



December 9, 2002

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

Re: Docket Number 02D-0389  
Response to FDA Call for Comments  
Guidance for Industry, Nonclinical Studies for Development of  
Pharmaceutical Excipients Draft Guidance

Dear Sir or Madam:

Reference is made to Federal Register notice: October 2, 2002 (Volume 67, Number 191) announcing the availability of Guidance for Industry, Nonclinical Studies for Development of Pharmaceutical Excipients – Draft Guidance.

AstraZeneca has reviewed the Draft Guidance document and our comments are attached.

Please direct any questions or requests for additional information to me or in my absence to Dr. Rajendar K. Sharma, Director, Preclinical Sciences, at (302) 886-5619.

Sincerely,

Lewis Kinter, Ph.D.  
Senior Director, Preclinical Sciences  
Safety Assessment – US – Development  
Phone (302) 885-8193

Enclosure

RKS/plm

02D-0389

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## Guidance for Industry – Nonclinical Studies for Development of Pharmaceutical Excipients

### General Comments

One reviewer thought the DRAFT Guidance for Industry Nonclinical Studies for Development of Pharmaceutical Excipients is straight-forward and in alignment with other relevant documents. This reviewer appreciated the recognition that functional toxicity endpoints (eg. Safety Pharmacology) will play as much of a role in establishing the safety of new excipients as traditional toxicology endpoints (eg. Histopathology)

Section	Page or Line Number	Comment or proposed replacement text
III, B, 1	Line 136	According to one reviewer, it has been accepted by Japan (and this reviewer thinks also the US) that acute toxicity studies in the non-rodent can be replaced by short term (MTD DRF type) studies provided proper dose levels and observations are employed (ICH-1). This option should be included.
III, B, 1	Line 143	Setting the MFD at 5 g/kg is inappropriate, as in one reviewer's experience, oral dosages of this amount have been associated with bowel impaction in rodents. For ethical reasons, it is inappropriate to dose to a level causing physical harm to test animals solely related to the bulk of the material administered. In this reviewer's experience, an MFD of 2-3 g/kg is sufficient, and unlikely to produce mechanical obstruction of the bowel.
III, D, 4, b	Line 231	Please provide some current examples of acceptable 'models sensitive to nongenotoxic carcinogenic events'.