U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

CDISC 2022 JAPAN INTERCHANGE

DATA QUALITY AND CROSS-STUDY ANALYSIS

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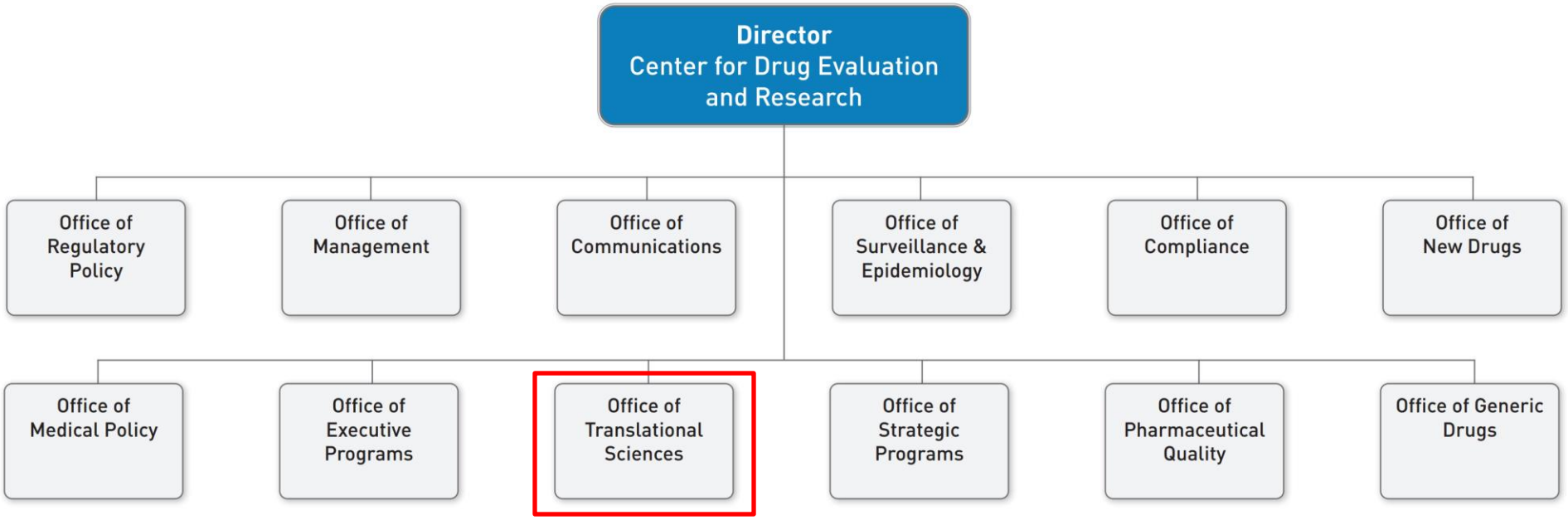
FDA Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Agenda

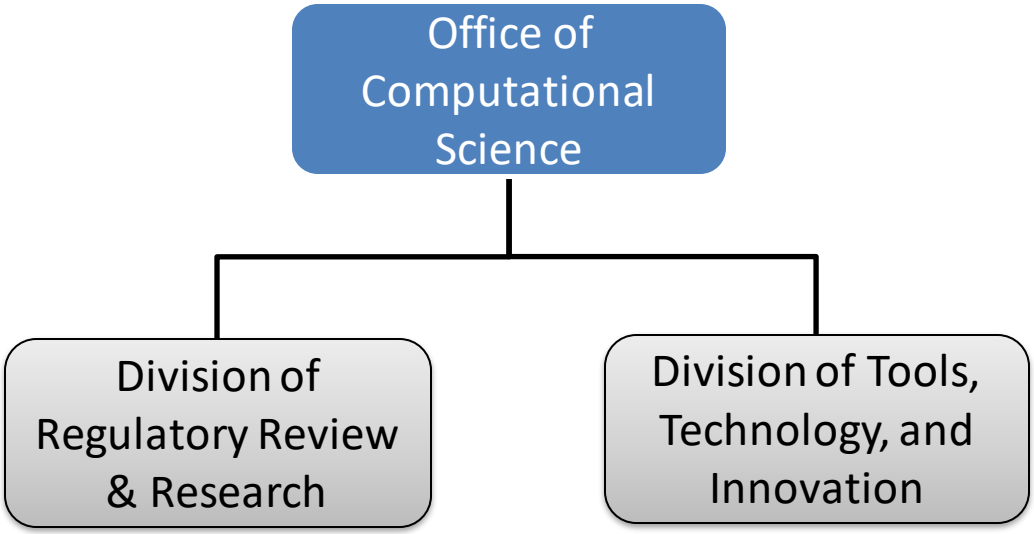
- Background
- CDISC Collaborations
- OCS Nonclinical Program
- Cross-Study Analysis Opportunities

CDER Organization Chart



- OCS is under the Office of Translational Sciences in CDER
- OCS supports multiple Offices across the Center
- Interacts with other Offices within Center for various initiatives

OCS Mission and Vision

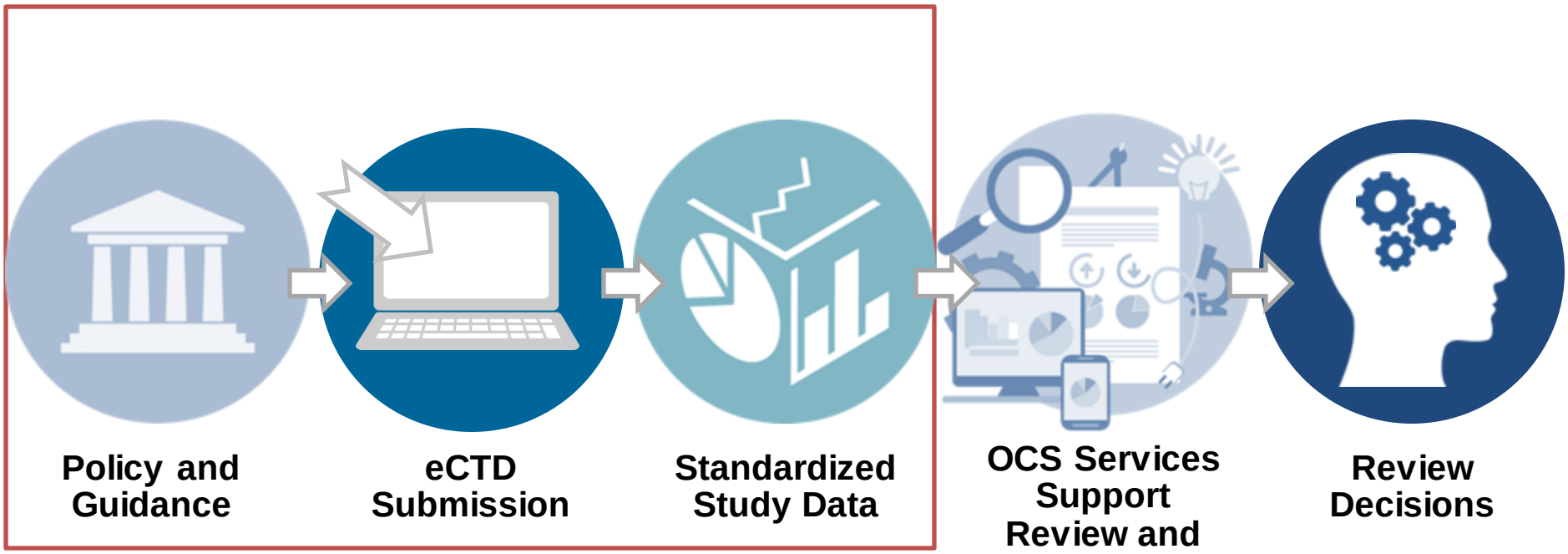


- Provide CDER reviewers solutions that improve the scientific review process by integrating data, tools, and training
- Drives modernization of CDER's scientific review process through the implementation of tools, services, and training to enable reviewers to apply their expertise to information

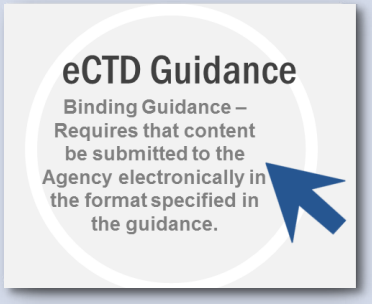
OCS Impacts to Regulatory Review

- Provides services for CDER reviewer use that validate data and provide data exploration and exploratory analyses
- Develops and support tools for CDER reviewer use that support data visualization and safety signal detection
- Develops and maintains OCS Data Central which loads validated data to different tools for use by CDER reviewers and OCS services
- Smart Template allows reviewer to input reviews that they are searchable across applications

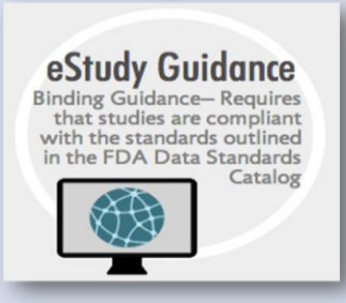
From Data to Review



Data Standards Resources



FDA *binding guidance and deadlines* for electronic submissions



FDA *binding guidance and deadlines* for submission of standardized study data

Lists *what* data standards are supported and required by FDA in electronic submissions

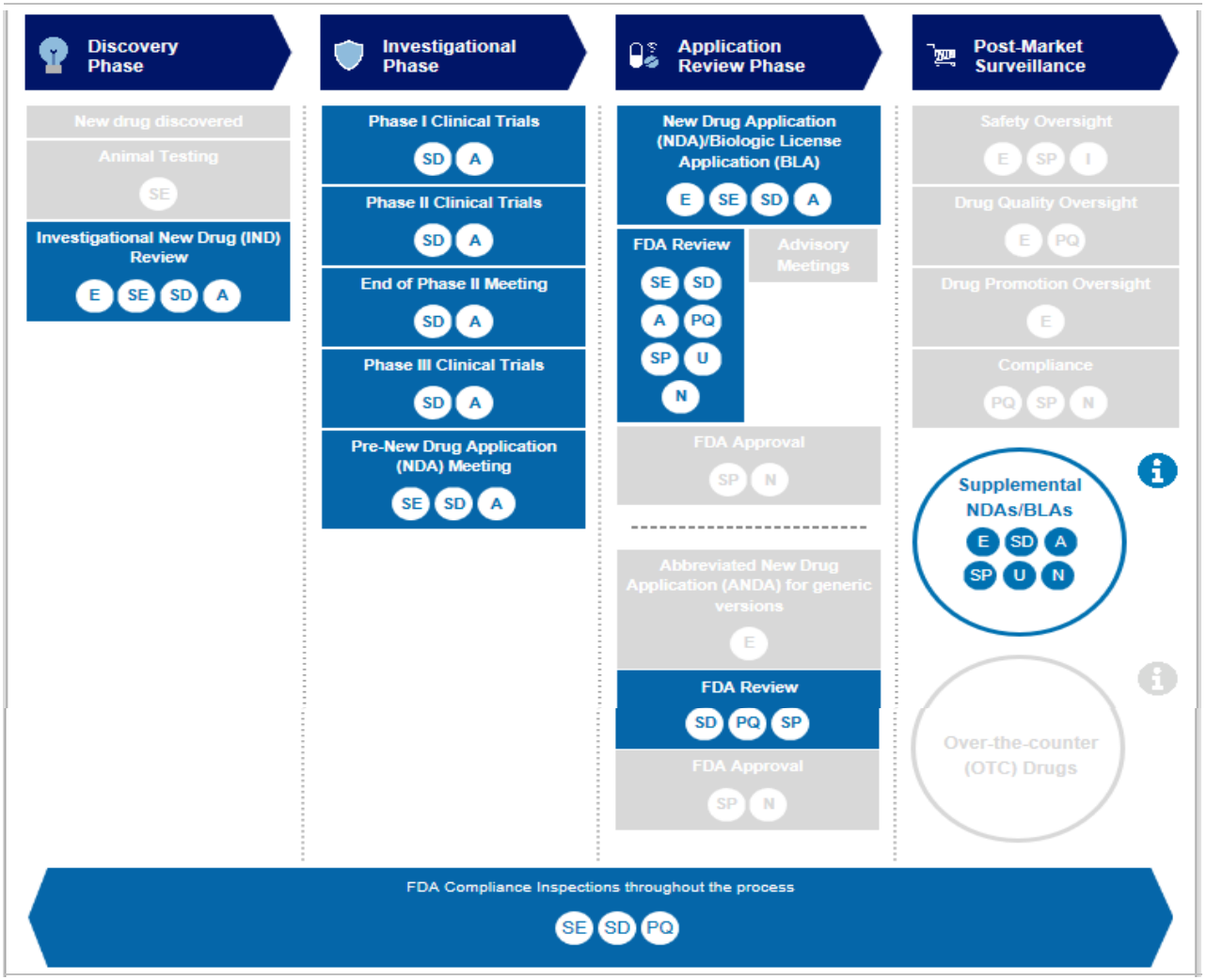
Describes *how* industry should submit standardized study data in NDAs, BLAs, INDs and ANDAs

Data Standards Resources

- Data standards help FDA receive and review submissions more efficiently and effectively

Interactive display to select from:

- All [All]
- PQ/CMC [PQ]
- eCTD [E]
- SPL [SP]
- SEND [SE]
- ICSR [I]
- SDTM [SD]
- UNII [U]
- ADaM [A]
- NDC/MPID [N]



https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm531293.htm

CDISC Collaborations: Face to Face (F2F)

- CDISC SEND Team and CDER Offices work together to produce a week-long F2F meeting every Spring and Fall
- CDISC SEND Working Groups meet throughout week to discuss updates/changes to make with various domains
- FDA public meeting on Wednesday morning describing updates from the Agency and topics of interest
- Collaborative environment intended to bridge gap between industry and regulatory agencies

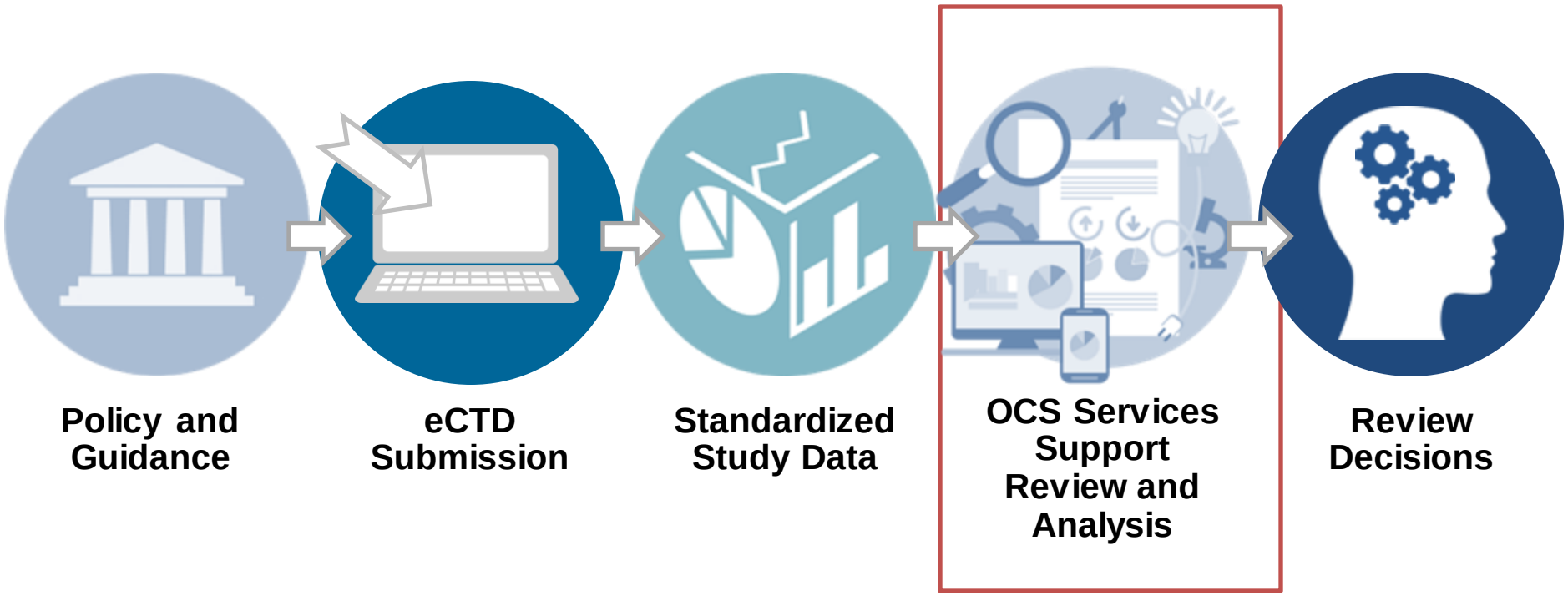
CDISC Collaborations: Proof of Concepts

- CDISC creates datasets to confirm that study data can be presented in domains
  - Enhances representation of a study compared to examples in IG
  - Informs tool development for industry
- FDA evaluates forthcoming CDISC-SEND standards
  - Enables FDA to receive example study data that supports adoption decisions
  - Supports development of CDER OCS tools and reviewer services
- Completed the Developmental and Reproductive Toxicology (DART) POC in July 2019

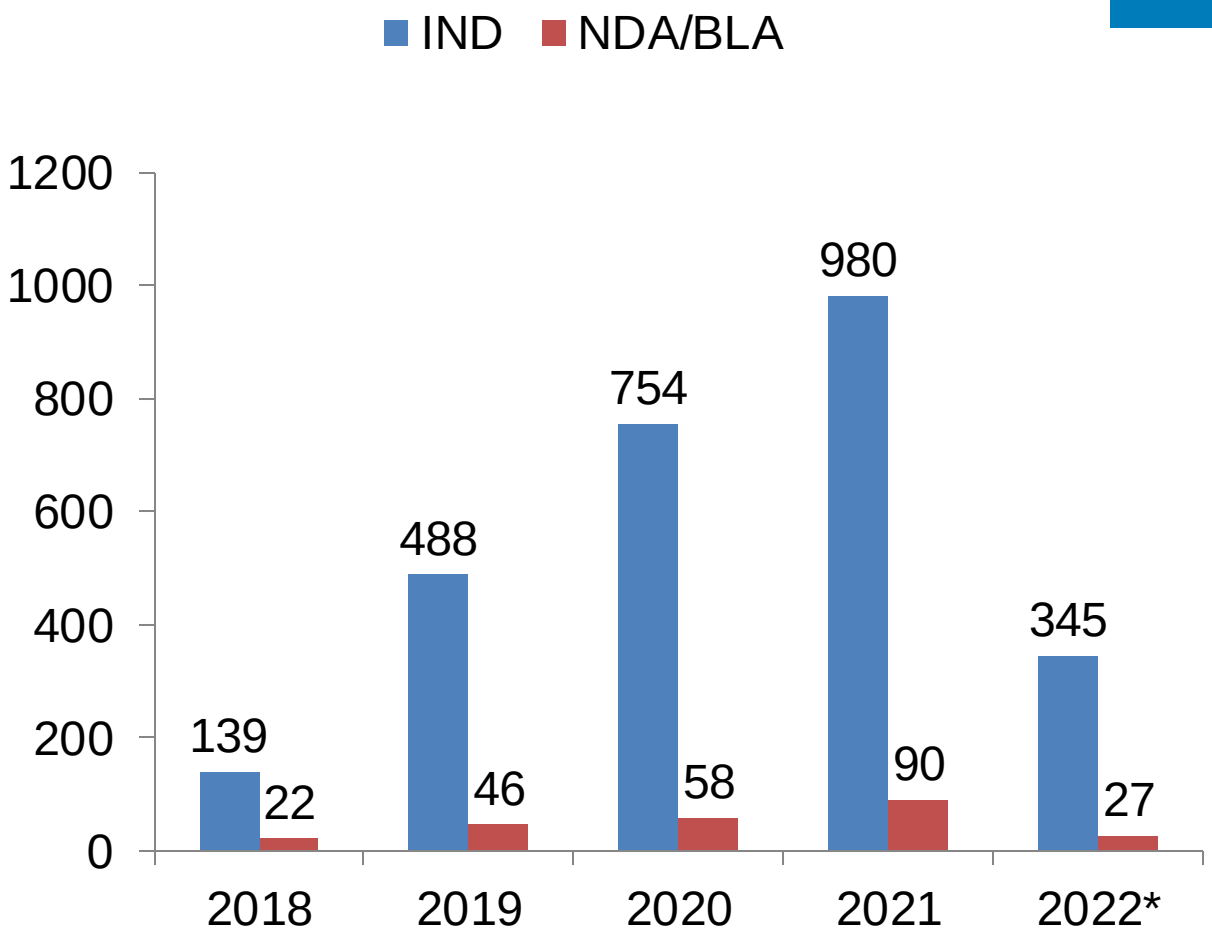
CDISC Collaborations: Fit for Use (FFU) Pilots

- FDA publishes Federal Register Notice
- FFU pilot uses “real” study data
- Intent to share anonymized datasets as public resource
- Informs standards development, future release(s) of IGs
  - Determine major problems to ensure these are prioritized for correction in future versions
  - Communicate additional adjustments to study data TCG to help ensure current SEND submissions are more useful
- Completed DART pilot in May 2021 with results posted May 2022

From Data to Review



Applications Received with SEND



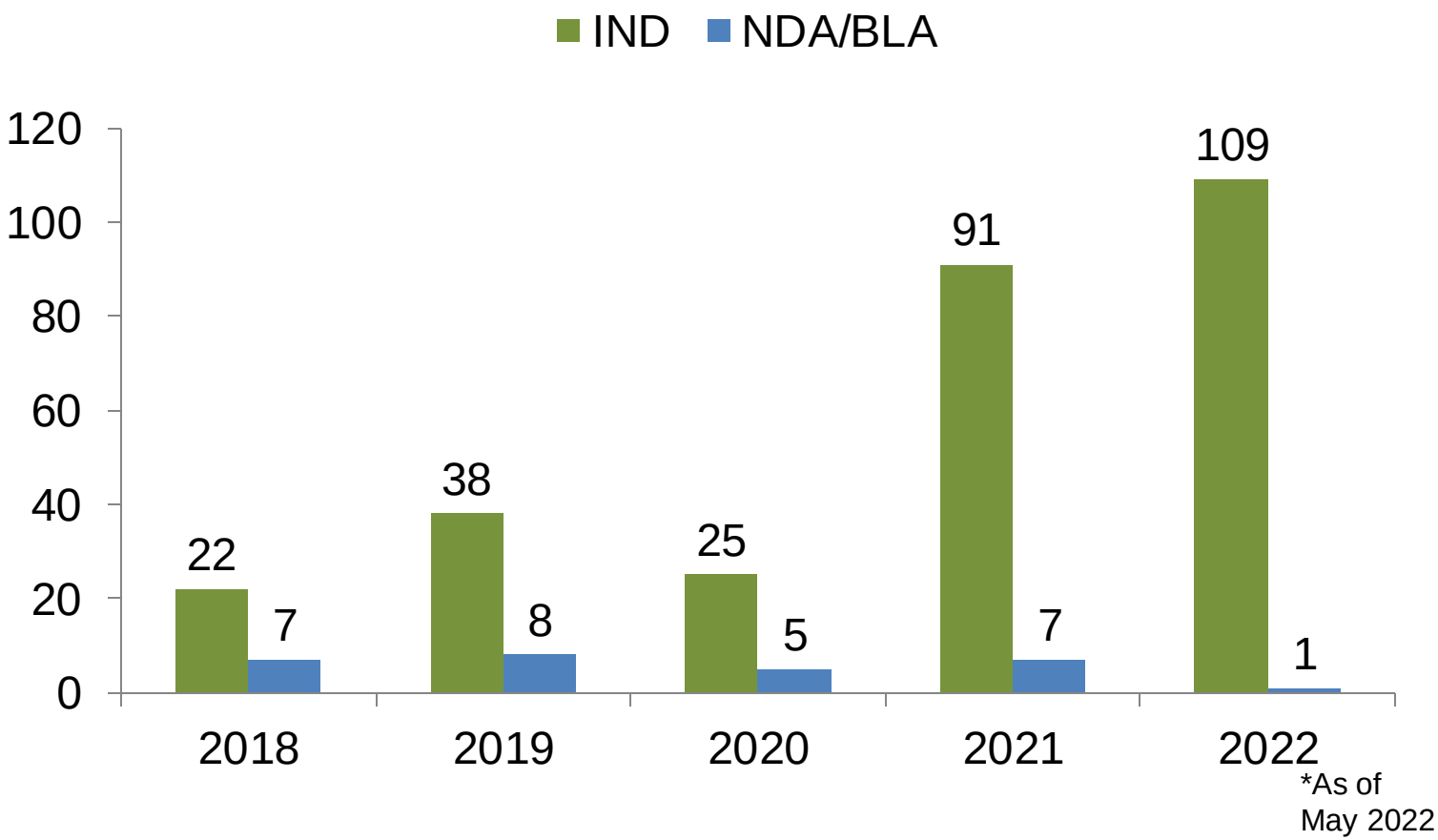
Number of Applications Per Calendar Year

The types of studies included Repeat-Dose Toxicity, Single-Dose Toxicity, and Carcinogenicity, Cardiovascular Safety Pharm, and Respiratory Safety Pharm.

OCS Nonclinical Services

- Nonclinical Services are offered by OCS to all Pharm/Tox reviewers for their applications.
- Recently updated to reach more reviewers and studies
- Services may include:
  - A preliminary data fitness assessment showing reviewers issues that may impact use of data
  - Prepare analysis and demographics outputs common in reviews
  - FDA tool demonstrations with studies requested for services
  - Providing data fitness reports to sponsors demonstrating what could be improved in future submissions

OCS Nonclinical Services for Review



Calendar Year Count, Nonclinical Services provided when:

- Study loaded into FDA Tools
- One or two studies per application generally reviewed

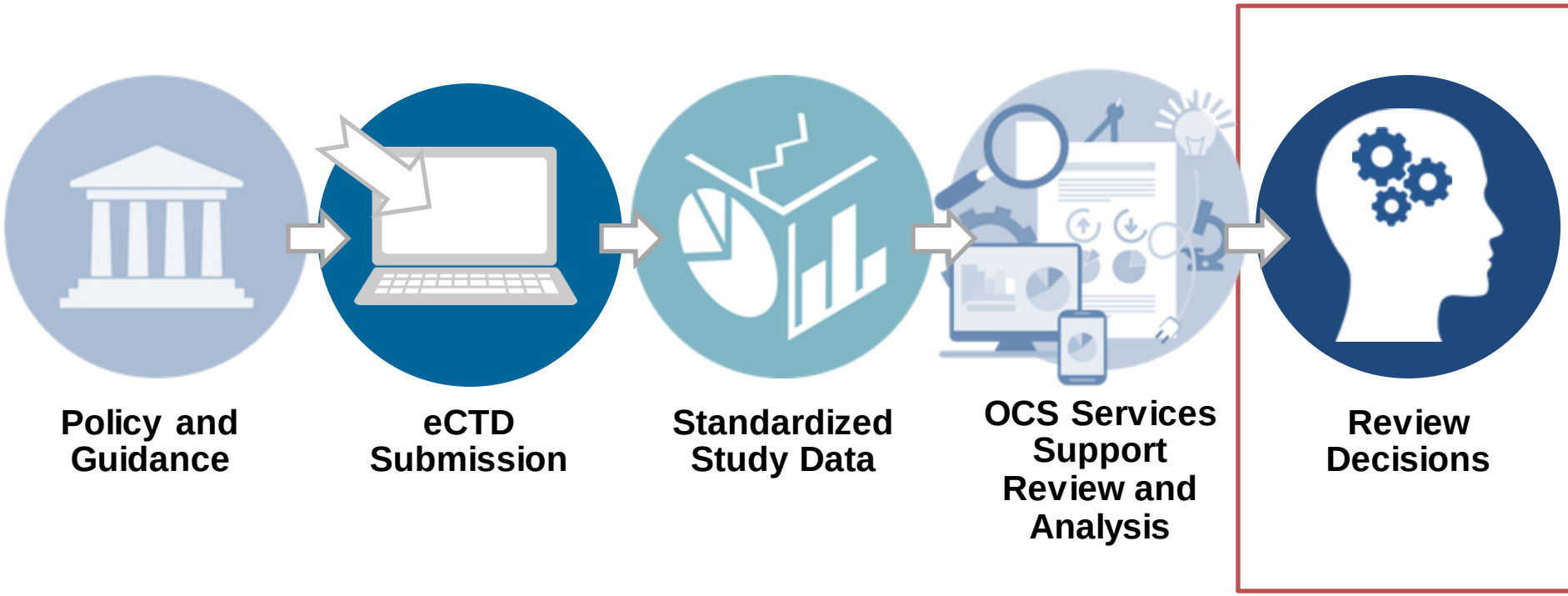
Data Quality Assessments

- Consists of automated and manual checks of SEND datasets and associated files
- Highlights data quality and usability issues
- Provides data quality reports for sponsor consumption to better understand gaps
- Items covered in this assessment include but not limited to:
  - Mapping of submitted SEND datasets to standard
  - Comparison of SEND datasets with study report
  - Overall assessment of submission quality
  - Identification of data that may not be used, or that can be used only with caveats, due to quality issues
  - Provides details of key data quality and usability issues, showing the impacts to review capabilities

Common SEND Data Quality Issues

- Common issues identified during OCS Nonclinical Services:
  - Define.xml: Submission Files, File Naming, StudyName Attribute
  - ISO8601 Values: Dates, Dates/Times, Durations
  - Standardization of Timing Variables: VISITDY/--NOMDY, timing relative to dose, and unscheduled tests
  - Categorical Results: LBSTRESN
  - Codes and Abbreviations: Impact on reviewers when undefined
- For more information, please visit: https://www.fda.gov/drugs/news-events-human-drugs/cder-send-common-issues-and-policy-update-06152020-06152020

From Data to Review



Additional External Collaborations

- FDA collaborates across stakeholder communities to promote dataset quality and increase cross-study analysis capabilities
- PHUSE and BioCelerate consortium offer potential to positively impact the use of CDISC standards across industry

PHUSE Initiatives

- Nonclinical Topics Working Group provides many opportunities for collaboration, including but not limited to:
  - Data Consistency: SEND datasets and the Study Report
  - SEND Dataset QC Best Practices
  - Nonclinical Study Data Reviewers Guide
- All collaborations within Nonclinical Topics show value in standardizing dataset package practices and use across industry

FDA-BioCelerate Collaboration

- Highlights need for SEND harmonization across studies to enable cross-study analyses
  - First manuscript describes need for harmonization: https://www.sciencedirect.com/science/article/pii/S0273230019303060X
  - Second manuscript provides use case and recommendations for harmonization: https://pubs.acs.org/doi/10.1021/acs.chemrestox.0c00317

Cross-Study Analysis Opportunities

- Consistent population of variables relevant to interest (e.g., PCLASS) may help to look at common effects across a drug class
- Standardized reporting practices may help FDA and Sponsors have more precise AGE calculations, which may allow for more meaningful evaluations across studies
  - Ex: AGEU consistently represented as DAYS instead of WEEKS
- Controlled terminology may allow for meaningful comparison on a given term to evaluate findings across studies

Cross-Study Analysis Priorities

- Standardizing terms and/or units within key variables
- Where possible, use or create Controlled Terminology necessary to promote standardized responses
- Consistent population of variables utilizing consistent terminology of interest that will allow for (e.g., PCLASS, UNII, etc.)

Conclusion

- OCS contributes to regulatory review through data quality and tool support for CDER reviewers
- CDISC collaborations promote understanding of data standards across industry
- Collaborations such as PHUSE and BioCelerate critical to adoption and consistent use of data standards
- Cross-study analysis may prove useful for reviewers but only if values populated in consistent way across studies

Thank You!

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CDER FDA


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