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January 15, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Subject: Comments on FDA's Draft Guidance for Industry Nonclinical Studies for Development of Pharmaceutical Excipients

Noveon, Inc. (Noveon) is submitting comments on FDA's draft guidance on non- clinical studies for excipients that were published October 2, 2002. Noveon recognizes the importance of conducting hazard assessments of its products. However, we are concerned that the guidance needs to be structured to fully utilize nonclinical data on the end-use drug, to avoid unnecessary and duplicative testing, to utilize most current test methods, and to utilize ancillary information (physical chemical properties, metabolism, etc.) in assessing specific testing needs. Effective utilization of this information is consistent with good science and will help conserve valuable resources including animals. Noveon also is concerned that the new draft guidelines may make the development of excipients financially prohibitive.

- Safety assessors need to fully utilize nonclinical data on the formulated drug in its safety assessment of new excipients.

The final formulated drug is a mixture of active ingredients (AI) and excipients that are intended to function as physiologically/therapeutically inert materials, or at most provide a modifying effect on the final drug product such modifying delivery time and or location. While AI's and excipients have their own physical/- chemical and toxicological properties, the final mixture or formulation will have its own unique toxicological and pharmacological properties. Therefore, while information on the intrinsic hazard of the excipient(s) provides valuable supportive information the ultimate safety and risks of the final drug product can only be established through the full nonclinical and clinical evaluations which are part of the current guidance for drug evaluation. Furthermore, these data provide information on the safety of the excipient.

- Guidance for nonclinical testing of excipients needs to avoid unnecessary duplicative testing.

A full assessment of the safety of excipients can only be obtained through nonclinical and clinical testing of the formulated drug. These studies provide information on possible interactions of the components as well as their intrinsic hazards. Nonclinical

studies of excipients also provides important information to help identify potential hazards and target organs and to support the safety evaluation of the drug. However, nonclinical testing of excipients does not need to be duplicative of those used to assess the safety of the drug.

Acute toxicity. It is important to understand the acute toxicity of excipients. Basic hazard information should include irritation and sensitization end-points as well as gross toxicity. "Limit tests" such as OECD 402 and 403 which reduce the number of animals should be used. Also, the Mouse Local Lymph node Assay is a valuable alternative to the traditional M&K and Buehler assays.

ADME Studies. Information on absorption, distribution, metabolism and excretion can help our understanding of mechanism of action, determining bioavailability, and identifying potential target organs. While ADME studies can provide valuable information, they are not essential in every case. The need should be based on the toxicology profile from other studies and after consideration of information on structurally similar chemicals and well-described metabolic pathways and enzyme systems. Also, FDA should not require ADME on high molecular weight polymers that meet the EPA polymer exemption guidelines for PMN's (40 CFR 723; 60 FR No. 60, March 29, 1995). These material are too large to be adsorbed and do not justify ADME studies.

In the 1984 final polymer exemption rule (49 FR No. 226, Nov. 21, 1984) EPA established 1000 Dalton as the threshold for exempting polymers. The Agency noted that molecular weight is a determinant of risk and stated that,

> *For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response.*

The Agency went on to state that,

If a chemical cannot penetrate the protective membranes to access a target site, it usually cannot elicit a response in the organism no matter what inherent potential it may have to do so. It can be further reasoned that if a chemical cannot elicit a response, it will not present a risk.

The Agency concluded that,

"---substances with molecular weights greater than 400 are not readily absorbed through the intact skin and that substances with molecular weights greater than 1000 are not readily absorbed through the gastrointestinal tract."

Genotoxicity. The genotoxic potential needs to be evaluated. It is important to include a bacterial point mutation assay and an assay that looks at clastogenic effects. FDA should require that validated assays be used. However, FDA should not require genotoxicity data on high molecular weight polymers that are not expected to be

bioavailable. Instead the hazard assessment should focus on the major impurities (i.e., residual monomers) and utilize the nonclinical data on these chemicals in assessing potential hazards of the polymeric excipient.

Mammalian Toxicity. The current proposal to tailor study duration to anticipated exposure has some merit. However, the proposal to require repeat dose testing on excipients beyond 90-days is unnecessary except in the case where potential carcinogenicity concerns exist. For excipients used in drugs that are intended for a maximum duration of clinical use of greater than one month FDA could require 90-day studies in rats and dogs. These studies could be used to assess potency and target organs. FDA should fully utilize the longer term nonclinical studies, and subsequent clinical trials, on the formulated drug to verify that these target organ effects are not seen at the typical or maximum use level. This approach would provide the necessary safety assurances while avoiding duplicative and potentially costly testing that could prohibit the development of new excipients.

Reproductive/Developmental Toxicity.

Conducting extensive reproductive and development testing in rats and dogs on both excipients and AI's is unnecessary and duplicative. Again, the safety assessment should fully utilize reproductive/developmental nonclinical studies on the formulated drug to verify that reproductive effects are not seen at therapeutic doses. Excipients should be screened for reproductive/developmental toxicity potential by using the OECD 421 screening assay. This data combined with pathology information on reproductive tissues in the 90-day studies can provide needed information on the reproductive/developmental toxicity potential of the excipients. This approach will provide the necessary safety assurances while avoiding duplicative and potentially costly testing that could prohibit the development of new excipients.

If you have any questions on these comments, please contact Dr. Robert K. Hinderer at 216-447-5181 or Robert.Hinderer@noveoninc.com.

Sincerely,

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