Editorial

Impact of NEDO Project on Microdosing Clinical Studies: Toward the eIND Study in Japan

Currently, less than 10% of new drug candidates entering Phase I clinical trials progress beyond the investigational stage and reach the market. This low success rate of clinical trials makes drug development quite challenging, with increased costs and time required for development. An early phase clinical study [exploratory Investigational New Drug (eIND) study] has been proposed to help identify promising candidates early in the drug-development process. Microdosing (MD) is one of the methods included in the eIND study and is now called the Approach 1 method (or Approach 2 for repeated dosing) in the ICH M3(R2) guidelines.1 In Japan, The Ministry of Health, Labor and Welfare issued guidance on MD clinical studies in 2008,2 and then the international standards for non-clinical safety studies were announced as ICH M3(R2) in 2010. The concrete purposes of MD clinical studies include the following:

1. To clarify bioavailability (BA) and pharmacokinetic profiles of test compounds in humans,
2. To clarify the metabolic profiles of test compounds in humans,
3. To obtain information on the tissue distribution of test compounds in humans by using molecular imaging technology.

MD clinical studies have drawn considerable attention as a new and unique strategy for ascertaining the best drug candidates to advance to Phase I clinical studies; however, there remain various arguments discrediting the usefulness of this new strategy, especially the possibility of discrepancies in the pharmacokinetic (PK) profiles observed in MD and therapeutic-dose studies. This argument arises from the fact that some metabolic enzymes and drug transporters are saturated at therapeutic doses, but not at MD levels; this fact could result in non-linear PK profiles at therapeutic doses.

In Europe, major pharmaceutical companies have collaborated with academia to form a consortium that has performed MD clinical studies on marketed drugs to verify the usefulness of the approach. In the first study by the Consortium for Resourcing and Evaluating AMS Microdosing (the CREAM trial), 3 of the 5 drugs tested showed consistency in their PK profile and oral BA between MD and therapeutic dose studies.3 The second study was performed by the European Microdosing AMS Partnership Program (EUMAPP) and 7 drugs (including one new drug candidate) were tested for their PK profiles and oral BA in a MD clinical study.4 Most, but not all, of the drugs tested showed consistent PK profiles and BAs in the MD study with those established in therapeutic-dose studies. In parallel with these activities by consortia, many pharmaceutical companies in the EU and USA, including small venture companies, have performed MD clinical studies and reported its potency to streamline the drug-development process.5

In order to promote eIND studies in Japan, a NEDO (New Energy and Industrial Technology Development Organization) project on MD clinical studies was started in 2008; the project is called Establishment of Evolutional Drug Development with the Use of Microdosing Clinical Trial: Based on the Quantitative Prediction Technology of ADME. Professor Sugiyama of the University of Tokyo served as the leader of this NEDO-MD project and I served as the vice-leader. Because the purposes, concepts, and expected outcomes of this project were introduced in detail in an Editorial in this journal in 2008,6 here, I will report briefly the main achievements of the project over the past 3 years, during which time more than 20 clinical studies were conducted with marketed drugs.

One of the most remarkable concepts that makes the NEDO-MD project unique and significant is that it aims to establish a method to predict PK profiles of test compounds at the therapeutic dose from MD clinical studies. The project results revealed that saturation of the intestinal first-pass metabolism and/or transporter-mediated membrane permeation is the main cause of nonlinear PK of most drugs. A mathematical gastrointestinal absorption model was developed to simulate the non-linear BA of test drugs when the dose is elevated to the therapeutic range by incorporating the data obtained by MD clinical studies and by in vitro experiments on metabolism and transport.

In some studies, multiple drugs were applied simultaneously as a cassette. This new protocol for MD clinical studies was very effective in selecting the compound having the most desirable PK profile among several candidates with similar pharmacological potency. Also, the cassette dosing protocol is applicable to investigate drug–drug interactions and inter-individual deviation of the PK profile due to generic polymorphisms of enzymes and transporters. In the cassette dosing study, non-radiolabeled drugs were administered at a MD level and their blood concentrations were successfully determined by high-sensitivity liquid chromatography/tandem mass spectrometry (LC-MS/MS).

Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

doi:10.2133/dmpk.DMPK-11-PF-906

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Use of molecular imaging technology is another aspect of this project. MD clinical studies with positron emission tomography (PET) were performed to determine the tissue accumulation profile of radiolabeled drugs to analyze the function of transporters in the liver and the kidney. Also, it was demonstrated that PET technology is quite useful to observe the process of gastrointestinal absorption and subsequent biodistribution of orally administered drugs.

Some of these results have already been accepted for publication in prestigious journals\(^7\)–\(^{12}\) and we firmly believe that various outcomes of this project have provided clear evidence on the usefulness of MD clinical studies in drug development. However, in Japan, eIND studies including MD clinical studies on newly developed compounds have not yet been performed by pharmaceutical companies, although some Japanese companies have already been involved in MD clinical studies in the EU or USA.

As part of the NEDO-MD project, we set up a consortium to carry out MD clinical studies in which 12 pharmaceutical companies, 7 institutions for clinical study, and 5 companies for bioanalysis participated. In addition to the concerns relating to the nonlinear PK profiles of drugs, discussions among the consortium members identified problems to be overcome for conducting MD clinical studies in Japan. These problems include:

1. The cost–benefit performance and the time required to complete MD clinical studies are still unclear. In particular, pharmaceutical companies are concerned about possible delays in drug development if MD clinical studies are introduced to the drug-development process.

2. The response of the Pharmaceutical and Medical Devices Agency (PMDA) for conducting MD clinical studies is still not clear in some aspects. Since all eIND studies, including MD clinical studies, should be conducted as clinical trials in the formal process of new drug development, they should meet with various regulations for clinical trials such as good manufacturing practice (GMP) compliance for drug materials and products, and these are sometimes quite difficult for pharmaceutical companies to apply quickly.

3. Infrastructure facilities to support pharmaceutical companies when conducting eIND studies are not well developed in Japan. Since MD clinical studies are performed mainly by the DMPK or preformulation department of a company before Phase 1 clinical trials are carried out, companies may need a specific institution that can carry out the MD clinical study under contract, including drawing up protocols, preparation of drug materials and GMP compliance, selection of volunteers, operation of the clinical study, and analysis of drug concentrations. In fact, in the EU and USA, several contract research organizations (CROs) are working with pharmaceutical companies as business partners to support all these processes in a comprehensive manner.

The NEDO-MD project is now at the final stage at which MD clinical studies are planned to be conducted in Japan on newly developed compounds. This is quite challenging, but this new approach is expected to make significant progress in overcoming the above problems and to result in the development of a framework that can promote eIND studies in Japan.

References


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