

Status of Human Dermal Safety Testing in Topical Drug Product Development

Hon-Sum Ko, MD, FACP
Medical Officer
Division of Dermatology and Dental Products
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Disclaimer/Disclosure

This presentation reflects the views of the presenter and does not represent FDA's views or policies.

Presenter has no conflicts to disclose.

Outline of Presentation

- Scope of human dermal safety testing for this workshop
- Experience from DDDP marketed products
- Challenges and opportunities
- Issues to be addressed in Workshop

Human Dermal Safety Testing for Topical Drug Products (1)

For this workshop, human dermal safety testing:

- refers to provocative testing studies currently used to support topical drug product marketing,
- is conducted in healthy volunteers with test articles applied to normal skin surface, and
- is often done concurrently with phase 3 clinical trials with the to-be-marketed formulation.

Human Dermal Safety Testing for Topical Drug Products (2)

For this workshop, human dermal safety testing:

- does **not** refer to studies used for formulation selection in early stages of drug development,
- does **not** include long-term safety studies conducted postmarket,
- does **not** include testing for transdermal drug products, OTC drug products or cosmetics, and
- is **not** indication-specific.

Human Dermal Safety Testing for Topical Drug Products (3)

For this workshop, human dermal safety testing refers to studies submitted to DDDP on:

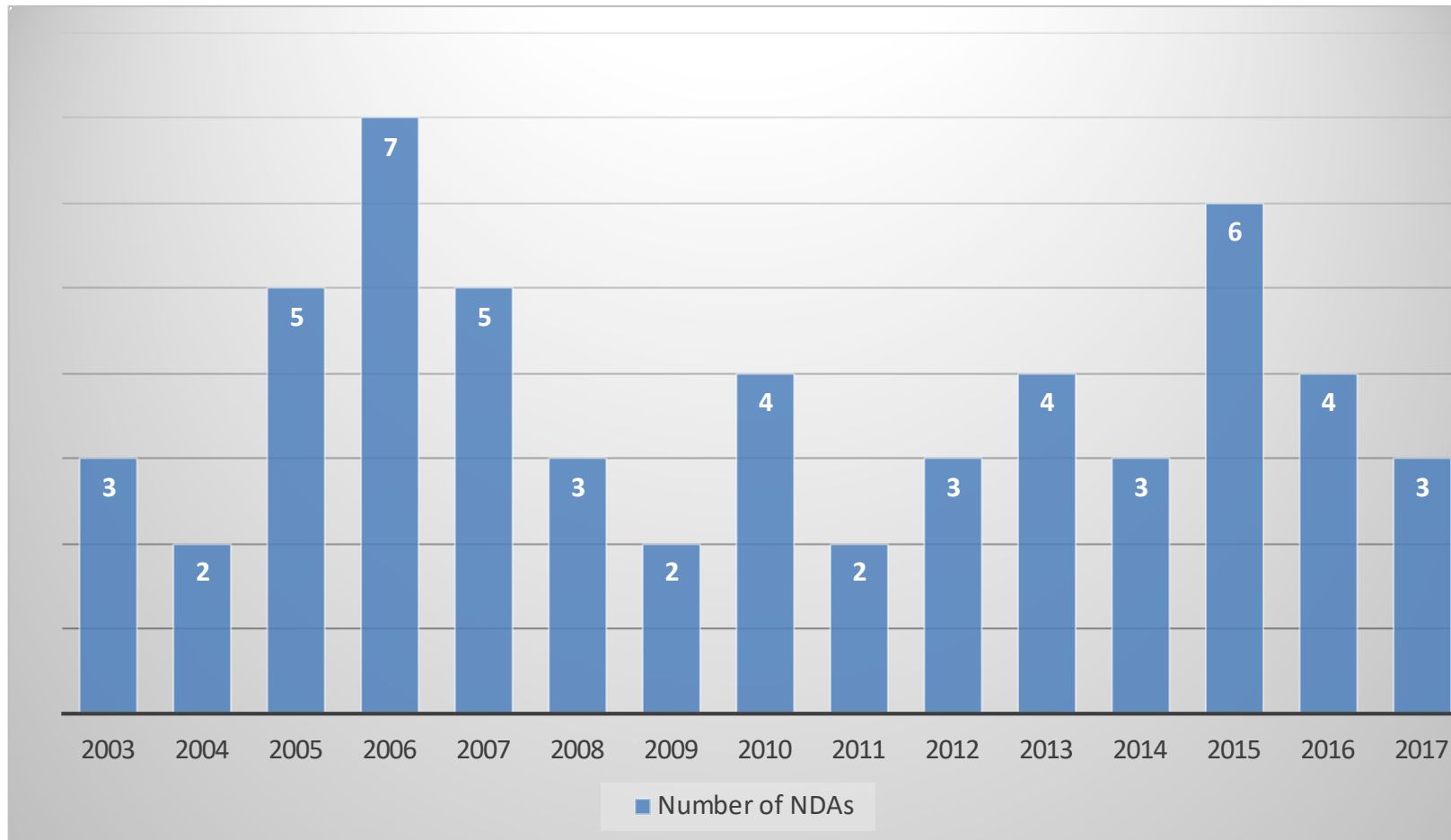
- Cumulative irritancy potential,
- Contact sensitization potential,
- Photoirritation (phototoxicity) potential*, and
- Photoallergenicity (photocontact allergy) potential*.

*Conducted when the product absorbs in the 290 – 700 nm spectrum

They will be the topic for a Session II presentation.

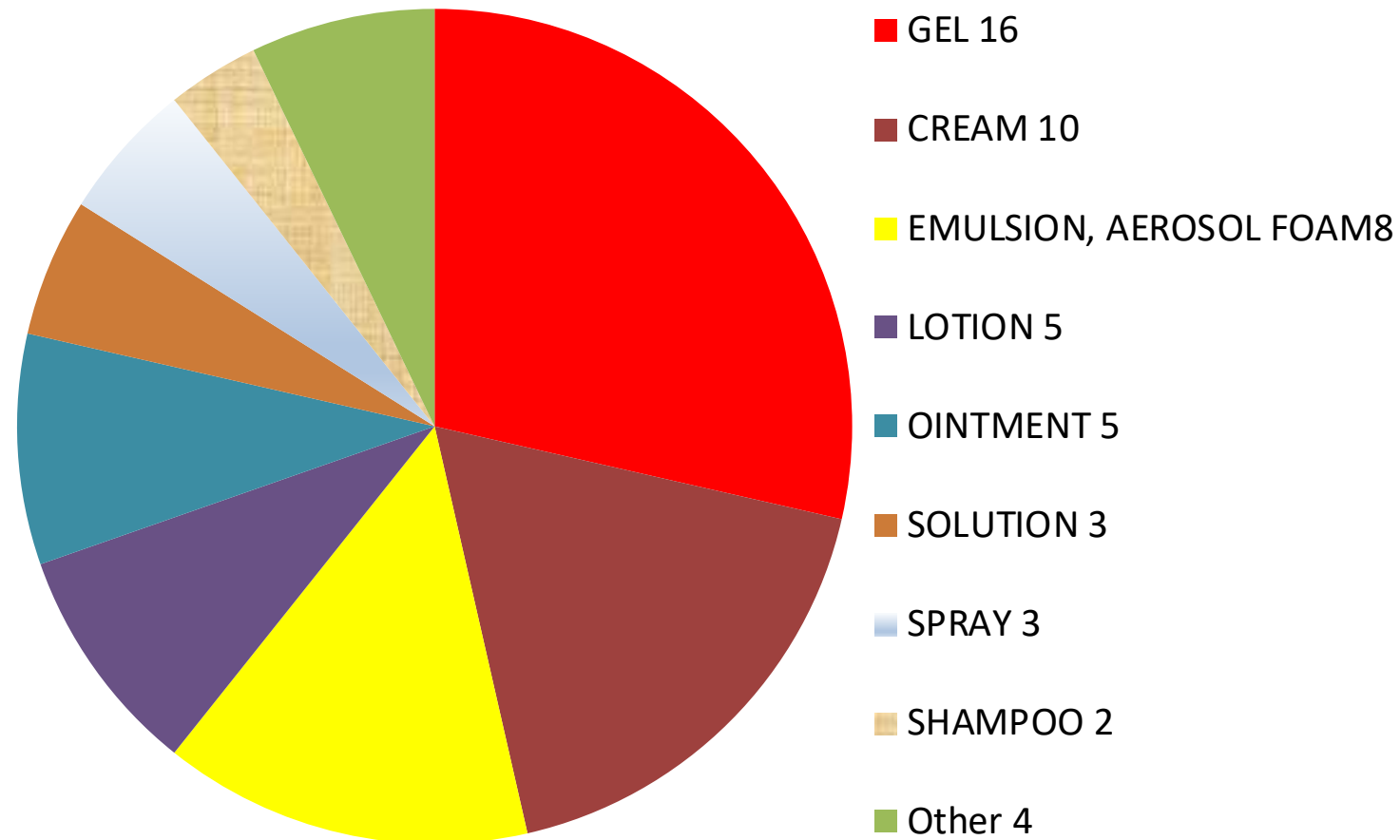
Experience from DDDP Marketed Products (1)

From CDER's database we found 56 topical drug approval actions for original NDAs on drug products to treat skin diseases over the 15-year period 01-01-2003 to 12-31-2017.



Experience from DDDP Marketed Products (2)

Dosage forms of the 56 topical drug products approved between 2003 and 2017:



Experience from DDDP Marketed Products (3)

Human Dermal Safety Studies supporting the 56 topical drug product NDAs:

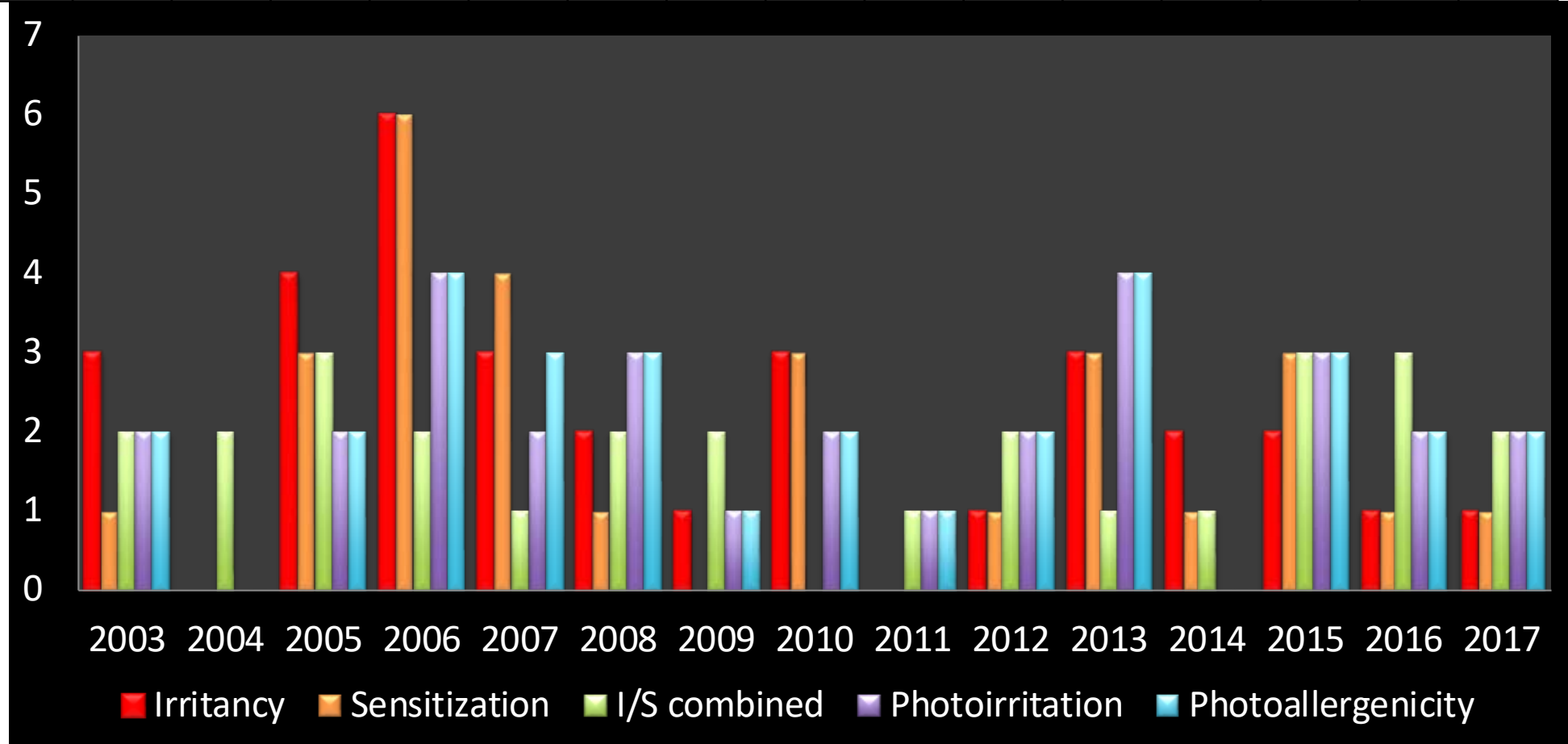
Human Dermal Safety Tests (DST) in Support of Topical Drug Marketing Applications	# of NDAs Supported by Human DST	
	Yes	No
Cumulative irritancy	32	4
Contact sensitization	28	2
Combined irritancy/sensitization	27	29
Photoirritation	29	27
Photoallergenicity	30	26

Experience from DDDP Marketed Products (4)



Distribution of human dermal safety testing studies for the 56 topical drug products among the years 2003 to 2017:

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
#App	3	2	5	7	5	3	2	4	2	3	4	3	6	4	3



Challenges and Opportunities (1)

Challenges:

- Potential \neq Risk
- Healthy volunteers \neq Patients
- Healthy skin \neq Lesions
- Test location \neq Clinical use location
- Adequacy of study sample sizes
- Ethical issues
- Overconservative or Underestimating?

Challenges and Opportunities (2)

Opportunities:

- Patient-centered approach in drug development
- Real world evidence for risk from clinical usage
- Initiatives to enhance labeling utility for the prescriber
- Considerations to replace, reduce and refine
- Interagency interest: skin sensitization working group
- Technological advances

Regulatory agencies must reconsider existing paradigms to align with changes in science and patient needs.

Charge to Participants

Morning Sessions will provide a background for human dermal safety testing in the clinical development of topical drug products. With this information, consider in your afternoon discussion:

- What we have been doing right in risk assessment and communication based on human dermal safety testing in the current regulatory environment?
- What needs improvement?

We appreciate your input today or comments to the docket [Docket Number: FDA–2018–N–2582].

Issues for Discussion (1)

- 1. Discuss your perspective on the role of current human dermal safety studies for the clinical development of topical drug products.
- 2. In light of the nonclinical assays listed in the ICH S10 guidance document to assess photosafety (e.g., in vitro 3T3 NRU-PT assay, reconstructed human skin models, in vivo animal assay), discuss your perspective on the role of human photosafety studies (i.e., photoirritation and photoallergenicity clinical studies).

Issues for Discussion (2)

- 3. Address the following issues as they impact the ability of dermal safety studies to inform product labeling:
 - Clinical relevance
 - Occluded application (vs non-occluded clinical use)
 - Intact skin (vs clinical use on diseased skin)
 - Location (patch application site vs disease distribution)
 - Sample size
 - Study duration

Issues for Discussion (3)

- 4. Discuss the types of local safety data that would be informative for product labeling.

- 5. Do you have any specific comments on approaches to the evaluation of human dermal safety of topical drug products:
 - a) irritancy,
 - b) sensitization,
 - c) phototoxicity,
 - d) photocontact allergenicity?



Questions?