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MICRODOSING AND 21 CFR PART 361

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In their Critical Path initiative (1*)*, the FDA have highlighted the need for a new development toolkit to improve predictability and efficiency of early human trials with new medical entities (NMEs). Sub-optimal human pharmacokinetics (PK) in Phase I is often a reason for drug failure in later stages of development. This can arise from the lack of predictivity of animal, *in vitro* and *in silico* metabolism models. In addition to being a reason for attrition *per se*, sub-optimal exposure to NMEs due to poor human PK properties can significantly contribute to drug failure due to efficacy or safety issues in patients. Recently, the concept of human microdosing (human Phase 0 studies) has been proposed that could significantly reduce the failure rate due to suboptimal PK.

Human microdosing studies center on the administration of doses of drug substance sufficiently low not to have observable pharmacological activity. Hence, microdose studies would not examine the safety and efficacy of novel drugs but are used solely to screen for ranking the ADME properties of several drug candidates. The resulting human PK information generated very early in the development process could be effectively used for early internal decision making by pharmaceutical sponsors on selection of more optimal NMEs for classical Phase I development.

Ultrasensitive and robust analytical techniques such as accelerator mass spectrometry (AMS) and in select cases, tandem liquid chromatography-mass spectrometry (LC-MS) are available today to measure drug and metabolite concentrations with sufficient precision to characterize the PK parameters of a microdose.

Microdosing is meeting with increasing interest in the pharmaceutical industry to support candidate selection (2,3). Furthermore, several pharmaceutical companies recently supported a microdosing evaluation project known as the 'CREAM' trial (CREAM = Consortium for Resourcing and Evaluating AMS Microdosing). In this trial, the PK properties of both a microdose and a pharmacological dose were examined for five generic drugs whose human metabolism was not predicted by animal or *in vitro* models (warfarin, ZK 253, diazepam, midazolam and erythromycin). The data for four drugs showed good predictivity of microdose PK for the pharmacological dose level. Other studies of which the authors are aware have shown similar results.

Human microdosing was endorsed in 2003 by the European Medicines Evaluation Agency (EMA) in a Position Paper on the non-clinical safety studies to support human microdosing trials (4). EMEA defined a preclinical toxicology package which is substantially reduced from the ICH M3 package (5) and the US Acute Toxicology Guidance (6) traditionally used for Phase I studies, indicating the European Agency's comfort with the safety of human microdosing.

The FDA is currently reviewing 21 CFR Part 361 as to whether or not new isotopically labelled new chemical entities destined for ultimate pharmaceutical use is covered by this Regulation. We are recommending that a new guidance document on 21 CFR Part 361 be prepared to include the following;

- Microdose administration to human volunteers of isotopically labelled NCEs be permitted (a microdose is defined as no more than 100 micrograms of NCE or 100th of the pharmacological dose whichever is the smaller) without submission of an IND
- A simplified toxicology package be permitted for microdose studies similar to that set out in reference 4.

Human microdosing may not be appropriate for every drug development program. However, in carefully selected cases, we are of the opinion that greater implementation of microdosing could improve the quality of development decisions through providing human ADME data before the investment is made in traditional Phase 1 clinical development. By improving the chances of selecting the best candidate, early human microdosing would significantly improve the success rate in clinical development (for a general

discussion of ways to accelerate drug development see reference 7) and fulfil one of the major goals of the Critical Path document.

Microdose studies are included considered under the draft Exploratory IND guidance document. However we believe the 21 CFR Part 361 approach is preferred for microdose studies of isotopically labelled new chemical entities since microdoses to be administered are sub-pharmacological, pose no safety risk and already fall under the *aegis* of this regulation. If 21CFR Part 361 does not include the ability to administer development drugs to humans for the first time then we see no purpose for the revision of this regulation. Indeed if novel PET ligands and AMS microdoses are excluded from 21 CFR Part 361 then a whole new community of academic and industry researchers will have to submit Exploratory IND applications which they did not have to do in the past.

References

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