ICAPPP

DATE:	May 5, 2008
TO:	U.S. FDA Center for Drug Evaluation and Research
PREPARED BY:	Troy Seidle and Samantha Dozier, PhD on behalf of U.S. members of ICAPPP
SUBJECT:	Docket No. FDA-2008-D-0142 Comments on FDA Draft Guidance on Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route

These comments are submitted on behalf of the International Council on Animal Protection in Pharmaceutical Programs (ICAPPP) and our more than 30 million members and supporters throughout the United States, Canada, Europe and Asia. ICAPPP's aim is to ensure the widest possible uptake of non-animal test methods and integrated testing strategies in concept papers and guidelines produced by the ICH and regional pharmaceutical regulators, in the interests of public health, sound science and animal protection. ICAPPP would like to thank FDA/CDER for the opportunity to comment on this draft guidance.

General Comments

While recognizing that the reformulation of a drug product, as well as alterations to the route and/or duration of human exposure relative to that of an approved drug, can sometimes lead to unanticipated toxicity, decisions regarding additional preclinical testing needs (if any) should foremost be based on an understanding of the PK/ADME properties of the new vs. approved route/formulation, and demonstrable efforts to bridge the two without additional *in vivo* testing. Where this is not possible, there are a number of opportunities for refinement of this guidance in ways that could substantially reduce testing costs and time, while encouraging the use of valid, non-animal methods for the evaluation of local effects. Specifically:

- We urge FDA/CDER to abandon the default two-species testing paradigm in favor of a single species approach, as we believe that the multitude of toxicity and PK studies conducted in support of the approved drug product should make it possible to identify a single, appropriate species for any subsequent testing.
- For a number of the study types recommended in this guidance (delayed hypersensitivity, photocarcinogenicity, etc.), validated testing protocols do not currently exist, nor does FDA (or international bodies such as ICH or OECD) have guidelines for their conduct.

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Specific Comments

A. Considerations for All Routes

The use of animals to evaluate local toxicities is ripe for replacement with *in vitro* models developed by companies such as MatTek (*MatTek.com*) and SkinEthic (*SkinEthic.com*). Available and validated model systems currently include several human epidermal equivalents, as well as human corneal, oral (gingival and buccal), tracheal/bronchial, and ectocervico-vaginal equivalents. These models are generally suited to both acute and subacute (3 week) exposure scenarios. In the case of local effects for which an *in vitro* method is currently unavailable and/or exposure scenarios beyond 3 weeks, any new *in vivo* testing should be expressly limited to a single species.

B. Route-Specific Considerations

New *in vivo* testing of reformulations should be strictly limited to the intended route(s) of human exposure. We strongly challenge the current suggestion that new route-specific testing "should be considered for all new formulations whether they are proposed for a new route or the same route as a previous formulation," and urge FDA/CDER to revise this guidance accordingly.

Oral

We concur that no additional testing is necessary or appropriate for this exposure route.

Dermal

We have several concerns regarding the dermal guidance, including:

- Line 158: The agency specifies that the "dermal hypersensitivity potential of the new formulation should be evaluated"; however, validated testing methods and/or internationally recognized test guidelines do not exist for this endpoint.
- Lines 165-8: The conduct of an additional non-rodent study of up to 90 days should be expressly limited to cases in which substantial toxicological concerns are highlighted on the basis of PK/ADME and/or other available data.
- Lines 170-7: We strongly question the reliability, human relevance and overall value of rodent (photo)carcinogenicity studies,[1] and challenge the view that additional studies of this magnitude would contribute vital new information for risk assessment purposes. We urge FDA/CDER to consider non-testing alternatives to these studies (e.g., stronger warning labels).
- Lines 179-80: In most cases, the use of both untreated and vehicle control groups is not scientifically justified. Instead, vehicles with a known toxicity (or lack thereof) should be chosen, in which case the latter will suffice. Guidance is also needed in relation to the appropriate number of treatment groups and group sizes for these studies.

Ocular

As above, new testing by this route should be (i) considered only if this is an intended route of human exposure, and (ii) limited to a single species.

[1] http://www.stopanimaltests.com/pdfs/Wasted$$$.pdf

Otic

Dermal irritation should be evaluated using the validated and EU-endorsed EPISKIN-Skin Irritation Test,[2] and the study of dermal hypersensitivity potential should be reconsidered, per the discussion above.

Inhalation

As above, new testing by this route should be (i) considered only if this is an intended route of human exposure, (ii) limited to a single species, and (iii) conducted using either a vehicle or sham control, but not both. We also invite FDA/CDER to consider data from the EpiAirway[3] model of the human respiratory tract, to the extent that investigation of absorption and local effects are deemed necessary.

Intranasal

The differences between rodent and human nasal passages, including cell type, architecture, and breathing pattern, is well established.[4]

Vaginal

Refer to above discussion of delayed hypersensitivity testing. Please also consider the use of EpiVaginal[5] model for this purpose.

Rectal

We concur that no additional testing is necessary or appropriate for this exposure route.

Intraoral

Given true that "early clinical monitoring of the oral cavity in early phases of clinical development can be used to ensure that excessive local irritation of the oral cavity does not occur in humans," it is inappropriate for the agency to suggest further preclinical *in vivo* testing as an "alternative" to the clinical approach. To the extent that further evaluation of local effects are deemed necessary, we invite the agency to consider the use of *in vitro* oral and gingival models from MatTek[6] and/or SkinEthic.[7-8]

Intracavernosal or Intraurethral

As above, new testing by this route should be considered only if this is an intended route of human exposure. Additionally, if the agency does not intend for this guidance to imply the conduct of a generational reproductive toxicity study, this should be clearly stated.

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[2] http://ecvam.jrc.it/ft_doc/ESAC26_statement_SkinIrritation_20070525_C.pdf
[3] http://www.mattek.com/pages/products/epiairway
[4] Parent R. (1992). Treatise on Pulmonary Toxicology. Boca Raton: CRC Press.
[5] http://www.mattek.com/pages/products/epivaginal
[6] http://www.mattek.com/pages/products/epioral
[7] http://www.skinethic.com/HOE.asp
[8] http://www.skinethic.com/HGE.asp

Intravesicular

New testing by this route should, again, be considered only if this is an intended route of human exposure. Moreover, the conduct of costly and animal-intensive reproductive and developmental toxicity studies should be expressly limited to cases in which substantial toxicological concerns are highlighted on the basis of PK/ADME and/or other available data.

Intrathecal or Epidural

Testing should generally be limited to the single, most appropriate species (as determined for the approved drug product).

Subcutaneous or Intramuscular

We concur that no additional testing is necessary or appropriate for this exposure route.

Conclusions

We appreciate FDA/CDER's efforts to modernize and streamline its testing guidance in line with the Critical Path initiative, and hope that our input will be reflected in the agency's final guidance on this subject.