



SEND UPS OVERNIGHT DELIVERY

September 14, 2000

7342 00 SEP 18 A9:37

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

RE: Docket No. 00D-1407

International Conference on Harmonization; Draft Guidance on Safety Pharmacology Studies for Human Pharmaceuticals; Availability

Dear Sir or Madam:

Reference is made to the August 7th, 2000 Federal Register notice (FR Doc. 00-19941 Filed 8-2-00; 3:33 pm) announcing the availability of International Conference on Harmonization; Draft Guidance on Safety Pharmacology Studies for Human Pharmaceuticals; Availability.

AstraZeneca has reviewed the draft guidance and our comments are as follows:

Comments on: Guideline on Safety Pharmacology Studies for Human Pharmaceuticals" (step 2)

General Comments

- **Comment 1:** The Guidance defines (for the first time) Safety Pharmacology (SP) and places SP within preclinical development context. The DRAFT defines a rational, scientific, and compound-by-compound approach with sufficient guidance to ensure that the studies conducted will focus upon generation of useful and relevant information for patient safety in subsequent clinical trials.
 - **Comment 2:** The sections (2.4) on dose setting for in vivo and in vitro studies need further clarification. The issues are:
 1. The dose/exposure ranges for in vivo studies should span from those established for the pharmacodynamic/therapeutic to the toxicologic ranges without interruption, to the extent feasible;
 2. The concentration ranges for in vitro studies should span and exceed (by appropriate multiple) those established for the pharmacodynamic/therapeutic to the toxicologic ranges without interruption, to the extent feasible; and,
 3. In the absence of identifiable toxicologic markers the high doses/concentrations for in vivo and in vitro SP studies will be established based upon feasibility and practicality.
- These concepts should be stated explicitly (see more below).

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19850-8355

C5

00D-1407

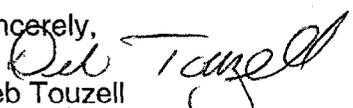
• **Comment 3:**

Section, Page Number, Line Number	Comment
1.3	<p>Scope of the guideline Should this guideline apply also for biotechnology-derived products? In that case it might be useful to include a definition or to specify what type of biotechnology derived products that are referred to.</p>
1.5 line 55	<p>Definition of SP - Line 55, CNS is a integrated system and effects on CNS are most often measured using behavioral parameters, therefore we suggest to change to "...effects of substance on physiological and behavioral functions..."</p>
2.3.3.1 line 131 line 134	<p>2.3.3.1 Sample size and use of controls -Line 131, It may be very difficult to really show absence of effect. Significant although very small effects might arise when the size of the group increases id very sensitive models or methods are used. Could this sentence be rephrased, to put the emphasis on the importance to use statistics and the size of experimental group when designing studies? -Line 134, Maybe limitation of number of controls is better than exclusion in well-characterized in vivo systems?</p>
2.4.1	<p>Dose Levels/In Vivo Studies This carefully worded paragraph appears to say 'The dose-range to be evaluated in in vivo SP studies should cover the 'therapeutic/pharmacological range' to the low/mid dose (or equivalent systemic exposure) toxicological range in the relevant animal model, to ensure that the entire dose/exposure-range is evaluated. If this is the intent, why not say so explicitly. It is much more important to relate effects to exposure than to doses. DMPK data and kinetic information should be used for the design and justification of dosing levels and duration and frequency of administration. Line 155-158, "the highest tested dose should equal or exceed those doses producing some adverse effects..." This might mean that you need to go to the Maximal Tolerated Dose found in the Toxicological studies. For very nontoxic/safe compounds this should not be necessary. It is more important that the doses/plasma levels used in the safety pharmacology studies are bridged to the lower doses/plasma levels used in the toxicology studies. -Line 162-163, How does this relate to row 155-158? The final sentence ("Testing of a single dose group...") appears to relate to the situation where no limiting effect (pharmacodynamic, toxicologic, etc.) is demonstrable and some sort of a maximum feasible (or limit) dose is used. While the Guidance allows for a single dose group, the Guidance does not address the salient issue of how to identify the dose for SP studies in this situation. This matter has been previously addressed in the 'Dose Selection for Carcinogenicity Studies for Pharmaceuticals' (ICH-S1C March 1995), and the same criteria (modified) would seem also apply. Suggest: 'In the absence of compound-related dose limiting pharmacodynamic of toxicological effects, a maximum dose for SP studies could be: 1. A dose that represents a 25-fold ratio of animal to human plasma AUC of parent compound and/or metabolites is considered pragmatic. 2. A dose based upon demonstration of saturation of absorption measured by systemic availability od drug-related substances is acceptable. 3. A Maximum Feasible Dose, based upon considerations including practicality and local tolerance.'</p>
2.4.2	Dose Levels/In Vitro Studies

	<p>The Guidance is too vague as written. Consider paraphrasing from the previous section (2.4.1). For example 'Generally, the concentration response for in vitro studies should be compared to concentrations necessary for the primary pharmacodynamic response in the test species or the proposed therapeutic effect in humans, if feasible. It is recognized that there are both species and methodology differences in pharmacodynamic sensitivity. Therefore, concentrations should include and exceed the primary pharmacodynamic, therapeutic and toxicologic ranges. In the absence of demonstrable/adverse effects, the highest tested concentration could be:</p> <ol style="list-style-type: none"> 1. A concentration that represents a 25-fold ratio of in vitro to human maximum plasma concentration (Cmax) of parent compound and/or metabolites. 2. A Maximum Feasible Concentration, based upon considerations including solubility, and practicality.'
2.5 line 169	<p>Duration of dosing -Line 169; Is not repeated dosing included in safety pharmacology? To what does 'non-clinical studies' apply?</p>
2.8.2.1	<p>Renal/Urinary System 'Glomerular filtration rate (GFR), renal blood (or plasma) flow rate (RBF, RPF), and urinary excretion of electrolytes and other solutes and water.' Should be added to the list of 'relevant renal parameters' provided.</p>
2.8.2.4 line 270	<p>Other organ systems, -Line 270, dependency potential belongs to CNS, since it is a clear CNS related effect. Use the term "drug dependence and abuse liability" instead of dependency potential!</p>
2.11 para. 4 line 330	<p>Application of GLP Paragraph 4 ('Safety pharmacology studies conducted...general screens..'). This paragraph suggests that a sponsor could avoid the intent of Section 2.11 simply by conducting SP studies as general screens. The paragraph should be expanded to indicate that in such case the requirements outlined in the first paragraph would apply. -Line 330, What does this mean? You might interpret this sentence as if there is no concern, for example the test compound has no affinity in general receptor screen, you don't have to perform the safety pharmacology studies on vital organ systems according to GLP? Needs to be better specified how to interpret this sentence.</p>

Thank you for your consideration.

Sincerely,


 Deb Touzell
 Regulatory Knowledge Associate
 AstraZeneca Pharmaceuticals
 (302-886-3566)