Lessons learned:
The SENDIG-DART FDA Fit-For-Use pilot

APR 2023

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Agenda

- SENDIG-DART FFU by the Numbers
- FDA Reviewer Feedback
- New FDA Validator Rules
- SENDIG-DART: Why and When

SENDIG-DART FFU by the Numbers

The SENDIG-DART 1.1 Fit-For-Use (FFU) pilot

- 2020 (22-Oct): Federal Register Notice issued (Docket No. FDA–2020–N–1806)
- 2021 (26-Feb): Requests to FDA for participation
- 2021 (30-Apr): Submission deadline for SEND packages
- 2021 (06-Jul): Participants received FDA feedback

Sponsor	1	2	3	4	5	6
Species (Route)	Rat (oral gavage)				Rat (Inhalation with IV)	Rabbit (SC)
Study type	6 Embryo-Fetal Development Studies GESTATION phase only					

Submission packages included SEND datasets, define.xml files, nSDRG, study report and protocol information

Number of SEND datasets submitted

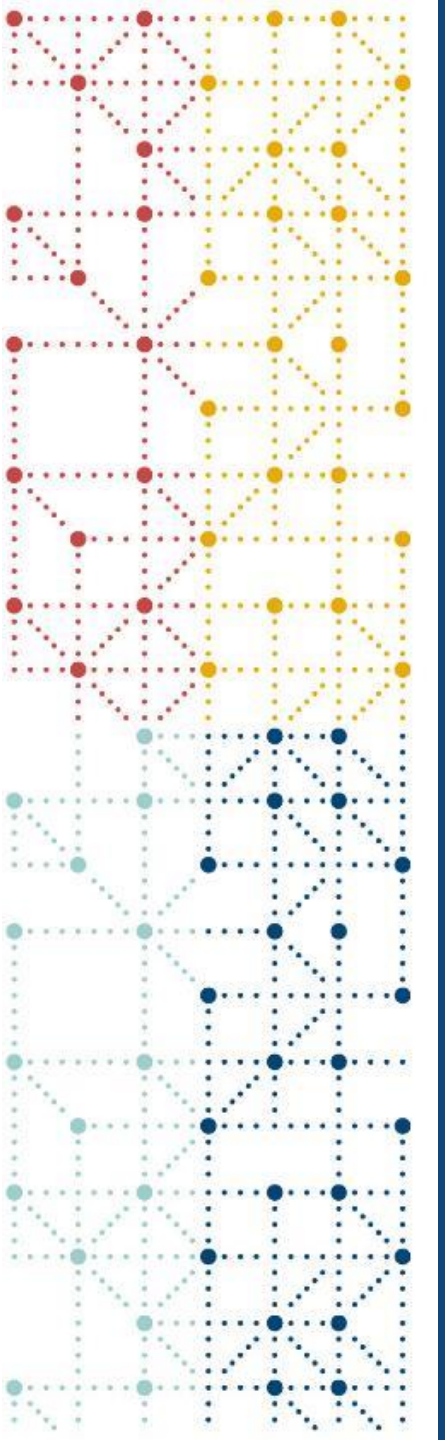
New Domains

Existing Domains (new variables or metadata changes)

POOLDEF and --SUPP datasets submitted not shown in list below

Dataset Name	Dataset Label	Domain Class	Datasets Submitted
TA	Trial Arms	Trial Design	6
TE	Trial Elements	Trial Design	6
TS	Trial Summary	Trial Design	6
TX	Trial Sets	Trial Design	6
TP	***Trial Repro Paths***	***Trial Design***	6
TT	***Trial Repro Stages***	***Trial Design***	6
CO	**Comments**	**Special-Purpose**	5
DM	**Demographics**	**Special-Purpose**	6
SE	Subject Elements	Special-Purpose	6
SJ	***Subject Repro Stages***	***Special-Purpose***	6
EX	**Exposure**	**Interventions**	6
DS	**Disposition**	**Events**	6

Dataset Name	Dataset Label	Domain Class	Datasets Submitted
BG	**Body Weight Gain**	**Findings**	2
BW	**Body Weight**	**Findings**	6
CL	**Clinical Observations**	**Findings**	6
DD	**Death Diagnosis and Details**	**Findings**	1
FW	**Food and Water Consumption**	**Findings**	6
LB	**Laboratory Test Results**	**Findings**	2
MA	**Macroscopic Observations**	**Findings**	5
OM	**Organ Measurements**	**Findings**	5
PC	**Pharmacokinetic Concentrations**	**Findings**	4
PP	**Pharmacokinetic Parameters**	**Findings**	4
PY	***Nonclinical Pregnancy Results***	***Findings***	6
IC	***Implantation Classification***	***Findings***	6
FM	***Fetal Measurements***	***Findings***	6
FX	***Fetal Pathology Findings***	***Findings***	6



FDA Reviewer Feedback

Define.xml

nSDRG

SENDIG-DART: Trial Design

SENDIG-DART: New Domains

SENDIG-DART: New Variables

SENDIG-DART: Existing Domains

Issues noted with Define.xml (1/2)

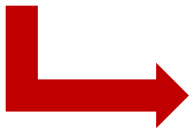
- ~57 items identified in Data Fitness Summary provided by FDA; not following define-xml 2.0 standard criteria / references
  - There is a perceived knowledge gap in the SENDIG-DART v1.1 audience pertaining to define-xml specifications implementation. This may be attributed to a lack of mature tools, templates, and business process readiness.

- Examples include
  - Appropriate description of dataset structure and declaration of keys
    - Pool-based vs. subject-based
    - Unused variables used as keys; surrogate key (--SEQ) should not be used unless unavoidable
  - Variable comments should be study relevant
    - DM.RFSTDTC described as 'Date of the first dosing', when it was not.
  - 'IsReferenceData' should contain correct information about the dataset
    - TS and TT should have IsReferenceData="Yes", since these datasets contain reference data
    - SE and SJ should have IsReferenceData="No", since these datasets contain subject data
  - Datasets should be listed in the order described in the ODM standard, referenced by the define-xml 2.0 standard.

Issues noted with Define.xml (2/2)

- Value for standard name and version must be correct
  - The value for def:StandardName should be "SENDIG-DART" and def:StandardVersion should be "1.1"

```
<MetaDataVersion OID="MDV.TEST001. SENDIG-DART.1.1" Name="Study TEST001 Data Definitions"
        Description="Test study for define exercise"
        def:DefineVersion="2.1.2"
        def:StandardName="SENDIG-DART"
        def:StandardVersion="1.1">
```



Date/Time of Define-XML document generation: 2023-04-18T10:49:07
Define-XML version: 2.1.2
Stylesheet version: 2018-11-21

Standard	SENDIG-DART 1.1
Study Name	TEST001
Study Description	Test study for define exercise
Protocol Name	Must equal the STUDYID value
Metadata Name	Study TEST001 Data Definitions
Metadata Description	Test study for define exercise

Issues with the Study Data Reviewer Guide (nSDRG)

- Limitations in standard implementations should be described
  - Exclusion Flag (--EXCLFL) should have been used for animals that were excluded in the study report
- Discrepancies between the study report and SEND should be explained
  - Data contained in SEND dataset, but not in study report (or vice versa)
    - Pre-mating data from the vendor
    - Litter data vs. individual fetal data
  - Different result categorization of fetal pathology
    - Findings classified as 'Variation' or 'Malformation' in the study report changed to 'Ossification' in SEND Dataset for ossification site alterations
  - Inconsistent use of GD 0 (Gestation Day 0) between SEND and the report
- Reviewers also asked if sponsors would consider specifying calculation methods for % fetal incidence, Litter Means (mean of litter means) vs. overall group means

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Issues with Trial Design Domains

- Both the SENDIG and SENDIG-DART must be used to completely model the study design, i.e. ALL Trial Design domains in SEND should be used
- SSTYP value in TS should be “EMBRYO FETAL DEVELOPMENT”
- Sponsors were unable to distinguish between
  - EPOCH and RPHASE
  - Treatment Elements vs. Reproductive phase and stage
- Start/End Rules in TT, TE should be consistent with dates in SJ, SE
  - The rule for Pre-treatment element in TE has a start rule of “Confirmation of Mating” and the start rule for the GESTATION30D stage in TT has the same value, however, the associated SESTDTC and SJSTDTC values are different

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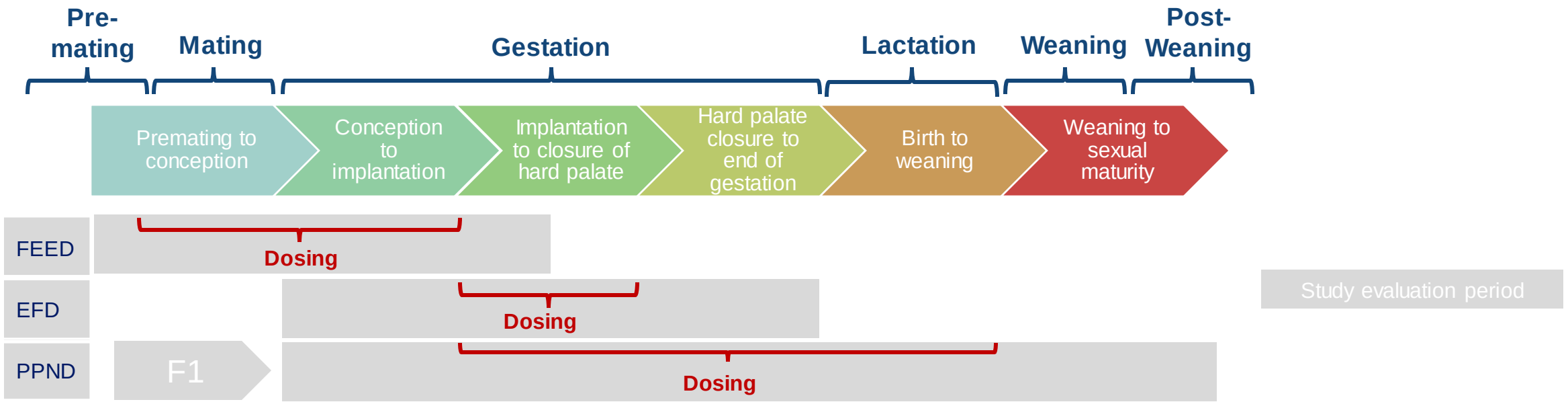
Reproductive timeline vs. Dosing timeline



Gestation Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	New Repro timing variables: --RPDY, --RPSTDY, --RPENDY, RPPLDY, RPPLSTDY, RPPLENDY
Dosing Day	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Existing SEND/SDTM timing variables: --DY, --STDY, --ENDY, --NOMDY

Reference date for day 1

Repro Phase Days	SJSTDTC (SJ)
SEND Study Day	RFSTDTC (DM)

FEED: Fertility and Early Embryonic Development; EFD: Embryo-Fetal Development; PPND: Pre- and Postnatal Developmental

Modified from: ICH S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals

Issues with new SENDIG-DART Domains (1/2)

- Implantation Classification (IC)
  - Discrepancies between variable label in metadata and the dataset
  - Implants that share implant site, should have different FETUSIDs
  - FETUSID should not be populated for resorptions

- Nonclinical Pregnancy Results (PY)
  - There was observed variability in what tests were submitted for individual subject (Female) litter-based test data. One explanation for not submitting some tests, was that the data is derived by reporting tools and not collected in the system.
  - An assumption should be added to the PY domain to address the situation when there are only single sex litters.
    - Example wording: “In the case of single sex litters, only weight data for the relevant sex should be reported. Weight tests for the other sex should be omitted.
  - A need to distinguish ‘Pregnancy Status’ from Pregnancy Outcome’ was identified
    - A new test should be added to Controlled Terminology to split the concepts for Pregnancy Status (Pregnant, Not Pregnant, Undetermined) and Pregnancy Outcome (Aborted, Early Delivery, Resorbed or Dead Litter, Live Litter).

Issues with new SENDIG-DART Domains (2/2)

- Fetal measurements (FM)
  - Some Test Names rely on FMLOC (Fetal Organ Weight, Ossified Skeletal Element Count), while for other tests FMLOC were null (Fetal Sex, Fetal Body Weight).
    - Consider using --LOC = “BODY” instead of “null” for reviewing consistency
  - Expect and IG update for use of the Nonclinical DART Sex (NCDSEX) CT list
  - Fetus ID submitted as a result instead of in dedicated variable FETUSID

- Fetal Pathology (FX)
  - Misalignment between SEND and the report
    - data collection process and lexicons are currently not designed with SENDIG-DART expectations in mind
  - FXLOC should be considered *de facto* Required
  - Use of acronyms/abbreviations should be avoided
  - Issues with standardization of results (next slide)

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Fetal Pathology standardization

FXORRES

‘KIDNEYS: Dilated renal pelvis’

What is the scheduled tissue?

‘KIDNEYS’

What is the observed result?

‘Dilated renal pelvis’

FXLOC	FXLAT	FXSTRESC	FXRESLOC
“KIDNEY”	“BILATERAL”	“DILATION”	“RENAL PELVIS”

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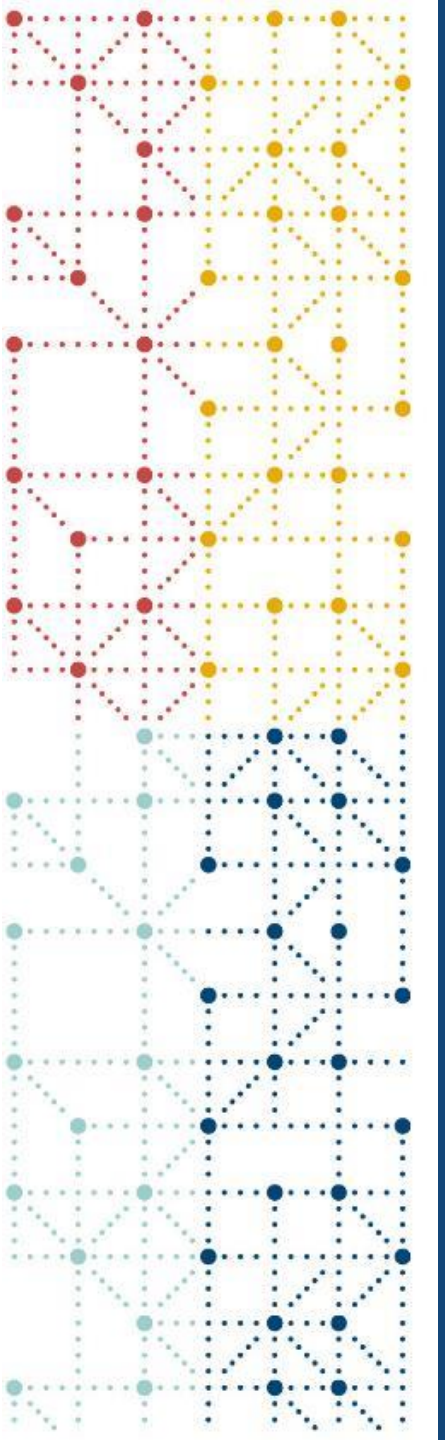
FDA Visualization tool for Fetal Pathology

Exam Type: External Examination		0 mg/kg/day	0.6 mg/kg/day	2 mg/kg/day	6 mg/kg/day
Number of Fetuses Evaluated:		0	0	0	13
Number of Litters Evaluated:		0	0	0	5
EYE					
B, ABSENT - MALFORMATION	Fetuses N (%)	.	.	.	2 (15.4)
	Litters N (%)	.	.	.	2 (40.0)
L, ABSENT - MALFORMATION	Fetuses N (%)	.	.	.	1 (7.7)
	Litters N (%)	.	.	.	1 (20.0)
R, ABSENT - MALFORMATION	Fetuses N (%)	.	.	.	1 (7.7)
	Litters N (%)	.	.	.	1 (20.0)
Tail					
NARROW - MALFORMATION	Fetuses N (%)	.	.	.	1 (7.7)
	Litters N (%)	.	.	.	1 (20.0)
SHORT - MALFORMATION	Fetuses N (%)	.	.	.	1 (7.7)
	Litters N (%)	.	.	.	1 (20.0)



New FDA Validator Rules

FDA Validator Rule Description	Domains
Trial Repro Stages (TT) dataset should be included for nonclinical Developmental and Reproductive Toxicology (DART) studies.	TT
Trial Repro Paths (TP) dataset should be included for nonclinical Developmental and Reproductive Toxicology (DART) studies.	TP
Subject Repro Stages (SJ) dataset should be included for nonclinical Developmental and Reproductive Toxicology (DART) studies.	SJ
TSVAL variable value should be 'SEND DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY IMPLEMENTATION GUIDE VERSION 1.1' for the SNDIGVER parameter in nonclinical Developmental and Reproductive Toxicology (DART) studies.	TS
Description of Repro Stage (RSTAGE) should be NULL, when subject's experience for a particular period of time is representedas an unplanned Repro Stage, where Repro Stage Code (RSTGCD) is equal to 'UNPLAN'.	SJ
Description of Repro Stage (SJUPDES) should be populated, when a subject's experience for a particular period of time is represented as an unplanned Repro Stage, where Repro Stage Code (RSTGCD) is equal to 'UNPLAN'.	SJ
The value of Repro Stage Code (RSTGCD) should be no more than 8 characters in length.	SJ, TP, TT
At least one of Rule for End of Repro Stage (TTENRL) or Planned Duration of Repro Stage (TTDUR) should be populated.	TT
Description of Repro Stage (RSTAGE) must have a unique value for a given value of Repro Stage Code (RSTGCD) within the domain.	SJ, TP, TT
Repro Stage Code (RSTGCD) must have a unique value for a given value of Description of Repro Stage (RSTAGE) within the domain.	SJ, TP, TT
The combination of Description of Repro Stage (RSTAGE), Rule for Start of Repro Stage (TTSTRL), Rule for End of Repro Stage (TTENRL), and Planned Duration of Repro Stage (TTDUR) should be unique for each Repro Stage Code (RSTGCD).	TT
Order of Repro Stage within Repro Path (TPSTGORD) variable value must be an integer.	TP
Repro Stage Code (RSTGCD) values should match entries in the Trial Repro Stages (TT) dataset, except for an unplanned Repro Stage (RSTGCD = 'UNPLAN').	SJ, TP
The combination of Repro Stage Code (RSTGCD) and Description of Repro Stage (RSTAGE) values should match entries in the TrialRepro Stages (TT) dataset, except for an unplanned Repro Stage (RSTGCD = 'UNPLAN').	SJ, TP
Repro Phase Start Reference Day (RPRFDY) must be 0 or 1 in the Trial Repro Paths (TP) dataset.	TP
The value of Planned Repro Path Code (RPATHCD) should be no more than 20 characters in length.	DM, TP
Repro Path Code (RPATHCD) values should match entries in the Trial Repro Paths (TP) dataset.	DM
Order of Repro Stage within Repro Path (TPSTGORD) must have a unique value for a given value of Planned Repro Path Code (RPATHCD) within the Trial Repro Paths (TP) dataset.	TP
Repro Phase (RPHASE) is required to be populated when any Repro Phase timing variable is populated: Planned Repro Phase Day of Observation (RPPLDY), Planned Repro Phase Day of Obs Start (RPPLSTDY), Planned Repro Phase Day of Obs End (RPPLENDY), ActualRepro Phase Day of Observation (--RPDY), Actual Repro Phase Day of Obs Start (--RPSTDY), Actual Repro Phase Day of Obs End (--RPENDY)	INTERVENTIONS, FINDINGS, EVENTS

SENDIG-DART: Why and When

Timetable for FDA requirement for SENDIG-DART

Thank you!

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