. 17, 2016**, must submit data in the data formats supported by FDA and listed in the FDA Data Standards Catalog. This applies to NDAs, BLAs, ANDAs, and subsequent submissions to these types of applications."

- "For INDs, the requirement applies for studies that start after **Dec. 17, 2017**."

- 'Technical Reject Criteria for Study Data' outlines criteria by which conformance may be evaluated
  - Implementation still underway

- This talk focuses on how clinical reviewers used information that was received

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

Clinical Reviewer Responsibilities

- Review of IND, NDA, and BLA submissions
  - Multiple submissions at one time, various disease areas and overlapping responsibilities

INDs

- Industry meetings
- Protocol reviews
- Safety reports/annual reports
- High volume, short time-frame, limited scope

NDAs and BLAs

- Initial applications (NMEs)
- Supplements (indications, population, regimen)
- Less frequent, longer clock, more material
- **HANDS ON DATA ANALYSIS**

Clinical Reviewer Characteristics

- FDA clinical reviewers:
  - are highly educated
  - often with an medical degree
  - specialization connected to the Division they work for
  - highly motivated for public service
  - personal satisfaction they play an important role in promoting public health

- Have been employed for a wide spectrum of years
  - creates a range of training, experiences and practices
  - different experience with tools, techniques, and technology

CDER 21st Century Review Process

Desk Reference Guide

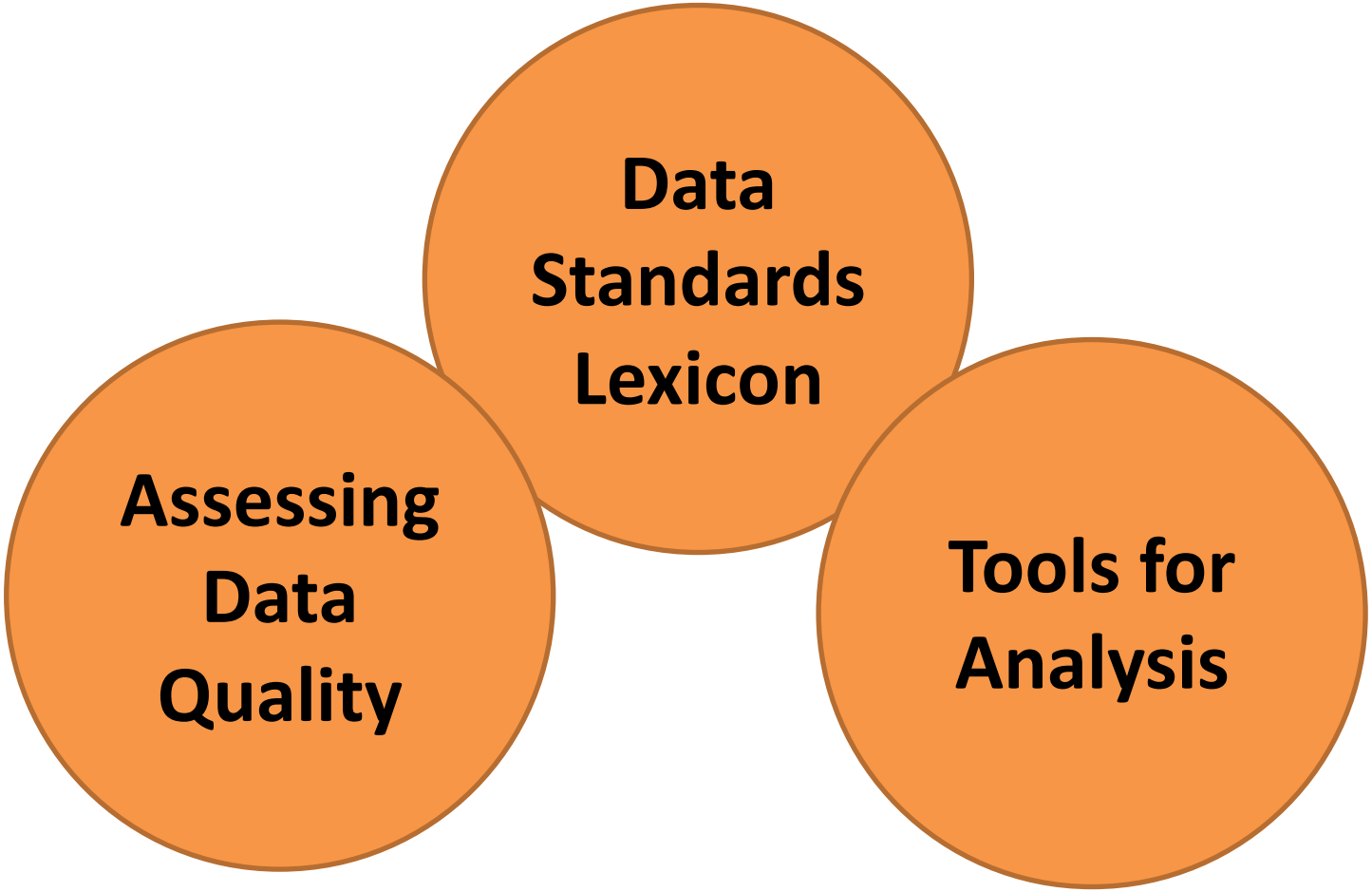
New Drug Application and Biologics License Application Reviews (NDA/BLA Review Process)

https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf

Elements of the Clinical Review Process

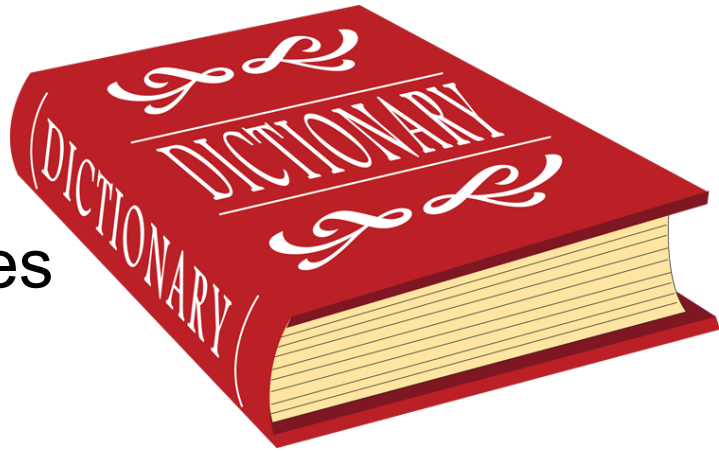
- Site selection/documentation of financial disclosures
- Understand key analyses from the Applicant
- Independently evaluate efficacy and safety findings and synthesize the materials into a comprehensive review
- Key milestone meetings through the review (potential for additional meetings and an advisory committee)
- Negotiation and synthesis of product labeling (provide rationale for changes from Applicant's proposals)
- Assessments are performed while being mindful of previous precedence and existing guidance

Recurring Concerns from Clinical Reviewers



Data Standards Lexicon

- Set of abbreviations, labels, and definitions that may not be intuitive
  - What are CDISC, SDTM, and ADaM?
  - Why are they using these names (can we use different names)?
- Relational datasets
  - Why is the data organized this way?
  - How am I supposed to look at this?



Assessing Data Quality

- Clinical reviewers are not experts on if data was submitted according to standards
  - How am I supposed to interpret data validation errors?
  - What am I supposed to look for?
  - How do I fix it?
- Data assessment is early in the review
  - I haven't started my review yet
  - I'm still learning about the submission

Tools to Use for Analyses

- The FDA reviewers have a few review tools available for analyzing data. New reviewers may have questions about
  - Which ones can be used with the data I have?
  - When I have a unique question, which permits me flexibility to explore the data?
  - Which tools generates review, presentation, and publication quality figures and tables?

Need for a Novel Skillset

Biomedical Informatics and Regulatory Review Science Team (BIRRS) within OND/IO

Director: **Vaishali Popat, MD MPH**

- Associate Directors for Biomedical Informatics (5)
  - Sarah Connelly (DAVP)
  - Doug Warfield (DPP)
  - Stacey Chin (DPARP)
  - Nhi Beasley (DCRP)
  - Joseph Tonning (DBRUP)

Vision:

To achieve excellence in evidence-based regulatory decisions through integration of medicine and analytical informatics to deliver safe and effective drugs to the public.

Mission:

To advance the CDER New Drugs Regulatory Program by bridging clinical expertise, data science, and regulatory review science to develop tools and best practices for complex analyses and interpretation, thereby empowering clinical reviewers to make data-driven decisions that impact public health.

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Drug Approval Reports by Month

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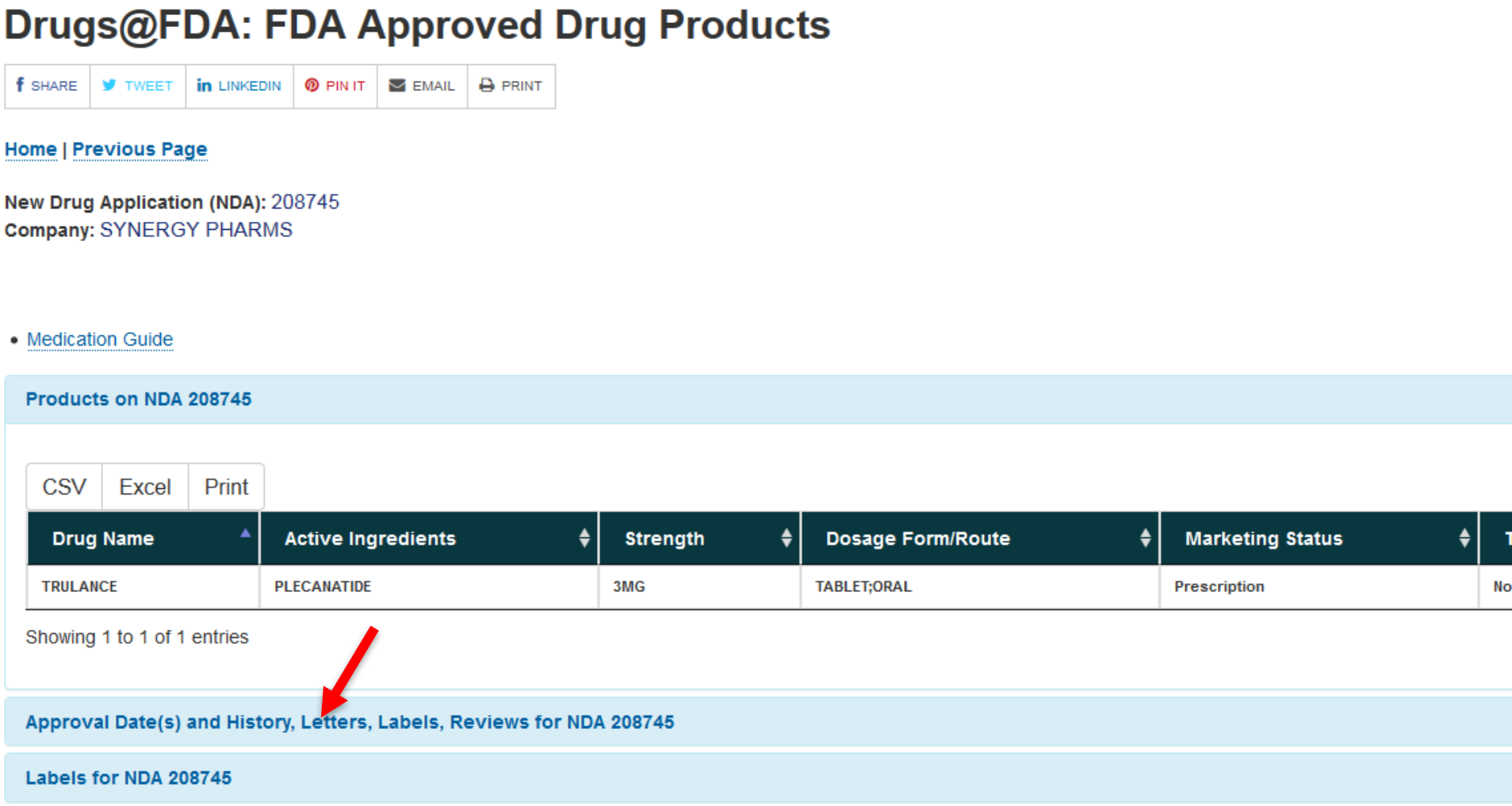
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Drugs@FDA (2)



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Company: SYNERGY PHARMS

- Medication Guide

Products on NDA 208745

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Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	T
TRULANCE	PLECANATIDE	3MG	TABLET;ORAL	Prescription	No

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 208745

Labels for NDA 208745

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208745

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Drugs@FDA (3)

Products on NDA 208745

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code
TRULANCE	PLECANATIDE	3MG	TABLET;ORAL	Prescription	None

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 208745

Original Approvals or Tentative Approvals

CSV Excel Print

Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert
01/19/2017	ORIG-1	Approval	Type 1 - New Molecular Entity	STANDARD	Label (PDF) Letter (PDF) Review

Showing 1 to 1 of 1 entries

Supplements

CSV Excel Print

Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert	No

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208745

Drugs@FDA (4)

Home > Drugs > Drug Approvals and Data

Trulance (plecanatide) Tablets

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Company: Synergy Pharmaceuticals Inc.
Application No.: 208745
Approval Date: 01/19/2017

Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance.

- Approval Letter(s) (PDF)
- Printed Labeling (PDF)
- Summary Review (PDF)
- Officer/Employee List (PDF)
- Office Director Memo (PDF)
- Cross Discipline Team Leader Review (PDF)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
- Statistical Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208745Orig1s000TOC.cfm

A Look Into the Clinical Review from data standards point of view

Methods:

- Focus on new molecular entities (NMEs) approved in 2017 (publicly available)
- Determine if SDTM and or ADaM datasets were provided for pivotal and supportive studies (no quality check!)
- Locate publicly posted (and redacted) clinical reviews for new molecular entities (NMEs) approved in 2017 (Drugs@FDA)
- Identify cases where reviewers noted issues with data quality or data integrity within the review and how it may have impacted the review (review section and information requests)
- **Note: This is not a comprehensive assessment of data quality and integrity issues as not all issues will be documented in a review, particularly if the issue has been resolved.**

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm

Two Styles of Clinical Reviews in 2017

Listed: Medical Review

- Prepared by clinical reviewer (may be with statistician)
- Benefit-risk assessment
- Includes detailed summari
  of safety often efficacy
- Summary of significant issues from other discipline
- AC, labeling, REMS, PMR/PMC

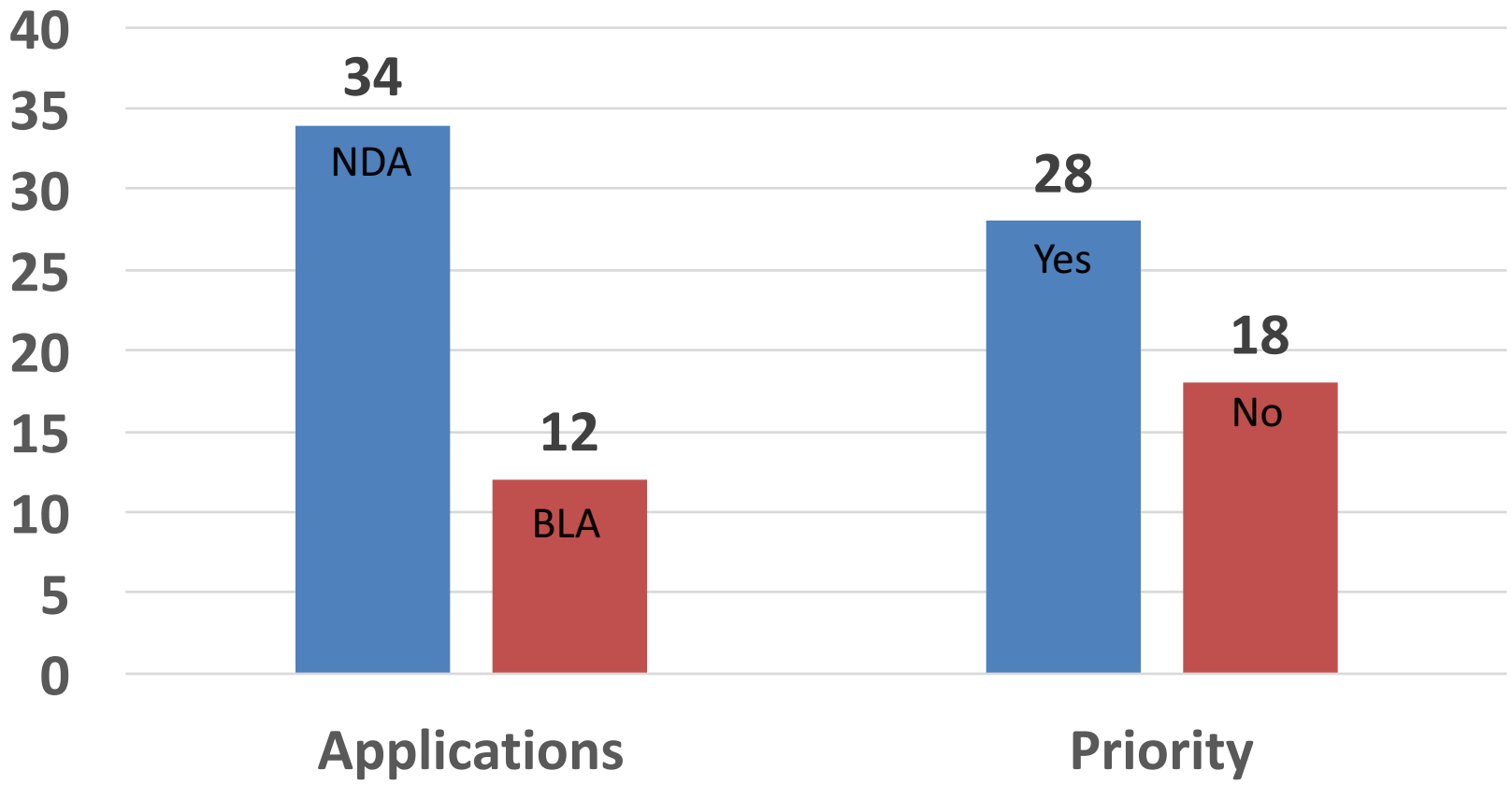
All included

Listed: Multi-Discipline

- Prepared (typically) by clinical, non-clinical, statistics, and clinical pharmacology
- efit-risk assessment
- des detailed summaries
  safety often efficacy
- Summary of significant issues from other discipline
- AC, labeling, REMS, PMR/PMC

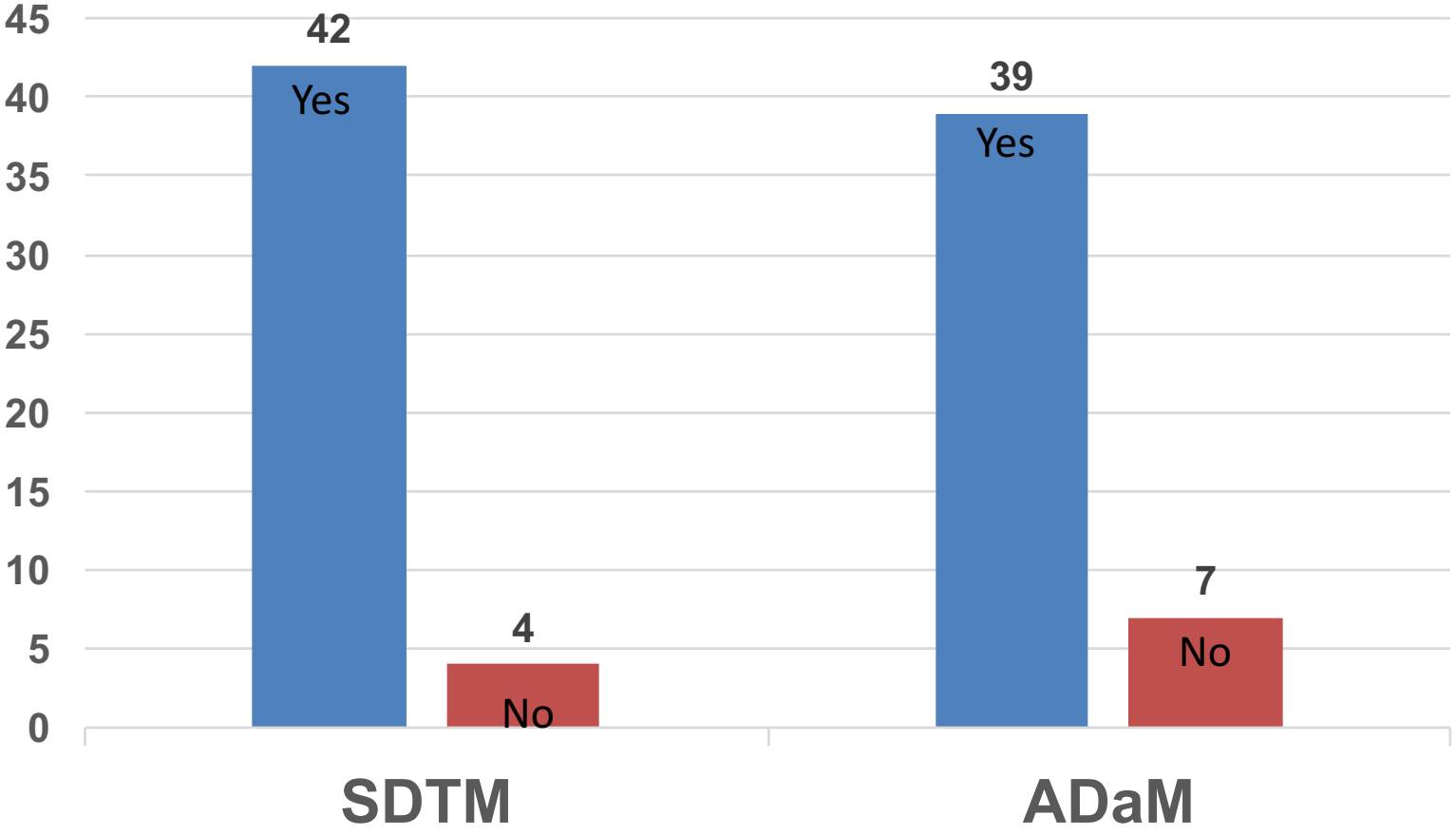
Scientific content is the same, but multi-discipline format eliminates redundant sections found in other discipline reviews and organizes a majority of the disciplines in a single document.

NMEs Approved in 2017 (n = 46)



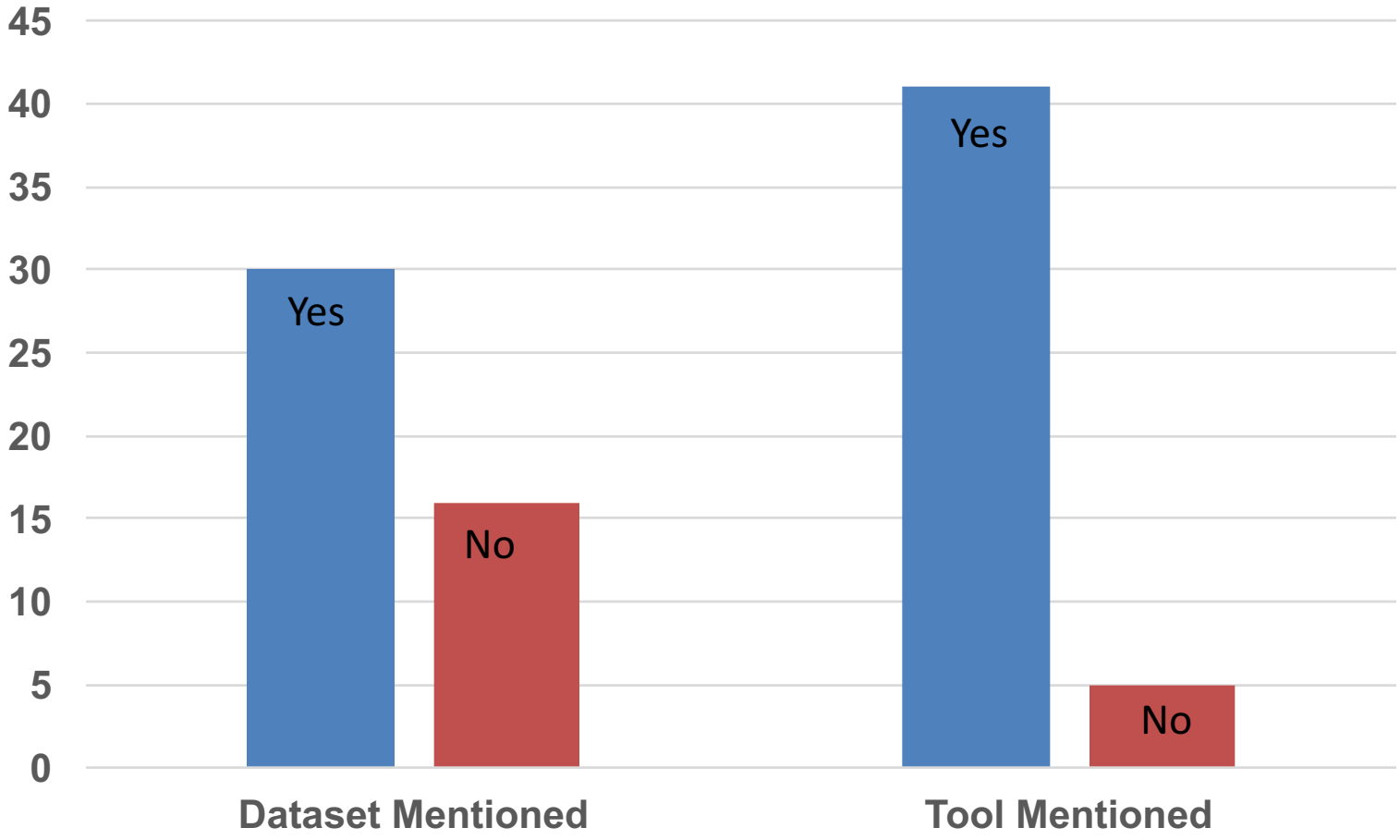
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm

How was Pivotal Study Data Provided? (focus on DM, AE, ADSL, and ADAE)



Source: Internal systems and publicly available reviews at Drugs@FDA; Counted as 'Yes' if one or more studies had information and does not reflect a quality assessment

How was Pivotal Study Data Analyzed?



Source: Internal systems and publicly available reviews at Drugs@FDA;

Takeaways from the Reviews

- Many reviews describe the source material for analyses presented in the review
  - Either reviewer analysis or materials from the sponsor
  - Datasets for the analysis were underneath the table/figure

- Analysis tools used were often described in the reviews:
  - MAED – MedDRA Adverse Event Diagnosis Service
  - JMP programs, SAS, JReview
  - JumpStart

- Examples: safety coding from the sponsor and documented cases where grouping may have differed

- Details on information request are available in a subset of cases
  - Cases where reviewer request additional analyses from sponsors
  - Few identified cases where data quality issues, and the ensuing discussion, were documented in the reviews

Summary

- Staff is receiving and reviewing data
  - questions about quality assessment, training for tools, and best practices
- Value in specialized skillsets for assisting reviewers
  - in navigating a changing technologic landscape
  - providing reviewer support for safety analyses and standards across Divisions
- A subset of Divisions have Associate Directors for Biomedical Informatics to assist with these needs
  - Dr. Beasley will provide additional information in June

Acknowledgements

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Questions


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