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Toxicological Assessment with Considerations for Sensitive Patient Populations



Kimberly Ehman, PhD DABT

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Overview

- Changes to evaluation of developmental and reproductive toxicity (DART) in the recently released ISO 10993-3:2026
- Overview of DART study designs
- Approaches to evaluating DART endpoints in the toxicological risk assessment (TRA)
- Case studies for selection of a point of departure (POD)
- Summary and Key Takeaways

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Recent Changes to ISO 10993-3

Prior version (2014)

- “Biological evaluation of medical devices – Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity.”

ISO 10993-3:2026

- “Biological evaluation of medical devices – Part 3: Evaluation of genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity.”
- “Evaluation” vs “Tests”
- Addition of developmental toxicity

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ISO 10993-3:2026
When Does Reproductive Toxicity Need to be Considered?

Reproductive toxicity evaluation shall be considered for devices intended for use in individuals of reproductive age under any of the following conditions:

- Devices have prolonged or long-term direct or indirect contact with reproductive organs or gametes;
- Devices have prolonged or long-term *in vitro* contact with gametes/reproductive tissue;
- Devices have prolonged or long-term use and contain known or presumed reproductive toxicants;
- Devices are absorbable or cure *in situ*, and are in close proximity to the reproductive organs, regardless of duration of contact;
- Materials which have not been used in a legally marketed device, for a similar intended purpose.

ISO 10993-3:2026
When Does Developmental Toxicity Need to be Considered?

Developmental toxicity evaluation shall be considered for:

- Devices with prolonged or long-term direct or indirect contact with embryos or fetuses; and
- Devices for prolonged or long-term use on individuals in early childhood and contain known or presumed developmental toxicants (e.g., endocrine disruptors). Potential exposure from a medical device contacting lactating women should also be considered.
- Devices are absorbable or cure *in situ*, and are in close proximity to the reproductive organs, regardless of duration of contact; or
- Materials which have not been used in a legally marketed device, for an equivalent intended purpose

Interpreting “Indirect Contact”

ISO 10993-1:2025

“*medical device or component thereof, having no physical contact with tissue, through which a fluid (liquid or gas), semi-solid or solid passes prior to contacting tissue*” (e.g., infusion equipment, ventilators)

My interpretation:

“Indirect Contact” = Extractables or Leachables

Concern within US Working Group that definition in Part 1 could be interpreted too narrowly and exclude devices with systemic exposure via E&L constituents

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Tampons

- Tampons can be used during the entire reproductive life of a female and are known to contain numerous chemicals that could present systemic and DART concerns (e.g., metals, VOCs, phthalates, etc…)
- Would they require DART evaluation according to the current definition of “indirect”
  - No
- Should they require DART evaluation due to potential E&L constituents reaching systemic circulation
  - Yes
- Evaluation does not mean conducting DART studies
  - Suggest evaluating in TRA
- Future revisions of ISO 10993-3 should clarify definition of “indirect”

When to Consider Developmental and Reproductive Toxicity?

Is your intended population of reproductive age?

- Devices have prolonged or long-term direct or indirect contact with reproductive organs or gametes
- Likely need to consider reproductive toxicity in all TRAs

Does your intended population include pregnant women or neonates?

- Devices with prolonged or long-term direct or indirect contact with embryos or fetuses (or individuals in early childhood)



What is Developmental and Reproductive Toxicity (DART)?



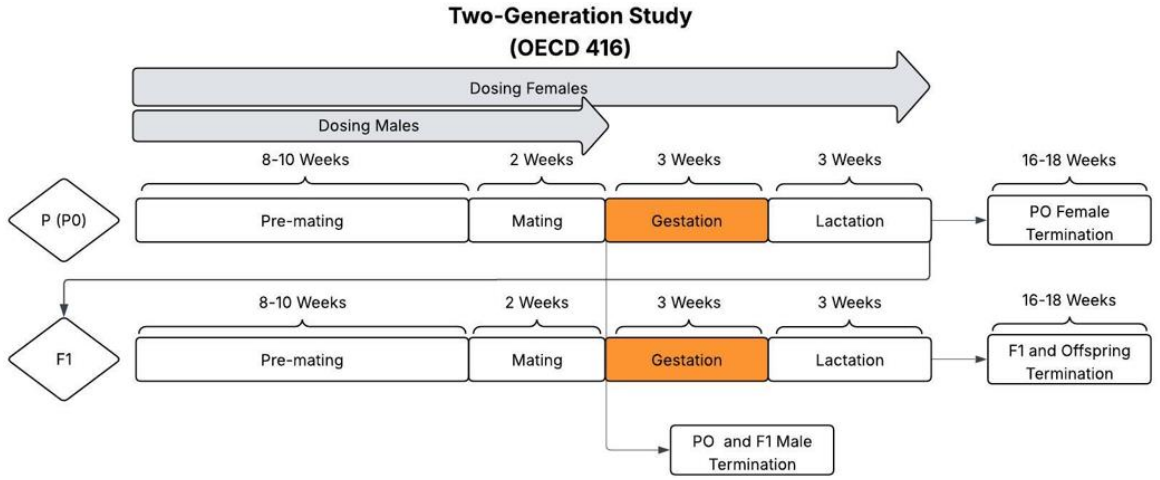
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What is Reproductive Toxicity?

Evaluation of adverse effects on the male and female reproductive system

- Sperm counts/motility and estrous cyclicity
- Mating behavior
- Sex ratios
- Litter size
- Growth and development of offspring

- Dose during premating period, mating, gestation, and lactation (parental and F1 generation)
- Species: Usually rat
- NOAELs
  - Systemic
  - Fertility
  - Developmental

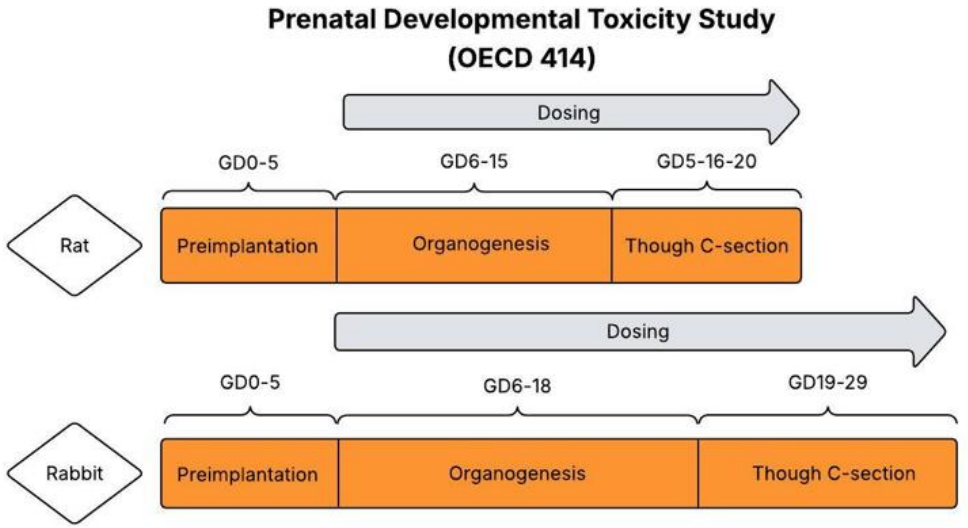


What is Developmental Toxicity?

Evaluation of prenatal exposure on the pregnant test animal and on the developing organism

- Maternal effects
- Fetal structural abnormalities (skeletal and soft tissue)
- Altered growth of the fetus
- Anogenital distance added in 2018 as an indicator of endocrine disruption

- Dose during gestation only
  - Usually begins post-implantation
- Species: Usually rat and rabbit
- NOAELs
  - Maternal
  - Developmental



Why are developmental toxicity studies conducted in two species?

Developmental toxicity is assessed in two species (rodent and non-rodent) as no one species can capture human development

- OECD 414: usually rat and rabbit

Certain birth defects only show up in a specific species

Decision to use two species was a direct result of a drug (thalidomide) that made it to market and resulted in severe birth defects (limb defects)

- Exposure during a very small window of development ~ 20 to 36 days post-fertilization in humans (~ GD 6 to 12 in rabbits)



How Does ISO 10993-3:2026 Approach DART Evaluations?

Assessment of reproductive and developmental risk should be made:

By toxicological risk assessment based on chemical characterization in accordance with ISO 10993-17 and ISO 10993-18 or;

By performing developmental and reproductive testing

- DART tests are not validated for mixtures (e.g., device extracts) or routes other than oral
- Very expensive

“Evaluation for medical devices shall first consider a toxicological risk assessment focusing on reproductive and developmental toxicity in accordance with ISO 10993-17”

Addressing DART in the TRA

ISO 10993-3:2026 provides guidance in informative Annexes on the following:

Evaluation of Endocrine Disruptors (ED)

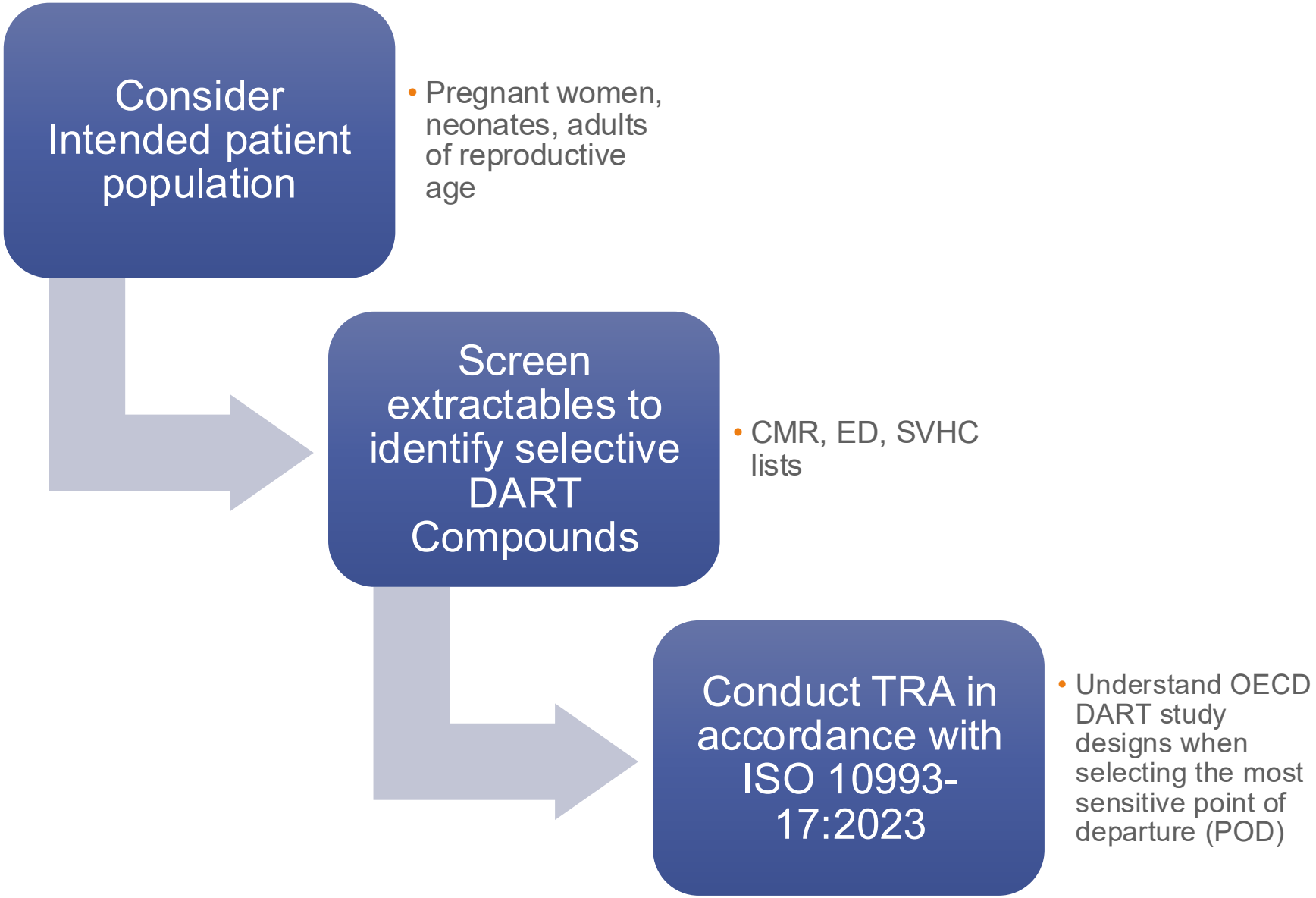
- Suggested screen of extractables to established ED lists

Evaluation of Reproductive and Developmental Toxicity

- Suggested screen of extractables to established lists for selective DART compounds (e.g., CMR, SVHC)
- Overview of common DART endpoints in OECD studies

OECD Study Number	Type of Study
414	Prenatal developmental toxicity study
415	One-generation reproduction toxicity study
416	Two-generation reproduction toxicity study
421	Reproduction/developmental toxicity screening test • Reduced one-generation study
422	Combined repeated dose toxicity study with reproduction/developmental screening test • 28-day toxicity study + a reduced one-generation study
443	Extended one-generation reproductive study

Suggested Approach



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Common OECD DART Study Designs

OECD 415: One-generation reproduction toxicity study

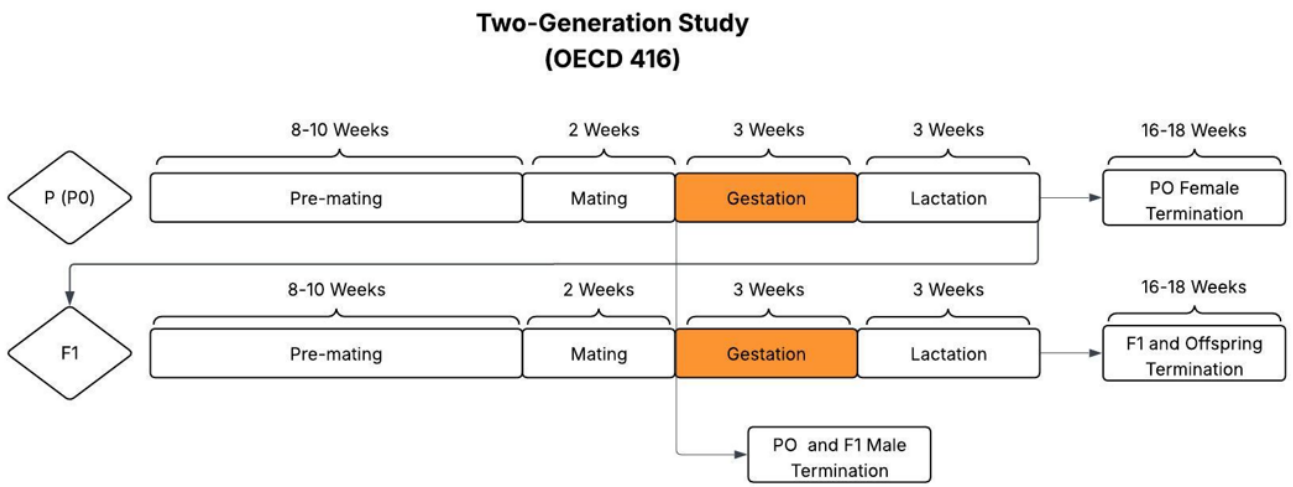
- Obsolete guidance as of 2019, but studies can still support certain reproductive endpoints

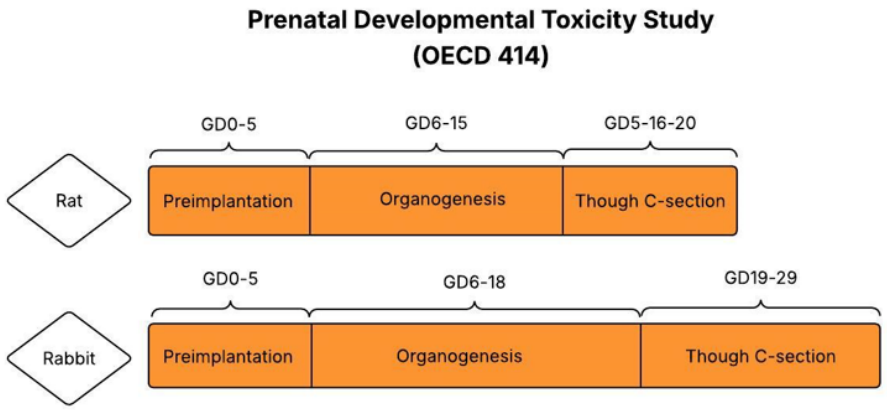
OECD 416: Two-generation reproduction toxicity study

OECD 443: Extended one-generation reproductive toxicity study

- Flexible study design with multiple cohorts (e.g., reproductive, neurotoxicity, immunotoxicity)
- “Extended” because F1 animals are followed beyond weaning, often through sexual maturity
- Has replaced OECD 415 and partially replaces OECD 416

OECD 414: Prenatal developmental toxicity study





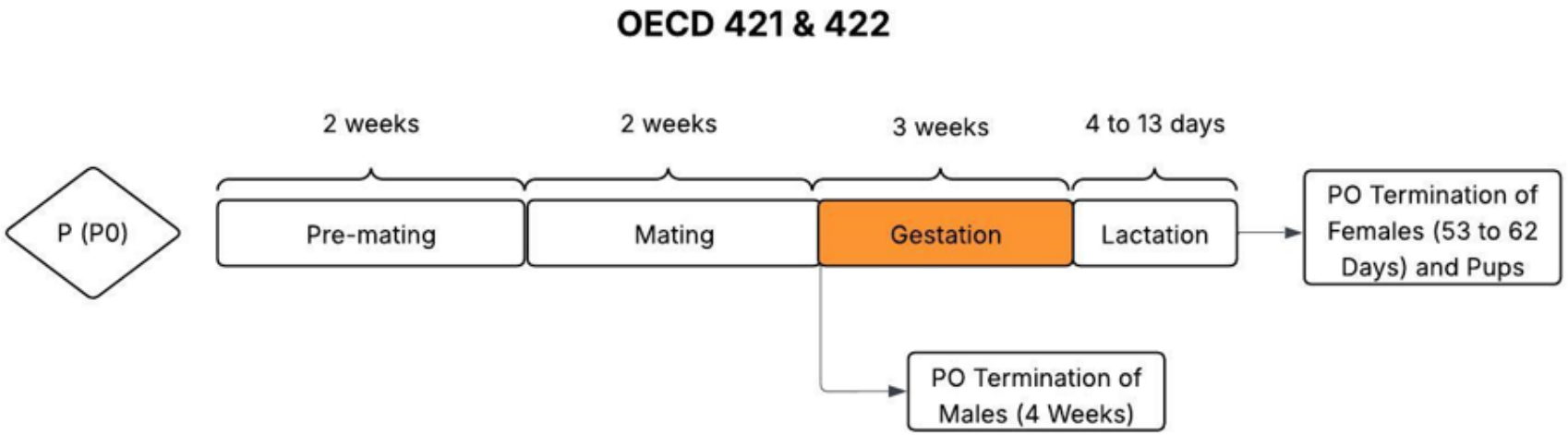
Common OECD DART Study Designs

OECD 421: Reduced one-generation study

- Generates limited information for male and female reproductive performance, including gonadal function, mating behavior, conception, development of the fetus

OECD 422: 28-day toxicity study and a reduced one-generation study

- OECD 421 + 28-day systemic toxicity study



Case Studies How to Select the Most Appropriate POD?

Case Study 1

- Duration of contact: Prolonged (up to 30 days); tissue contact
- Patient population: Adults, including pregnant women, children and neonates
  - Consider systemic toxicity and DART
- The following toxicological data are available for Chemical A:

28-Day NOAEL (Systemic)	OECD 416 NOAEL (P0 Systemic & Fertility)	OECD 414 NOAEL (Developmental)
300 mg/kg/day	200 mg/kg/day	100 mg/kg/day

- Which NOAEL is appropriate to derive a tolerable intake (TI)?

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- Which NOAEL is appropriate to derive a tolerable intake (TI)?

Developmental NOAEL would be protective for systemic, reproductive, and developmental toxicity

Case Study 2

- Duration of contact: Long-term (> 1 year); tissue contact
- Patient population: Adults, including pregnant women, children and neonates
  - Consider systemic toxicity and DART
- The following toxicological data are available for Chemical A:

28-Day NOAEL (Systemic)	OECD 416 NOAEL (P0 Systemic & Fertility)	OECD 414 NOAEL (Developmental)
300 mg/kg/day	200 mg/kg/day	100 mg/kg/day

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Case Study 2

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- The following toxicological data are available for Chemical A:

28-Day NOAEL (Systemic)	OECD 416 NOAEL (P0 Systemic & Fertility)	OECD 414 NOAEL (Developmental)
300 mg/kg/day	200 mg/kg/day	100 mg/kg/day

Why?

- Consider the uncertainty factors (UFs) that would be applied to derive the TI

Case Study 2

28-Day NOAEL (Systemic)	OECD 416 NOAEL (P0 Systemic & Fertility)	OECD 414 NOAEL (Developmental)
300 mg/kg/day	200 mg/kg/day	100 mg/kg/day

TI based on 28-day study (full systemic toxicity evaluation):

- MF 10,000 (10 for intraspecies, 10 for interspecies, 10 for oral to parenteral, 10 for subacute to chronic)
- **TI = 30 µg/kg/day**

TI based on OECD 416 (2-Generation) study (PO M/F dosed ~ 12 wks to 18 wks) :

- MF 6,000 (10 for intraspecies, 10 for interspecies, 10 for oral to parenteral, 6 for subchronic to chronic)
- **TI = 33 µg/kg/day**

TI based on developmental study:

- MF 1000 (10 for intraspecies, 10 for interspecies, 10 for oral to parenteral)
  - Note: No UF for duration because developmental toxicity occurs during a critical window of development and should not be extrapolated
- **TI = 100 µg/kg/day**

Summary and Key Takeaways

- ISO 10993-3:2026 is now published with more guidance around when and how to consider developmental and/or reproductive toxicity in the TRA

- Inclusion of “indirect contact” for both developmental and reproductive toxicity essentially includes all devices (unless contraindicated for a specific population)
  - More discussion and clarification around the term “indirect contact” is needed

Summary and Key Takeaways

Consider Intended patient population

- Pregnant women, neonates, adults of reproductive age

Screen extractables to identify selective DART Compounds

- CMR, ED, SVHC lists

Very few medical device extractables are selective DART or ED compounds*

Conduct TRA in accordance with ISO 10993-17:2023

- Understand OECD DART study designs when selecting the most sensitive point of departure (POD)
- **Review dosing durations (e.g., M vs F and P0 vs F1) to select appropriate POD**
- **For most DART studies, systemic POD is lower than DART POD**

**SOT Poster: Prabhakar et al. 2024; The Toxicologist. Vol. 198. No. 3351.*

Summary and Key Takeaways

When selecting a POD from a developmental toxicity study, remember that developmental toxicity occurs during a critical window

- For example, thalidomide would only cause birth defects in rabbits if exposed from during a very specific period of organogenesis (~GD6-12)
- If using developmental toxicity as the POD, there is no need to apply an additional UF for duration
- If using maternal toxicity from the same study, an additional UF for duration could be applied

Future evaluations may also want to consider combined *in silico* approaches to strengthen the overall weight-of-evidence

- Park & Hood: *Advancing the developmental and reproductive assessment in medical device preclinical safety evaluations*. Regulatory Toxicology and Pharmacology. 161 (2025) 105853

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Thank you

Get in touch

Kimberly.Ehman@mds.EurofinsUS.com

Medical-Device@BPT.EurofinsUS.com

www.Eurofins.com/Medical-Device

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