



FDA Draft Exploratory IND Studies, issued April 2005

Call for comments and suggestions

Response from Xceleron Ltd., UK

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Xceleron wish to congratulate the FDA on publishing their draft guidance document 'The Exploratory IND'. We believe this is an innovative and farsighted document which meets one of the objectives of the FDA's Critical Path Initiative of improving drug development. Our comments relate solely to the microdosing aspects of the Draft Exploratory IND, rather than doses designed to elicit a pharmacological affect, as this is our main area of both knowledge and interest. Our experience, gained over a number of years, is that microdosing is a valuable weapon in the drug selection armoury (1 - 2). Microdosing may not be applicable for every development drug and *in vitro*, *in silico* and animal models remain valuable tools in lead optimization. The predictability of such models however, can be notoriously unreliable (3). Microdosing on the other hand, enables the generation of early metabolism and pharmacokinetic data in the target species, namely man. The Exploratory IND goes some considerable way to clarifying the regulatory position of microdosing studies in the United States, thus facilitating the conduct of these valuable studies. Our specific comments on the Draft Exploratory IND are as follows.

1) Emphasis is placed on the acquisition of single dose toxicity data to enable single dose studies in humans. Whilst in principle this is sensible, it leaves an

ambiguity in respect to a cross-over design. In a cross-over study, two, three or more doses are administered (eg using different routes of administration) to the same volunteers, with a suitable wash-out period between each dose occasion to allow for the systemic depletion of the drug.

This is different to a repeat dose study, where the intention is to achieve the cumulative effects of repeat administration during clinical use.

A repeat dose study is not appropriate in the microdosing context but a cross-over design is very valuable as, for example, the pharmacokinetics derived from the therapeutic route usually oral can be compared to an intravenous dose in the same volunteers. We would like to see this ambiguity clarified stating that a cross-over design is acceptable, providing a suitable wash-out period is part of the study. A limit on the number of dosing occasions could be included; we would suggest four. (This comment should be viewed in the light of 5 below.)

2) The Draft IND recognises that microdosing is relevant to the selection of lead compounds from multiple candidates. This involves the separate administration of several candidates to different groups of volunteers. In our experience, pharmaceutical companies often use microdosing to select from a structural series of compounds. It would therefore seem appropriate to allow the dosing of several candidates under the auspices of a single toxicology package based on a representative candidate from the series.

Alternatively, a situation could be envisaged where toxicology was performed on a mixture of candidates, each with the 100 fold safety margin. For example, four candidate drugs could be dosed to the animal species selected for the safety testing as a mixture consisting of 10 mg of each. If there were no adverse effects then dosing 100 µg of each candidate drug separately to human volunteers would represent no significant risk. This approach recognises that the resulting microdose in humans may have to be lower than it would otherwise be, if each candidate underwent its own toxicology tests. The approach however, would provide flexibility in the study design and facilitate the provision of early human data. (This comment should be viewed in the light of 5 below.)

3) Page 9 makes reference to minimum toxicological effects (line 324). This implies that multiple doses may have to be administered to the toxicology species and we feel that this may not necessarily be the FDA's intention as the alternative of

using a margin of safety is mentioned on the same line. We would suggest that this is clarified to say that if no effects are seen using a safety factor of 100, then there is no requirement to obtain toxicity data above this dose level.

4) The Draft Exploratory IND states that the choice of toxicology species is made on the basis of *in vitro* metabolism data. This does not seem entirely logical to us, as *in vitro* data are being used to make a choice under circumstances where such data are suspected of being non-predictive. Given the 100 fold safety margin and the defined ceiling dose (100 µg) it would seem more sensible to state that the rat is the preferred toxicology species, unless data are available on the candidate, or molecules with similar chemistry, to suggest otherwise. The EMEA position paper (referenced in the Draft Exploratory IND on page 9) takes the approach that the rat is used as the toxicological species. This comment should be viewed in the light of the suggestions in 5 below.

5) Whilst the FDA should be commended for their visionary approach to the toxicological requirements, to allow the administration of a microdose to human volunteers, we are not convinced that such a minimalist strategy is applicable in all cases.

We suggest that in addition to the intended clinical route, an intravenous administration is also given to the toxicology species. Microdosing is used in the pre-development phase where there is likely to be a deficit of pharmacokinetic data. The absence of toxicological effects after oral administration may therefore, be due to unsuspected poor bioavailability in the toxicology species. Furthermore, it would seem judicious to state that other toxicological tests might be appropriate, depending upon the known action of the candidate drug. If, for example, the candidate drug is designed to have an affect on the heart, then acquisition of some minimal cardiovascular safety data might be sensible in an appropriate test species. We agree with the sentiment that genetic toxicology data are not generally required for single administrations. For cross-over designs however, (see 1 above) such data might be beneficial. We would point out that it is likely that at least an Ames test and an *in vitro* chromosomal aberration study would have been undertaken by the time a microdosing study is conducted as part of the normal preclinical development program.

6) The Draft Exploratory IND recognises that there may be a requirement to administer radiolabelled drug in microdose studies and indeed cross reference is given to 21CFR part 361 (footnote 9 on page 5). The situation with the use of

radioactivity is however, left ambiguous. The relationship between the Exploratory IND and 21CFR part 361 should be made clear. In certain European countries there is a history of dosing 200 nCi (7.4 KBq) in the absence of animal dosimetry data. Since the human body contains approximately 200 nCi of naturally-occurring radioactivity (^{14}C and ^{40}K) then a further short-term 200 nCi dose represents a negligible risk (4). It would therefore be useful if some definition of what constitutes a low dose of radioactivity could be made. We would suggest 200 nCi, without a requirement for any animal dosimetry studies. We would also suggest that it is clearly stated that cross-over studies using 200 nCi per dose are acceptable (see 1 above).

7) On page 7, it should be made clear that, providing a low dose of radioactivity is given (6 above) then manufacturing details are not required for radiolabelled drug (only “cold” substance). Radiolabelled microdosing studies are usually designed around the use of Position Emission Tomography (PET) or Accelerator Mass Spectrometry (AMS). For AMS studies, only very low levels of radioactivity are administered and the drug dosed typically does not contain more than 2% of its mass as radiolabelled compound (based on a typical molecular weight of 500 and a dose of 100 μg , 200 nCi). The same may not be true of PET studies, but here special difficulties exist as isotopes used for PET imaging have half-lives of a few hours at most. We do not wish to make further comment on PET studies and we will leave this to the PET community.

8) Superficially, it may seem obvious that the toxicology studies are performed on “cold” drug and not the radiolabel. The concepts in the Exploratory IND however, may be far reaching and might impact on those who have little experience with the use of radiotracers. We would therefore suggest that it is made clear that if radiolabel is used, there is no requirement to include it in any toxicological studies.

9) Although it is understood that separate guidance is being drafted on the requirements for GMP material, we would like to see this made clear. In our view, the scenarios given in the Draft Exploratory IND (eg a single batch of test substance reserved for toxicology tests and administration to human volunteers) negates the requirement for GMP material. To us, the driver behind GMP is the *reproducible* quality of manufacture and since microdosing requires only a single batch to be synthesised, GMP becomes unnecessary.

10) Finally, although the FDA's Draft Exploratory IND shows great innovation, it is nevertheless different to the EMEA position paper (5). We would like to see, at some time in the future, a harmonized guideline between the United States and Europe.

References

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