Innovative Early Development Regulatory Approaches: expIND, expCTA, Microdosing

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The Food and Drug Administration (FDA) Critical Path Initiative[1] as well as the European Medicines Agency Road Map to 2010 (ref. 2) call for opportunities for more efficient drug development. One of the initiatives that has emerged in this context is the elaboration through guidance of exploratory investigational new drugs (INDs)/clinical trial applications (CTAs). This article reviews the history of these emerging guidances as well as the experience to date in their use by the industry.

Over the last few decades, we, as an industry, have moved to a somewhat rigid paradigm for first-time-in-human studies for small molecules. Typically upon the identification of an interesting compound, selected from animal and/or *in vitro* data, an investment is made into the development of a scaled-up synthetic process for a pilot plant synthesis of up to 10 kg of the drug substance. This substance is extensively characterized and used to assess safety issues through the conduct of 2- or 4-week toxicology studies in the rodent and non-rodent as well as gene toxicology and safety pharmacology studies. In addition, significant investment is made in the area of drug metabolism and in pharmaceutical development for the elaboration of a suitable delivery system for the compound. The time required for these activities to a first dose in humans is very compound and company dependent but typically would be 1.5–2 years. It is not surprising that the industry has been looking for a more efficient way to test their compounds in humans initially as well as to select compounds with human data rather than animal data. The underlying theme in this desire is the leap of faith that compounds or programs selected or deselected based on human data is intuitively a better process.

A new paradigm where compounds could be investigated more efficiently for their pharmacokinetic profile emerged as the micro-dose European Medicines Agency position paper.[3] Toxicology testing limited to the rodent as extended single-dose studies (via the i.v. route and the intended clinical route as well as gene toxicology and safety pharmacology studies) allowed entry into humans with a laboratory batch of drug substance. The definition of a micro-dose was 1/100th of the projected pharmacologic dose in humans or a maximum of 100 µg. This very low dose presented two major challenges. The first was the bioanalytical analysis of the drug circulating systemically. In most cases, carbon-14 labeled drug substance had to be administered to allow analysis to be performed using accelerated mass spectrometry (AMS), an approach analogous to carbon dating. The second challenge was in the interpretation of the data generated from a micro-dose study. The concern in the interpretation of the data stems from the enzyme kinetics of transporters primarily in the gastrointestinal wall and liver. A pharmacologic dose usually saturates these enzymes limiting the kinetics to a V_{max}, a zero-order process. However, a micro-dose provides a substrate concentration low enough that the kinetics are first order or directly related to the concentration and not limited in rate. This perceived concern was tested by a consortium in Europe named the Consortium for Resourcing and Evaluating AMS Microdosing project. This project tested five compounds with micro-doses via the i.v. and p.o. routes in addition to pharmacologic doses. The conclusion of the study was that the pharmacokinetics at a pharmacologic dose was accurately predicted by micro-doses for only three of the five compounds.[4] Despite this concern, companies have employed micro-dosing approaches. For example, Speedel has presented its strategy for the selection of a compound for development in its follow-up renin inhibitor program.[5] Speedel brought three compounds to man with carbon-14 labels and micro-dosed cohorts of subjects via the i.v. and p.o. routes. The compound demonstrating the highest absolute bioavailability was selected for further development in phase II clinical trials.

The next evolution of exploratory studies in humans, at least by a health authority guidance, was the publication of the FDA exploratory IND guidance in January, 2006 (ref. 6) which was linked to the Critical Path Initiative.[1] This document was not a guidance on how to conduct exploratory studies in humans but instead was a guidance on how the IND process could be used with more flexibility illustrated by providing three examples. The implication seems to be that the FDA would consider a unique

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preclinical program for exploratory INDs. Of the three examples offered, I will limit my comments to the first two. The first example in the guidance addressed micro-dosing. The concept evolved significantly from the European Medicines Agency guidance in that only the route intended for the clinical study needed to be used in an extended single-dose rodent toxicology program and no gene toxicology or safety pharmacology data were required.

The second example accurately reflected a proposal made to the FDA by Pharmaceutical Research and Manufacturers of America (PhRMA), the USA pharmaceutical trade association. The paradigm allowed entry into humans based on a full 2-week good laboratory practice (GLP) compliant rodent toxicology study in both genders as well as a non-rodent study in a very limited number of animals dosed at one dose level (the no adverse effect level (NOAEL) of the rodent extrapolated based on body surface area) for the intended duration of the human trial. Dosing in humans is limited with a start dose criterion (1/50th of the rodent NOAEL extrapolated on body surface area) as well as stop dose criteria based on the dose and exposure observed in the toxicology program—1/4th of the rodent NOAEL dose extrapolated by body surface area, ½ the exposure (area under the blood level curve (AUC)) at that same dose or the exposure (AUC) observed in the non-rodent study. Multiple dose studies in humans were limited to 7 days. The filing is a single administrative procedure allowing more than one compound and protocol. This paradigm has been successfully employed by the industry since the issuance of the guidance for >25 INDs to date. I will return to these examples at the end of the article.

The next health authority guidance that appeared for exploratory studies in humans was posted in the Belgian health authority web site in June, 2007 (ref. 7). This national guidance incorporated the FDA paradigm in terms of the first two examples in the FDA guidance with some changes. As a direct consequence of the TGN 1412 episode in the United Kingdom, a new paradigm evolved for setting the first dose in man assuring the dose would be below the minimum anticipated biological effect level (MABEL). MABEL is to be assessed from all appropriate preclinical data extrapolated to humans. In addition to the rat NOAEL start dose criterion, this guidance includes the MABEL principle. Another change from the FDA guidance allowed dosing in humans up to 2 full weeks. Provisions were made to allow dose escalation in humans above the FDA stop dose criteria (translated to focus solely on exposure and not the rodent NOAEL dose). Escalation could proceed if the toxicology of the substance was of a non-life-threatening nature and was monitorable. This guidance also offered a new paradigm, which had been evolving through European Federation of Pharmaceutial Industries, the European trade association. This approach allowed entry into humans based on GLP compliant 2-week rodent and non-rodent studies where the top dose in each species was capped at an exposure level ten fold higher than the exposure desired in the clinical program. This "capping of the upper dose" offered the advantage of being able to predict compound requirements accurately for the complete early development program, a significant savings to the industry. In addition, if target organ toxicity was observed in either or both species, an opportunity was offered to move directly into a classical phase I program. To my knowledge, this paradigm has yet to be used by the industry. Another change in the Belgian National Guidance was in the area of micro-dosing. The guidance allows the micro-dose to be given in divided doses and also allows for 100 μg doses to be given up to five times as separate doses with an appropriate washout period between doses. This latter approach requires a 7-day GLP rodent study to support it. These micro-dosing changes are considered to be an important step forward for imaging studies.

As with the FDA expIND, this is a single administrative procedure for more than one compound and protocol and to date Belgium has received four expCTAs.

The most recent health authority activity for additional opportunities for exploratory studies in Europe was in Bonn, Germany, 15 September, 2007. BfArM (Das Bundesinstitut für Arzneimittel und Medizinprodukte; Federal Institute for Drugs and Medicinal Devices) held an all-day workshop with stake holders exploring the possibilities of exploratory clinical trial applications (CTAs) in Germany. It will be very interesting to see how this initiative evolves in the near future.

As already indicated, several examples are now available on the use of the exploratory IND guidance, example 2. The companies that have come forward publicly with their examples are J&J, Merck, Novartis, and Pfizer. Without exception, subjects participating in these trials have not been compromised in any manner. In each case, the corporate objectives have been achieved through huge savings in the synthesis of material, huge savings in non-rodent animals, and huge savings in the time intervals to first-in-human dosing. The primary objectives in these examples appear to be mainly related to pharmacokinetic profiles for the selection of compounds; however, some projects also successfully explored pharmacodynamic markers. It is of interest to note that J&J has strategically employed the expIND to position their back-up compounds for their main development programs. At Novartis, seven exploratory IND programs have been planned to date. One program was terminated based solely on the limited toxicology package and never went to humans. Three projects have now been filed and two of these have been successfully completed in the clinic. Each of these projects had a very clear objective leading to the selection or deselection of compounds or programs for further development. If a project cannot be positioned in a manner where a clear decision can be made, then it probably should not go the exploratory IND/CTA route. These exploratory approaches, unlike a typical phase I approach, are designed to make a decision rapidly on the future of a compound or program. A phase I approach is a decision to define the tolerability and acute safety of a compound staging it for full development (**Table 1**).

In our experience, pre-meetings with the reviewing division of the FDA have been extremely useful and the spirit of flexibility around the IND process as touted in the guidance has been reflective in our dealings with the FDA. For example, we were allowed to dose humans for 12 consecutive days rather than seven and I am aware of another big PhaRMA company that was allowed to dose escalate above the stop dose criteria. It has been a learning experience for all who wish to participate (and several companies

Table 1 First-in-human studies

	Phase I IND/CTA	Exploratory IND/CTA
Preclinical expectations/ requirements	Large batch of one API 2- or 4-week rodent and non-rodent studies Gene tox Safety pharmacology Extensive API characterization ADME package Clinical service form with stability	Laboratory batch of several APIs Rodent study with/or without limited non-rodent study including toxicokinetics Gene tox (not for micro-dose) Safety pharmacology (not for micro-dose) Limited API characterization No ADME package Pragmatic delivery system with appropriate stability
Primary clinical objectives/ limitations	Safety/tolerability MTD assessment Stages compound for phase II	Selection/deselection of a compound for development Selection/deselection of a research program Limitations on dose levels No MTD assessment

ADME, absorption, distribution, metabolism and excretion; API, active pharmaceutical ingredient; IND, investigational new drug (application); CTA, clinical trial application; MTD, maximum tolerated dose.

have chosen not to) and the most difficult aspect of initiating projects has been internal hurdles and not regulatory hurdles.

Of the seven projects that Novartis has planned, all have had a pharmacokinetic element as the primary objective. Two projects had a pharmacodynamic marker as a secondary objective. Relative bioavailability was planned as a selection criterion between two anti-infectives. In one project, the compound with the shortest half-life of two was selected for further development. A short half-life was important for the appropriate pharmacology. In another project, one compound of three is to be selected for further development based on its absolute bioavailability. Absolute bioavailability is being assessed by administering to a single cohort of subjects an oral pharmacologic dose with a concomitant micro-intravenous dose labeled with carbon-13 (The original plan was to use carbon-14 but the sensitivity in the mass spectrometer allowed carbon-13 labeling). Using this dosing design, the issues discussed earlier around micro-dosing are avoided as the body load in total is at a pharmacologic level. The toxicology package supporting both the oral and intravenous doses was solely an oral package which gave sufficient multiples in exposure to support the human micro-intravenous dose.

In summary, exploratory approaches for first-in-human studies designed to select or deselect compounds or programs are still evolving in the USA as well as Europe. These paradigms have been brought to the International Conference on Harmonisation process for incorporation into the International Conference on Harmonisation M3 guidance rewrite. In early 2006, European Medicines Agency's Committee for Medicinal Products for Human Use issued a concept paper[8] inviting comments on the Safety Working Party's recommendation to draft a guideline on non-clinical data to support these various exploratory clinical trial approaches. Since then, no Committee for Medicinal Products for Human Use guidance has been issued but we hope that the interest expressed by the Belgian and German health agencies may help to move this forward.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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