Dermal Absorption in the Setting of OTC Rulemaking

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A MUsT shows your nonprescription drug is absorbed.

Now what????

Nonprescription Drugs

Nonprescription drug products generally have these characteristics:

- Can be adequately labeled such that
  - The consumer can self-diagnose, self-treat, and self-manage the condition being treated
  - No health practitioner is needed for the safe and effective use of the product
- Drug has low potential for misuse and abuse
- Safety margin is such that the benefits of over-the-counter (OTC) availability outweigh the risks

Drug or Cosmetic??

Drug
FD&C Act, Section 201(g)(1)

Articles intended for disease:

- Diagnosis
- Cure
- Mitigation
- Treatment
- Prevention
- **Intended to Affect the Structure or Any Function of the Body of Humans or Animals**

Cosmetic
FD&C Act, Section 201(i)

Articles intended for:

- Cleansing
- Beautifying
- Promoting Attractiveness
- Altering Appearance

Products meeting both definitions must meet requirements for BOTH drugs and cosmetics

Two Regulatory Pathways

New Drug Application	Over The Counter (OTC) Monograph
Product specific (including formulation and labeling)	Therapeutic category-specific regulations (product can contain permissible active ingredients in a monograph compliant formulation)
Certain subsequent labeling and formulation changes require prior approval through supplemental application	Changes do not require approval when in compliance with monograph
Confidentiality during the approval process	Public process for monograph changes
Safety and effectiveness testing required for each individual product	Safety and effectiveness testing of each individual product not required if compliant with monograph
Application submitted for premarket approval	No FDA product-specific premarket application or preapproval
Application fees (i.e., user fees)	No user fees
Adverse event and other reporting requirements	Limited reporting requirements (serious adverse events only)
Comply with good manufacturing practices	Comply with good manufacturing practices
A period of market exclusivity (if certain conditions are met)	No market exclusivity

New Drug Application or Monograph?

Current OTC Drug Regulation

- OTC drug review established in 1972
  - Implemented 1962 Congressional directive to review the safety and effectiveness of drugs
- Rather than review hundreds of thousands of individual OTC products, FDA began issuing monographs establishing conditions under which OTC drugs are generally recognized as safe and effective (GRASE)
  - Monographs are "rulebooks" establishing indications, strengths, dosing information, warnings, etc., for OTC products containing the covered ingredients to be GRASE
  - Each monograph generally provides for the marketing of hundreds or thousands of products
  - Products meeting the specifications of a monograph are not required to be reviewed by FDA before marketing
- The monographs cover some 800 active ingredients for over 1,400 different uses, authorizing over 100,000 products
- Each monograph is established by regulation
  - There are >150 final rules related to OTC drugs
  - Approximately 88 ongoing rulemakings in 26 broad therapeutic categories

FDA Proposed Rule: Sunscreens

- Proposed rule issued February 21, 2019
  - Comment period open for 90 days: Docket No. FDA-1978-N-0018
- Describes conditions under which OTC sunscreen monograph products are generally recognized as safe and effective
- Part of ongoing effort to ensure sunscreens are safe and effective for regular, life-long use
- Goal to improve the quality, safety, and efficacy of sunscreens
- FDA will continue to work with industry and stakeholders to make sure consumers have access to safe and effective sunscreens

Sunscreen Safety Data Framework

- Rationale
  - Changing patterns of use
    - Used as preventive drugs, over a lifetime period of exposure, in a population spanning all age groups
  - Evolving scientific knowledge
    - Different formulations with greater SPF and broad-spectrum protection
    - Ingredients may be absorbed through the skin→

    Need to consider systemic effects (carcinogenicity, endocrine, reproductive)
- FDA's proposed safety framework supported by an independent Advisory Committee as a good starting point (September 2014)

Safety Data Requested for Sunscreens

Clinical Studies	Nonclinical Studies
Human Irritation and Sensitization study whether the ingredient causes skin irritation or an allergic reaction	**Dermal Carcinogenicity** study the long-term effect of dermal administration of the ingredient to see if it causes tumors of the skin or the rest of the body
Human Photosafety study whether the ingredient causes skin irritation or an allergic reaction when exposed to light	**Systemic Carcinogenicity** study the long-term effect of the ingredient in the body to see if it causes tumors
Human Absorption/Maximal Usage Trial (MUsT) evaluate whether and the extent to which an ingredient is absorbed into the body	**Developmental and Reproductive Toxicity (DART)** study developmental and reproductive risks, which can include endocrine effects
Pediatric Considerations additional studies may be needed to ensure that a sunscreen active ingredient would be GRASE for use in pediatric populations if results from other studies suggest a narrow margin of safety	**Toxicokinetic** study whether and to what extent the ingredient is absorbed in animals to help calculate a safety margin for human use

Proposed GRASE Status for Sunscreen Active Ingredients

GRASE* for use in sunscreens	Not GRASE** for use in sunscreens	***Insufficient data for use in sunscreens
Zinc oxide and titanium dioxide	Aminobenzoic acid (PABA) and trolamine salicylate	Cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, avobenzone

*GRASE= Generally Recognized as Safe and Effective **These ingredients are not currently marketed. ***For those ingredients in the "insufficient data" category, FDA proposes that it needs additional data to determine that sunscreens with these ingredients would be GRASE.

- Request for additional data does not mean FDA has concluded that 12 ingredients are unsafe
- **Consumers should continue to use broad spectrum sunscreens with SPF 15 or higher in conjunction with other sun protective measures to reduce the risk of sunburn, skin cancer, and early skin aging caused by the sun**

Nonclinical Safety Studies for Sunscreens

Overview

Nonclinical Studies
Dermal Carcinogenicity study the long-term effect of dermal administration of the ingredient to see if it causes tumors of the skin or the rest of the body
Systemic Carcinogenicity study the long-term effect of the ingredient in the body to see if it causes tumors
Developmental and Reproductive Toxicity (DART) study developmental and reproductive risks, which can include endocrine effects
Toxicokinetic study whether and to what extent the ingredient is absorbed in animals to help calculate a safety margin for human use

– Other studies to address specific concerns (e.g., hormonal disruption, metabolites)

Nonclinical Development for OTC Monograph, Compared to NDA

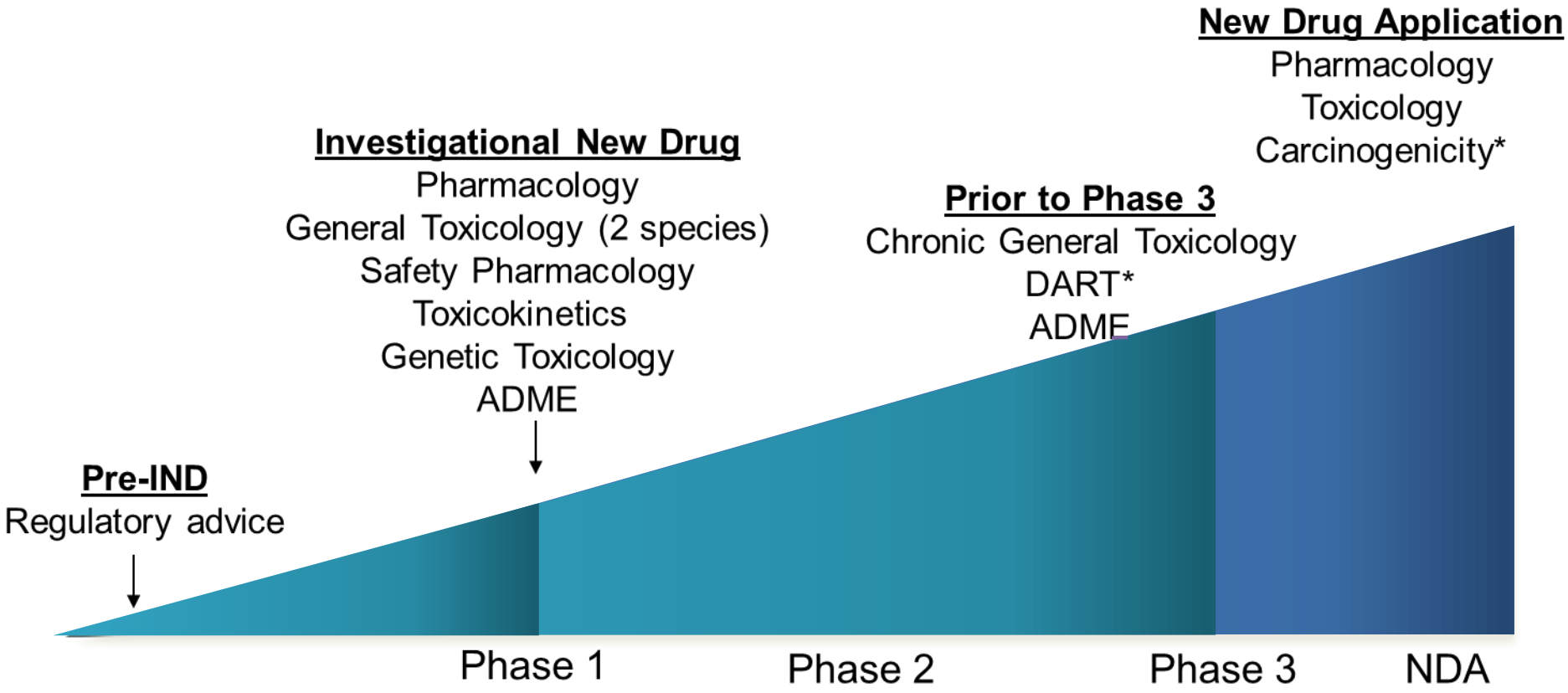
<u>Common Elements</u>

- Requires an integration of exposure and toxicity data across many study types to inform safety in humans
- Based on principles that are generally harmonized with regulatory bodies in Japan and Europe

<u>Difference</u>

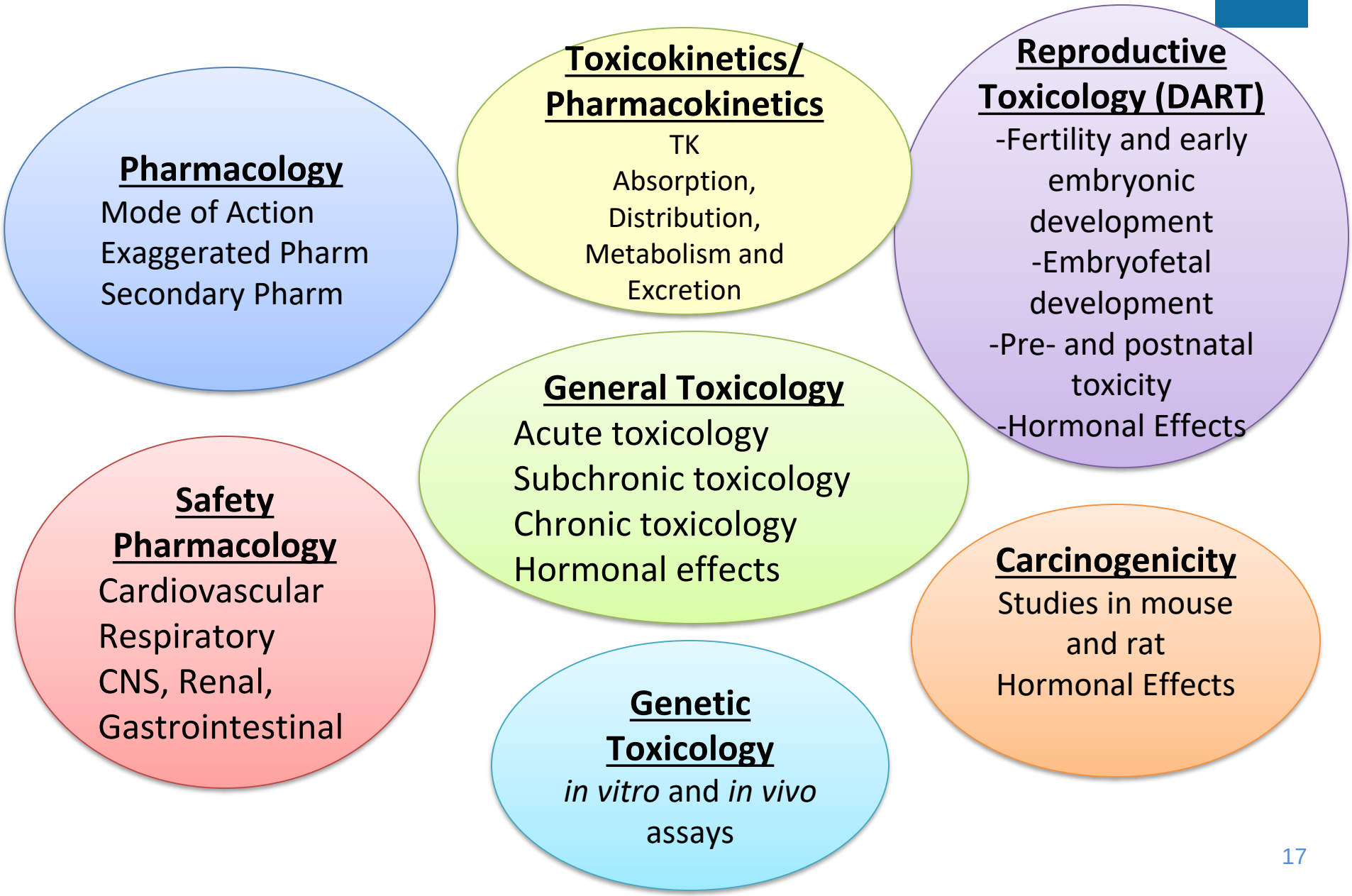
- Fewer in vivo studies, recognizing previous human use required for OTC monograph

NDA: Nonclinical Development to Support Clinical Trials and Marketing Approval



*Requirements are on case-by-case basis

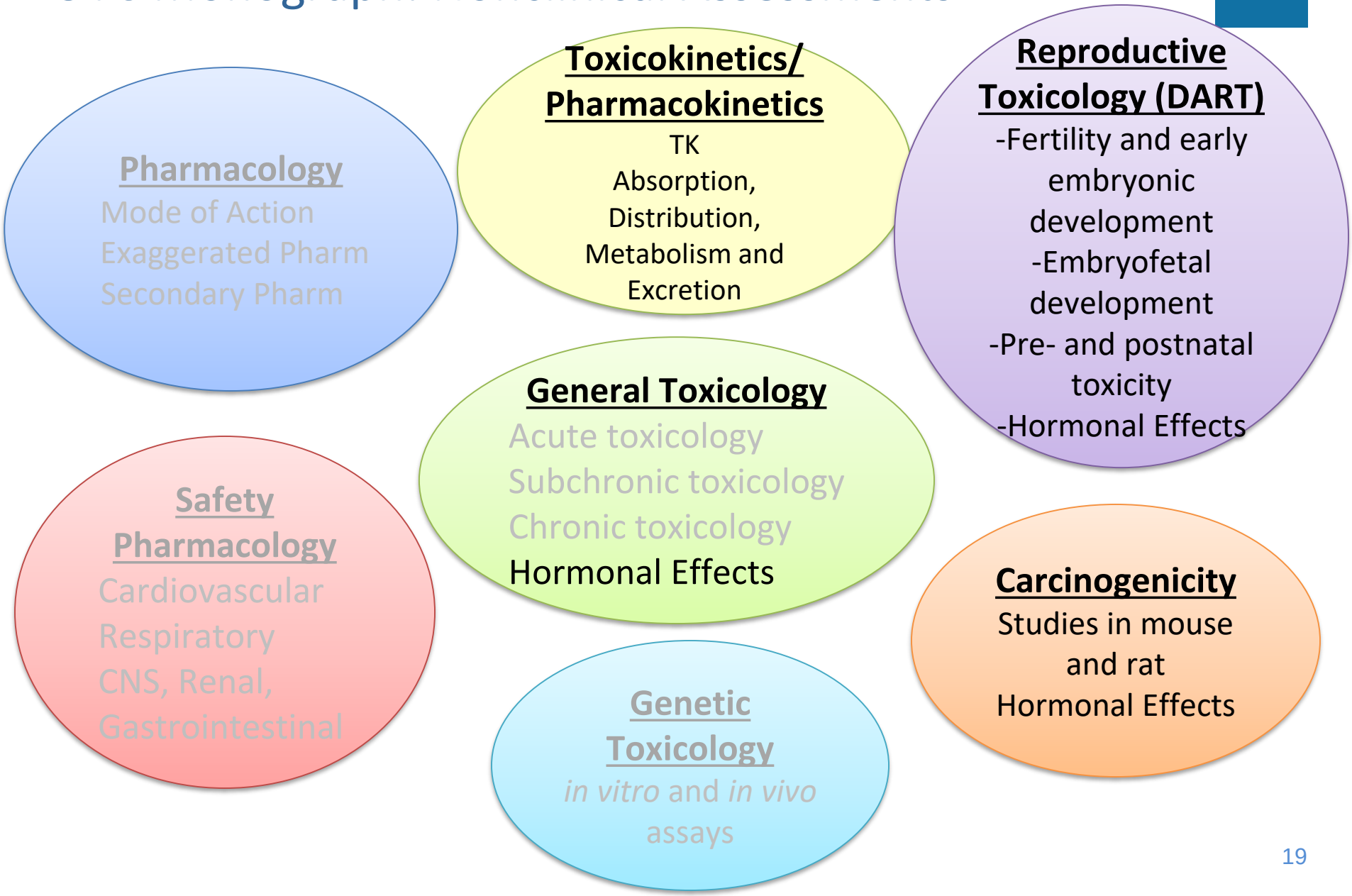
NDA: Nonclinical Assessments



OTC Monograph: Nonclinical Safety

- OTC Monograph Active Ingredient
  - Previous human experience (marketed prior to 1972)
  - Most over-the-counter indications are considered chronic or chronic intermittent
- Nonclinical (animal) studies for safety
  - Focus on information not addressed by clinical use:
    - Carcinogenicity
    - Developmental and Reproductive toxicity (DART)
    - Hormonal Effects
    - Toxicokinetics, Absorption, Distribution, Metabolism, Excretion (ADME)

OTC Monograph: Nonclinical Assessments



Why Nonclinical Assessments?

- Some safety evaluations are not adequately characterized in pre- and post-marketing human trials
  - Number of people in trial or length of time is burdensome
  - Assessment is confounded by multiple drug exposures, inadequate monitoring, or sporadic reporting
  - Assessments may not be ethical
- In these cases, nonclinical studies inform the risk of a toxicity and provide an estimate of exposure margins

What the Data Tell Us…

Type of Study	What the Data Tell Us
Carcinogenicity studies (dermal and systemic)	Determine safety margin for tumors; Other systemic and organ toxicities
Developmental and Reproductive Toxicity (DART) Studies	Determine toxicities related to -fertility -teratogenicity -pre- and postnatal development -hormonal effects
Toxicokinetic measurements (from carcinogenicity or DART studies)	Inform the relevance of nonclinical toxicological findings to clinical safety

-Other studies to address specific concerns (e.g., hormonal disruption, metabolites)

Why Nonclinical Assessments?

What are we missing without nonclinical studies?	How is it addressed?
Toxicity at the tissue and organ level	Histopathology
Toxicity at higher exposures than in humans to determine exposure margins for toxicity	Carcinogenicity studies , DART studies
Effects from chronic or lifetime exposure	Carcinogenicity studies
Endpoints that can not be evaluated due to either ethical reasons or because insufficient controls, monitoring and reporting	Carcinogenicity, DART studies

Carcinogenicity Assessments

- Generally performed for drugs that are applied for a minimum of 6-months of a user's lifetime
- Typically conducted as two assessments

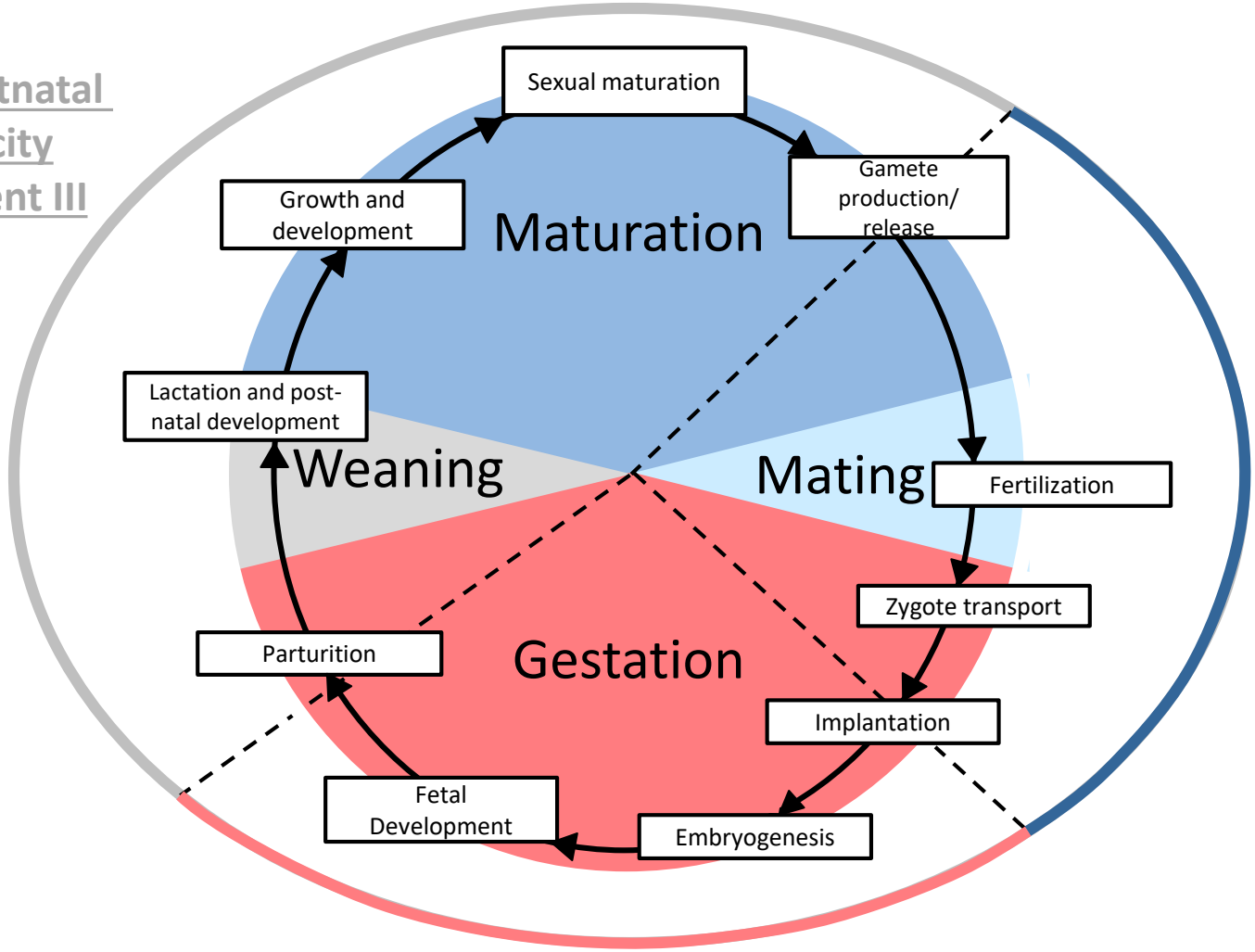
Study No.	Route	Species	Advantage
1	Dermal	Mouse	Most relevant route of administration
2	Oral	Rat	Higher systemic exposure

  - data from two different species to increase the probability of detecting a signal

- Two year dosing period for drug exposure over a lifetime
  - Proposal for using a transgenic model will be considered

- Informs risk and exposure margins at doses which exceed the clinical dose

Developmental and Reproductive Toxicity (DART)



Developmental and Reproductive Toxicity (DART) Studies

- DART studies address potential effects on
  - Reproductive competence of sexually mature male and female animals
  - Developing offspring from fertilization, throughout gestation and post-natally until sexual maturation of exposed pups
- Gestational and neonatal stages of development may also be particularly sensitive to hormonal activity (endocrine effects)
- Non-routine assessment may include
  - Evaluation of vaginal patency, preputial separation, anogenital distance, and nipple retention
  - Behavioral assessments (e.g., mating behavior) of offspring, can detect neuroendocrine effects

Toxicokinetic Data

- Data provide a bridge between toxic levels seen in animal studies and potential human adverse events associated with dermal exposure to sunscreen ingredients

- Toxicokinetic data can be incorporated into the design of in vivo toxicity study (e.g., carcinogenicity, DART studies)

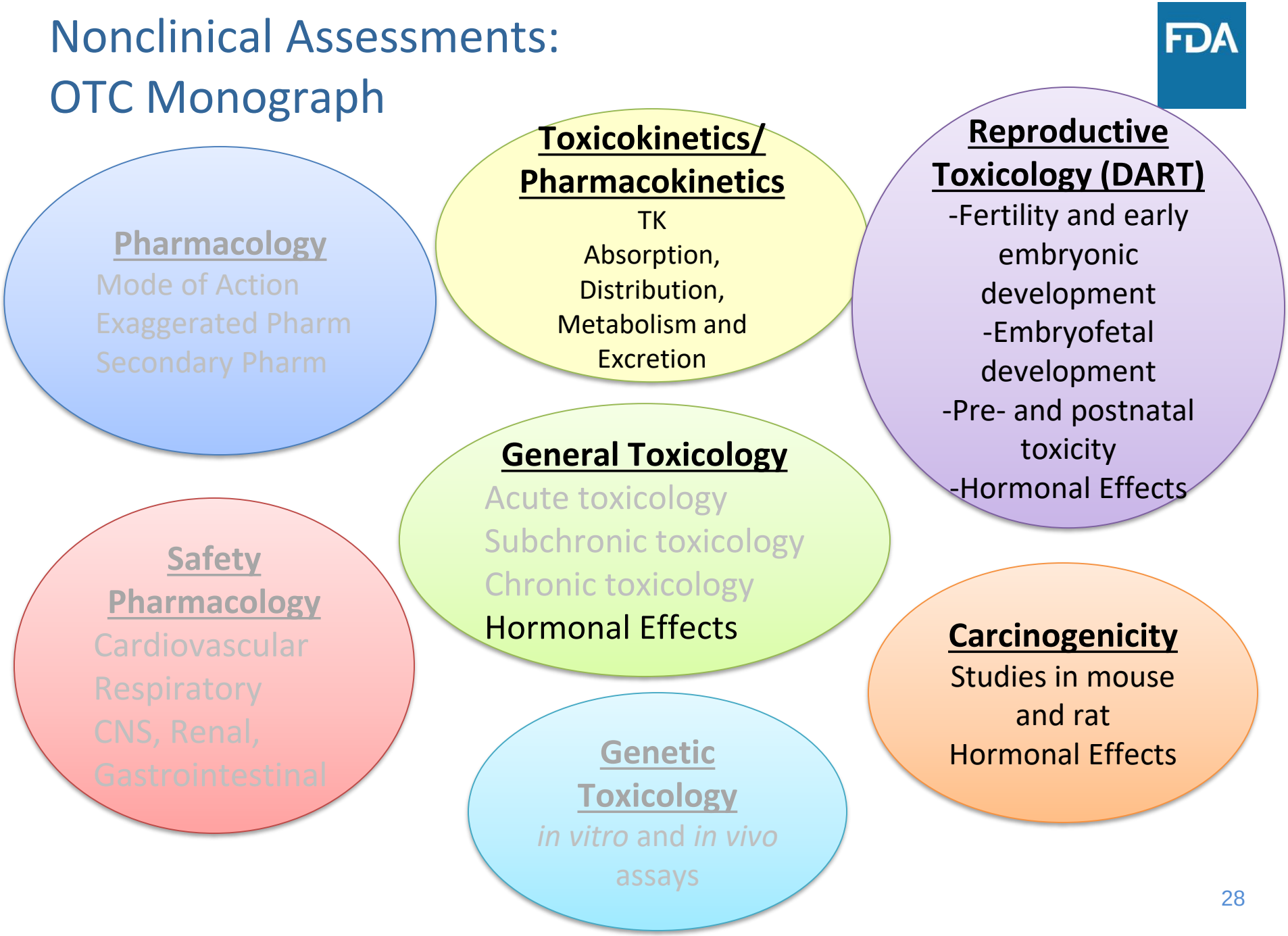
- Nonclinical toxicokinetic data are compared to clinical pharmacokinetic data in Maximal Use Trial (MUsT) to determine an exposure margin which informs safety assessment

Summary

- Determining elements of nonclinical safety evaluation integrates all available data
  - Previous clinical experience
  - Nonclinical information
- Nonclinical studies recommended for OTC Monograph ingredients are similar to recommendations for NDA products and in accordance with ICH guidelines
- OTC Monograph supports ingredient-based review
- Resource: Guidance for industry Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonprescription-sunscreen-drug-products-safety-and-effectiveness-data

Nonclinical Assessments: OTC Monograph

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