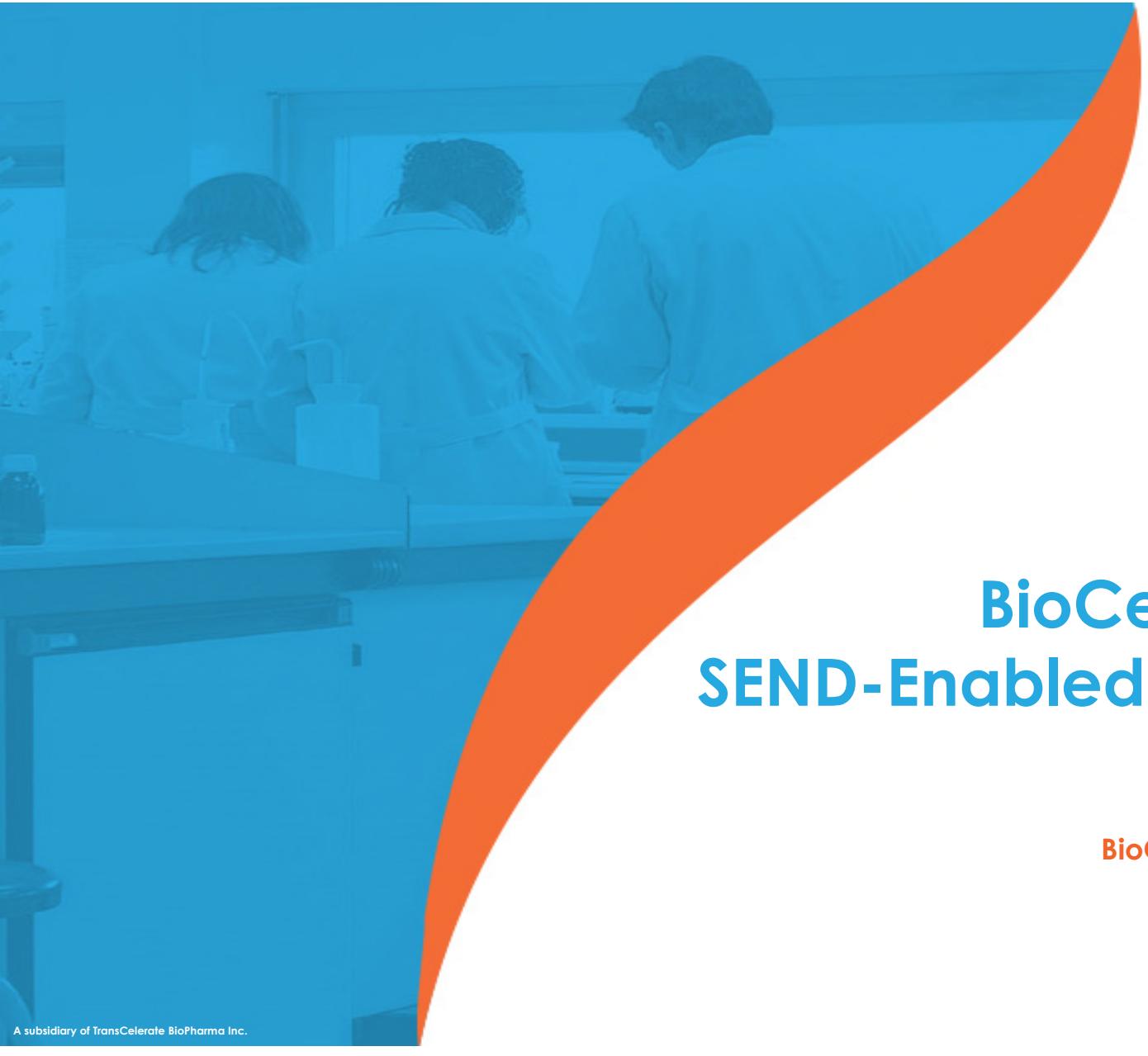
Objectives for this Workshop

- ❑ Discuss challenges and opportunities for the use of SEND in cross-study analysis
- ❑ Identify priorities that must be addressed to enable high value cross-study analysis use cases
- ❑ Summarize and discuss practical next steps



BioCelerate

A subsidiary of **TransCelerate BioPharma, Inc.**

BioCelerate Assessment of SEND-Enabled Cross-Study Analysis

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BioCelerate Nonclinical Study Optimization Leader

June 11, 2019
PhUSE Computational Science Symposium
Silver Spring, MD, USA

BioCelerate has undertaken a new initiative to examine barriers to the use of SEND for cross-study analysis

BioCelerate Goals

- Improve **data-driven decision making**
- Broaden industry **knowledge base**
- Improve **quality** of study execution
- Enable new process and cost **efficiencies**

SEND Implementation for Study Analysis

The **CDISC SEND** format is growing in adoption across industry, but variability in its use and implementation results in inconsistent study data packages and reports, making **cross-study analyses** difficult. Initial output includes:

- Examination of **implementation variabilities** for CDISC SEND and **challenges** in the use of SEND data packages to facilitate cross-study comparisons

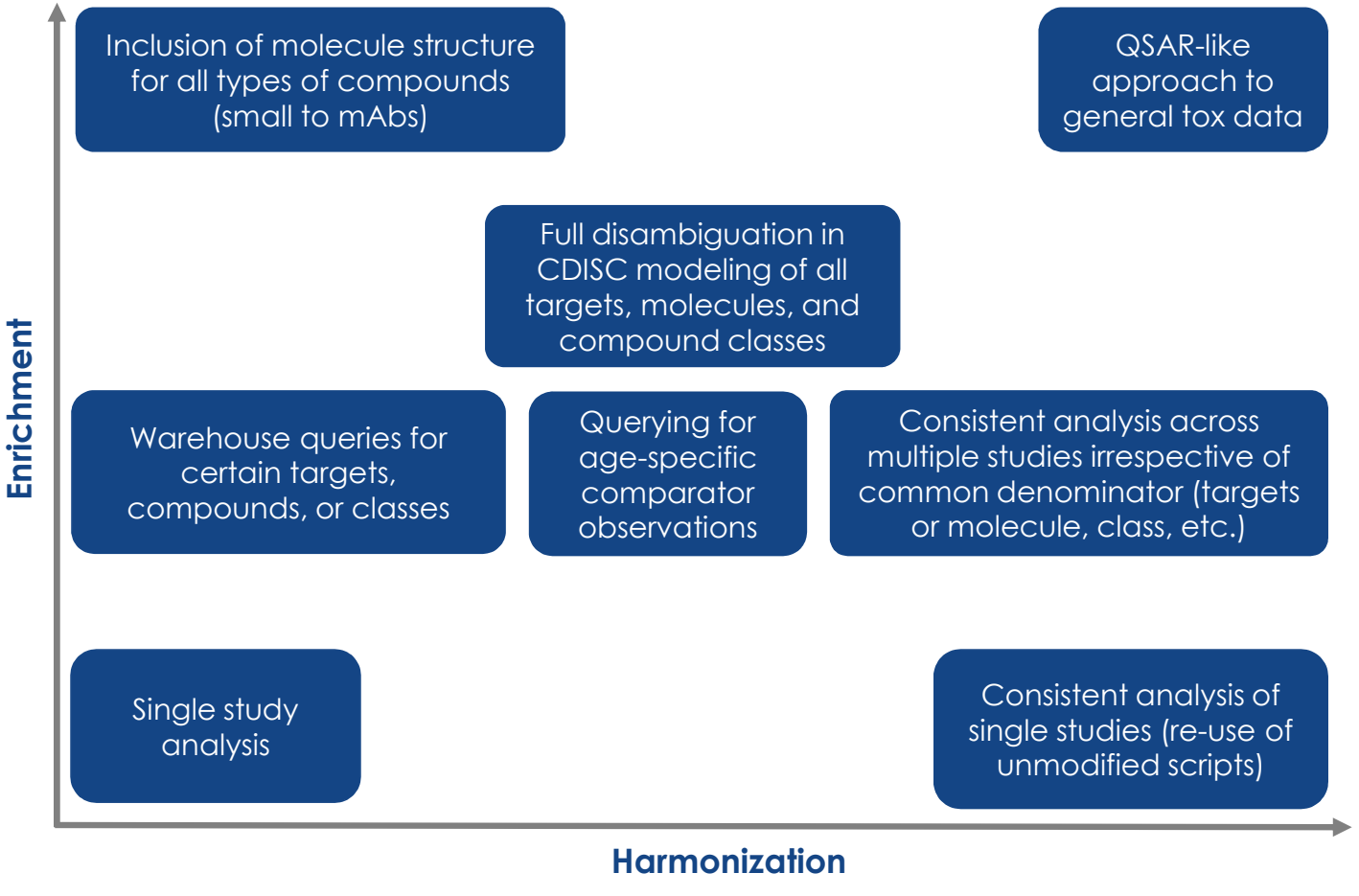
Several analysis use cases may be enabled using SEND datasets compiled across various sources

Cross-Study Analysis Use Case Examples

Understanding the **toxicity profile** for all studies performed for one compound, as well as understanding the **effects of longer exposure**	Understanding **off-target toxicity** / multiple compounds binding to the same target as well as understanding **trends for a class** of compounds or MOAs	Understanding the **effects of vehicles** that might be used on different studies	Understanding **frequency of rare and incidental findings** from background control studies	Enabling application of SEND data within **QSAR**
58% Respondents who consider this a #1 priority use case	**31%** Respondents who consider this a #1 priority use case		**11%** Respondents who consider this a #1 priority use case	

** % response totals from polls fielded across two webinar sessions on March 5, 2019 (10 AM ET & 8 PM ET). Registrants of the webinars voluntarily self-identified as either a Research Sponsor/BioPharma (45%), Tech Vendor (16%), CRO (12%), Other Service Provider/Vendor (11%), Health Authority (9%), or Industry Group/Consortium (7%). Registrant geographies included North America (64%), Asia (26%), Europe (9%), and Central/South America (1%).*

Two dimensions of *harmonization* and *enrichment* can support new applications of SEND for cross-study analysis



Harmonization

Reaching greater consistency in approach to the usage, format, and terminology for key SEND variables

Enrichment

Supplementing SEND datasets with additional meaningful information which may not be required for single study analysis

Thank you

Visit our website for more information:

http://www.transceleratebiopharmainc.com/biocelerate/

TransCelerate BIOPHARMA INC.

BioCelerate

U.S. FOOD & DRUG ADMINISTRATION

CROSS STUDY ANALYSES AT THE FDA

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

OVERVIEW

Types of Cross Study Analyses at the FDA

Cross Study Analysis Examples

1. Investigating a Clinical Finding within a Drug Class
2. Investigating a Nonclinical Finding within a Drug Class
3. Exploring a Possible Cause of a Nonclinical Study Finding
4. Predicting a Clinical Adverse Event (AE) for a Drug Class with Nonclinical Data
5. Establishing a Drug Class Profile

TYPES OF CROSS STUDY ANALYSES AT THE FDA

Drug class profiles

- Provides an overview of the drug class & helps identify common toxicities
- All applications in a drug class – looking at study reports & pharm/tox reviews
- All studies for each application
- Updated periodically

Exploring finding(s) of concern with a specific drug product or a drug class

- Toxicity of concern identified in nonclinical or clinical studies
- Analyses conducted for a wide variety of reasons
  - Identify duration of treatment required before toxicity occurs
  - Establish progress of the toxicity over time
  - Establish an exposure margin
  - Determine the mechanism of action (MOA)
  - Determine if the clinical AE can be predicted by nonclinical data
  - Help determine what additional nonclinical studies might be useful to explore a finding
- Multiple studies across one application or all applications in a drug class (can be extensive)
- One or multiple species

1 Investigating a Clinical Finding within a Drug Class

BACKGROUND

- Clinical Serious Averse Event (SAE) identified in clinical trial with several drugs in the same drug class spanning multiple therapeutic areas
- Mechanism for SAE unknown

OBJECTIVES

- Determine if nonclinical studies can predict the clinical risk for developing the SAE
- Establish if the SAE is limited to certain indication populations
- Define an acceptable safety margin to inform dose selection

1 Clinical Finding within a Drug Class: Cross Study Analysis Search

- All applications for the drug class (>100 IND applications)
- All repeat dose toxicology studies (1-month, 3-month, and/or 9-month) for one non-rodent species
- Specific hematology parameter changes (value changes below a certain level) – establish a LOAEL & NOAEL
- Mortality & cause (if related to hematology change)
- Possible treatment-related dosing holiday during the study
- Chemical structure - different modifications – classified based in structure
- Clinical reports for SAE MedRA term
- Drug indication
- BSA, not PK data, used to calculate safety margin

2 Investigating a Nonclinical Finding within a Drug Class

BACKGROUND

- Severe skin finding causing limb amputation or euthanasia in one non-rodent species with several drug products in the same class
- Finding occurred at clinically relevant exposures
- Potentially clinically relevant finding

OBJECTIVES

- Determine if finding is limited to one species
- Establish at-risk anatomical locations and reversibility of finding
- Identify any associated prodromal clinical signs or clinical chemistry changes that are monitorable in human subjects
- Establish possible MOA

2 Nonclinical Finding within a Drug Class: Cross Study Analysis Search

- All applications for the drug class (>10 IND applications)
- All non-rodent toxicology studies for each application
- Microscopic & macroscopic findings in skin (severity, location & dose- and time-dependence)
- Clinical signs (e.g., swelling)
- Any associated clinical chemistry changes
- Reversibility of findings
- Exposure (AUC and Cmax) at which findings occurred
- Selectivity (Ki and IC50) for target enzyme compared to off-target enzyme activity
- Clinical exposure (AUC and Cmax) at the maximum human recommended dose

3 Exploring Possible Cause of a Nonclinical Study Finding

BACKGROUND

- Microscopic non-neoplastic change (ranging from minimal to marked) in Organ A in the carcinogenicity study at all dose levels
- Finding observed in other toxicology studies
- Possibly clinically relevant & difficult to monitor clinically
- Sponsor attributed change to treatment-related changes in associated organs (Organs B & C)
- Organ A expresses targeted receptor – although function not determined

OBJECTIVES

- Determine if the microscopic change in Organ A is associated with changes in the other organs in repeat dose toxicology studies
- Establish possible temporal correlation between any changes across studies; do changes in Organs B & C precede changes in Organ A
- Determined if microscopic changes in Organs A, B & C occurred in any other species

3 Exploring a Nonclinical Finding with a Drug Product: Cross Study Analysis Search

- One application
- All repeat dose toxicology and carcinogenicity studies
- Microscopic change and severity of finding in Organ A & microscopic changes in Organs B and C in each animal across all toxicology studies
  - Development of changes over time
  - Determine if the changes in Organ A correlate to changes in Organs B & C in individual animals
- Reversibility of changes
- Exposure (AUC) at which changes in Organ A occurred

4 Predicting a Clinical AE for a Drug Class with Nonclinical Data

BACKGROUND

- Clinical AE for a drug class is difficult to predict from nonclinical studies
- Clinical AE limits dose
- Important to be able to predict AE for long acting formulations (i.e., administered 1X/week)

OBJECTIVES

- Determine if there is a nonclinical treatment-related change that consistently correlates with the clinical AE

4 Predicting a Clinical AE: Cross Study Analysis Search

- >10 IND applications
- Initial search of each application
  - Adverse effects in all pivotal safety pharmacology and repeat dose studies for rodents and non-rodents
    - Safety pharmacology studies: neurological, pulmonary, cardiovascular, and GI changes
    - Repeat dose studies: clinical signs, body weight, food consumption, clinical chemistry, hematology, organ weights, and macroscopic and microscopic findings (incidence, dose-dependence, and severity)
    - Dose and PK data (Cmax and AUC) at LOAEL and NOAEL for each notable change
  - Clinical dose and PK data at LOAEL and NOAEL for clinical AE for each application
  - Chemical structure
  - Clinical indication (two different indications)
- Second, more directed search of each application
  - Daily/weekly food consumption across the study at all doses – all rodent repeat dose studies
  - PK data (Cmax and AUC) at each dose

5 Establishing a Drug Class Profile

- Look through all applications in the drug class - study reports and completed reviews
- Findings in all pivotal repeat-dose toxicity studies for all species evaluated
  - Target organs (weight, macroscopic, and/or microscopic changes)
  - Meaningful clinical chemistry, hematology, and urinalysis changes
  - Changes in biomarkers (kidney, bone, etc.), if evaluated
  - ADA development, if evaluated
  - Body weight changes
  - Mortality
  - Clinical signs (e.g., convulsions)
- Tumor findings in carcinogenicity studies
- Possibly clinical AEs
- Target receptor binding, pharmacodynamic activity & adverse reproductive and developmental changes – beyond the scope of SEND

THANK YOU

Todd Bourcier, PhD

Jessica Hawes, PhD

Jeffrey Quinn, PhD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Up Next: Table Breakout Discussion

Activity	Allotment
Breakout overview and use case assignment per table	5 minutes
Discuss at your table: (1) Which parameters are important to be able to search across studies to enable your use case (max 10)? (2) Which of these parameters are a *top priority* (top 1-2)? Why? (3) Which of these parameters would be the *most challenging* to harmonize?	20 minutes
Document / write-up outcomes of discussion in preparation for full group readout	5 minutes

Table Breakout Discussion

Use Cases

A. Understanding the **toxicity profile** for all studies performed for one compound, as well as understanding the **effects of longer exposure**

B. Understanding **off-target toxicity** / multiple compounds binding to the same target as well as understanding **trends for a class** of compounds or MOAs

C. Understanding the **effects of vehicles** that might be used on different studies

D. Understanding **frequency of rare and incidental findings** from background control studies

E. Enabling application of SEND data within **QSAR**

1. Investigating a Clinical Finding within a Drug Class
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Example: 'Effects of Vehicles' Use Case

Understanding the **effects of vehicles** that might be used on different studies

(1) Which parameters are important to be able to search across studies to enable your use case?

(1) Vehicle description in TS with % specified for each component of the vehicle

(2) Exposure duration (--DY)

(3) Dose level subject received EX

(4) MI findings, CL (feces obs), LB

(2) Which of these parameters are a *top priority*? Why?

Items 1-3 above and feces obs (to set maximum acceptable dose levels)

(3) Which of these parameters would be the *most challenging* to harmonize?

Vehicle and CL

Table Readout

Use Cases

A. Understanding the **toxicity profile** for all studies performed for one compound, as well as understanding the **effects of longer exposure**

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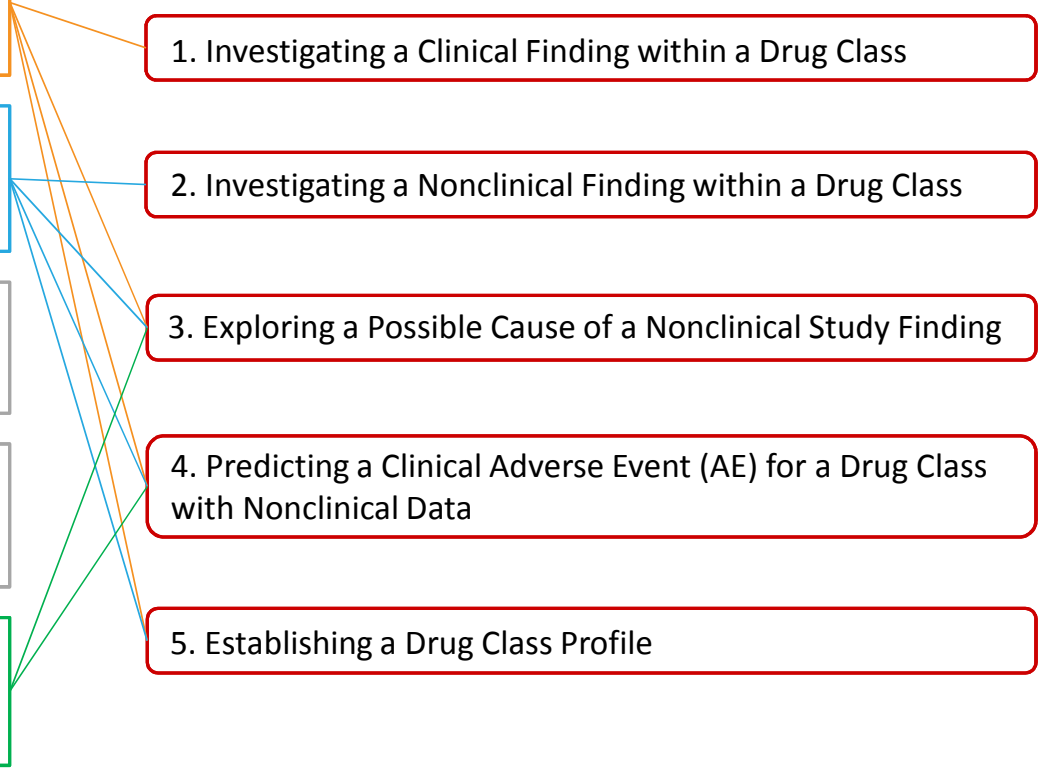

Table Breakout Questions

(1) Which parameters are important to be able to search across studies to enable your use case (maximum 10)?

(2) Which of these parameters are a *top priority* (top 1-2)? Why?

(3) Which of these parameters would be the *most challenging* to harmonize?