Treatment Vehicles in SEND

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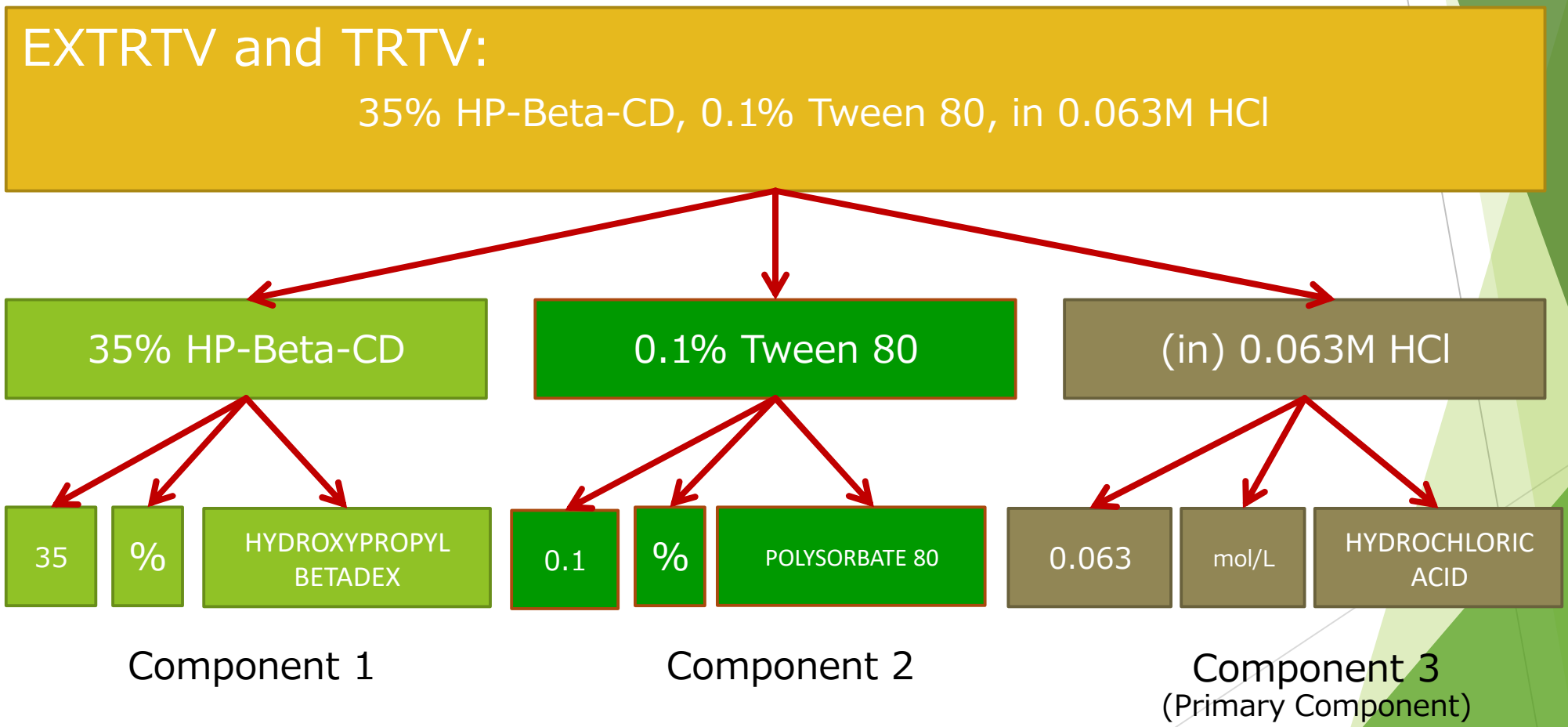
Topics

- What is a vehicle?
- What is meant by a structured vehicle?
- Why is structuring vehicle descriptions important?
- Concept development
  - Evaluated Prototypes
  - PHUSE deliverables
- Solution in SENDIG v4.0
- Benefits of Full Scope
- Acknowledgments

What is a vehicle?

- Toxicology studies typically include a vehicle (also called a carrier) mixed with a test article to facilitate:
  - Reproducible and accurate dose administration
  - Appropriate solubility, stability, and systemic exposure of the test article
  - Avoids exacerbating or obscuring effects of the test article
- The vehicle is typically administered to a control group on the study without the test article.

Structuring a Vehicle Description



Why is structuring vehicle descriptions important?

- Ideally, animals selected from historical control groups to be used in a Virtual Control Group on a new study will have similar vehicles to that planned on the new study.
- Historical control data incidents and ranges:
  - When interpreting a study with a notable finding in only one of 4 animals in a mid-dose level, knowing the natural incidents of such a finding is helpful.
  - Matching similar administration levels of vehicle components is ideal.
- When planning new toxicology studies, the effects of similar vehicle mixtures is helpful to consider.

SOP referenced by EMA's Draft Qualification Opinion on VCGs

- https://www.ema.europa.eu/en/documents/other/draft-qualification-opinion-virtual-control-groups-vcg-replace-concurrent-control-groups-ccg-rat-non-glp-dose-range-finding-drf-studies_en.pdf

5.2. Data Standard and Curation

As described above, the expected data format is SEND. If there are no controlled terminologies for specific parameters or terms (e.g. harmonized description of vehicle composition) the study director or data manager may use in-house terminologies which need to be documented and archived according to GLP requirements.

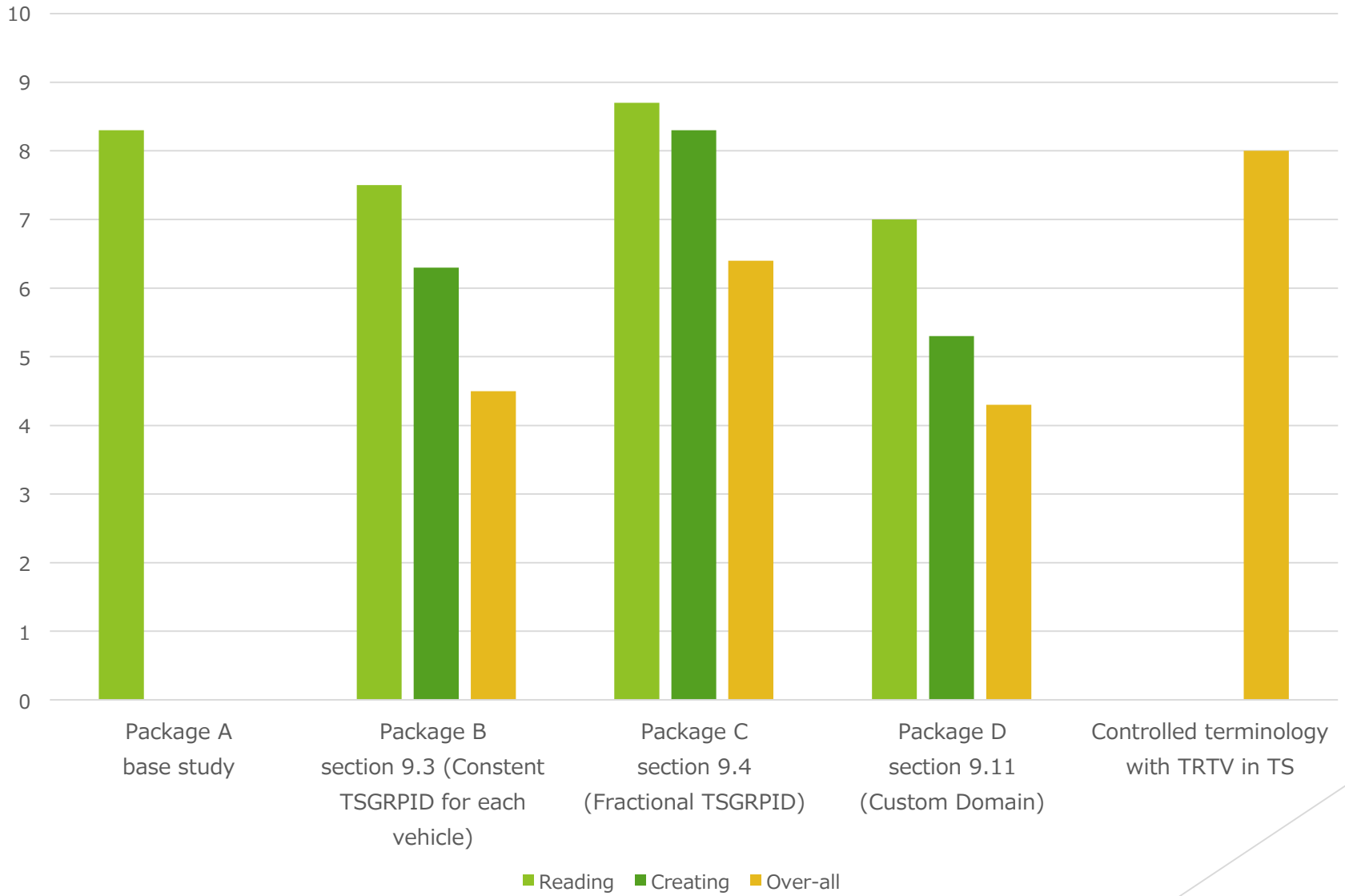
6.3. Required animal number in VCGs

If the pool of animals in the matched HCD is higher than the desired control group size, animals for the VCG should be sampled randomly from this pool. However, in case the number of animals in the selected HCD for constructing VCGs is smaller than the desired control group size, the study director may relax the matching criteria to expand the selected HCD pool size (see section 6.2) and document the criteria and scientific rationale in the protocol. Examples may include QD and BID studies, studies with similar vehicles, or extending the time windows beyond 5 years in the past.

Concept Development

1. The need was identified by BioCelerate
2. Launched PHUSE Project to develop requirements and develop concept
3. Prepared 9 alternatives
4. Discussed with CDISC SEND and CDISC Global Governance Group
5. Selected 3 for deeper evaluation
    1. Created datasets
    2. Public Survey (Pilot)
        1. Read the datasets
        2. Create similar datasets
        3. Best overall approach
6. Created script to determine potential success extracting meaning from TRTV
7. Poster: Recommendations for Exchanging Vehicle details using SENDIG v3.1 https://www.lexjansen.com/css-us/2021/POS_PP06.pdf

Evaluated Prototypes



PHUSE deliverables

1. Asked CDISC to consider project for the next SENDIG v3.2(?)
   → FULL SCOPE: To store each component (Concentration, Unit, Name) into separate variables or parameters.
   → MINIMUM SCOPE: To establish controlled terminology for vehicle component names for use within existing TRTV variable/parameter.

- Develop R script parseTRTV, available in PHUSE github repository, to extract vehicle components and concentrations
  - Frank Bringezu as part of VICT3R evaluated LLM parsing with Claude, ChatGPT(many version), DeepSeek and abandoned them due to incomplete dissection of components and errors in standardization. Using a parseTRTV based approach he has now achieved successfully parsing all 3028 vehicle records he attempted. The VICT3R DB is now already using the SEND structured vehicle description published in the SEND 4.0 draft.

Solution selected for SENDIG v4.0 – Appendix A1

- Format
- The string for the Treatment Vehicle Structured Description has the following overall format, where at least 1 component description (UNII display name) is required and the formulation attribute list is permissible:
- <component 1 description> | <component 2 description> | <component n description> | {<formulation attribute list>}
- where each <component n description> has the following format, where the component name is required and the component attribute list (e.g., concentration) is permissible:
- <component name> {<component attribute list>}
- and each <component attribute list> and the <formulation attribute list> are permissible lists of name-value pairs that describe the component, formatted as follows:
- {<attribute 1 name>: <attribute 1 value> <permissible Units for Attribute 1>; <attribute 2 name>: <attribute 2 value> <permissible Units for Attribute 2>; <attribute n name>: <attribute n value> < permissible Units for Attribute n> }

Example:

METHYLCELLULOSE (400 MPA.S) {Concentration:0.5 %(w/v); UNII:O0GN6F9b2y; Molar Mass:454.513 g/mol}|WATER {UNII:059QF0KO0R}

Benefits of Full Scope

- TRTVDESC enables structured information to be exchanged however it packs a full table into 1 field
- Answering common questions like these are much simpler if stored in a table structure:
  - List all the studies with vehicle component Y with a concentration > 10%
  - List all the animal that were administered at least 1 dose that included component X at a level of 2 mg/kg or higher.
- If SEND adopts a table structure for TRTVDESC, scripts leveraging vehicle structured information will be more likely to run in multiple environments with minimal adjustments.

Acknowledgements

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- Jennifer Feldmann – simplifying comments
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- PHUSE CSS Nonclinical Topics Leadership