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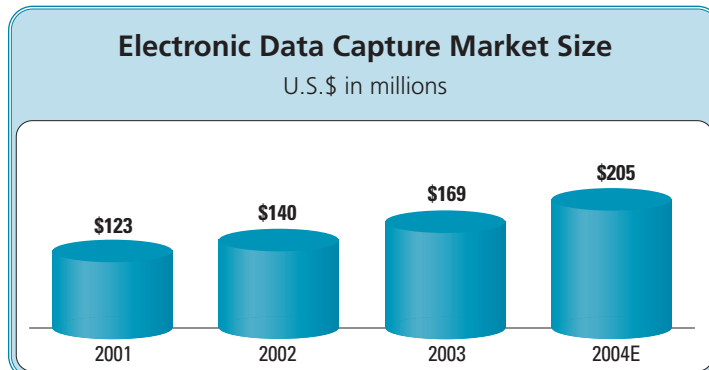
Volume 12, Issue 2

CROs, EDC Companies Partnering for eClinical Trials Adoption

► Despite the benefits of implementing eClinical trials, including reduced costs for pharmaceutical sponsors, many CROs have resisted transforming from traditional paper-based clinical trials to electronic environments. In particular, CROs whose main business involves managing clinical trials are not anxious to switch to a process that could require fewer monitors and billable hours. Some CROs have seen EDC vendors as competitive threats.

► Trends show that larger CROs are standardizing with one EDC vendor as much as possible, in order to benefit from efficiencies of scale, and smaller CROs are developing multi-vendor strategies. Both strategies have their drawbacks.

Contract research organizations (CROs), which for years have resisted electronic data capture (EDC) technology for fear it would cut core revenue streams, increasingly are adopting the technolo-



Source: Thomson CenterWatch estimates, 2004; analysis of company reports, 2004.

gy in order to stay competitive. Some CROs contract with vendors on a project-by-project basis only when sponsors specifically require an electronic process for data collection. Yet others fully embrace the technology and have signed multi-year licensing agreements with EDC vendors; these CROs have changed their internal processes in order to use EDC without hurting their revenues. While a handful of CROs have been paperless since their founding and bill themselves as eCROs, most notably Target Health and Pharmalink-FHI, the vast majority of CROs have had to convert from paper to electronic processes over time.

Recent deals between CROs and EDC vendors indicate a trend toward CROs' making commitments to incorporate the technology into their business models. Quintiles, the world's largest CRO, has a tentative agreement with etrials for a reported \$15 million to improve software that Quintiles developed for its phase IIIb and IV trials. At the same time, Quintiles, which has done more than 130 EDC trials, now claims it can offer sponsors lower fees for an outsourced EDC trial compared with an equivalent paper trial for some phase II and III studies.

A number of deals reflect the trend. Cato Research, which has

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Zeroing in on Microdosing

► Industry observers expect the number of microdose studies, also called human phase 0 trials, to increase in the United States once the U.S. Food and Drug Administration issues a draft guidance next month that will ease preclinical safety data requirements for microdose studies, making it easier to conduct them as exploratory studies rather than traditional phase I programs.

► During the past year, acceptance of microdose studies has grown more quickly in Europe. The growth of phase 0 could cut into the rapid rise of phase I trials, which sponsors have also used to kill drug candidates earlier.

Microdose studies, during which trace doses of new drugs are tested in humans to evaluate pharmacokinetics and drug metabolism before entering phase I trials, are being touted as a new way to speed up early drug discovery efforts, identify

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eliminating themselves from competing for business if a sponsor uses a different vendor for its electronic data capture. “I think there is benefit to choosing one or two vendors and developing teams internally that are very proficient in using that vendor’s technology,” said Medidata’s Sherif. “I think this industry will support at least three strong companies, maybe two very strong companies. At that point, it’s a lot safer to make a decision to be with one or another. I don’t see that people will commit on an exclusive basis until you see a bit more consolidation at the top. Having said that, CROs definitely are forming strategic alliances with different vendors.”

While trends show that large CROs are standardizing with one vendor as much as possible, in order to benefit from efficiencies of scale, and smaller CROs are developing multi-vendor strategies, both approaches have drawbacks. “They have to satisfy the requirements of the sponsor company, which means different EDC systems for different clients,” said Novartis’ Collins. “Each vendor’s EDC system is different and CROs have to invest in knowledge transfer, infrastructure, and train staff on the different EDC systems. This is a challenge. There is a dramatic economy of scale. The cost per page decreases significantly as the number of trials using the same EDC system increases. If you do only one EDC trial, EDC becomes very expensive. The larger the number of trials using one EDC system, the greater the savings. If at Novartis, we had to use more than one EDC system, we would not be talking about all the savings that we have made,” she said.

Rather than contracting with EDC vendors, some CROs are exploring options to license software and customize the tool themselves. Under DataLabs’ CRO Partner Program, which sells perpetual licenses for its software to CROs, CROs can adapt and conform the software to meet their technol-

ogy needs. DataLabs’ Langford said the CRO Partner Program offers CROs an alternative to working with EDC vendors. “CROs have to have a process that can be adaptable to the different processes sponsors ask for. We’ve created software that is highly adaptable,” he said.

The DataLabs CRO Partner program includes the DataLabsXC software for clinical study design, EDC and data management, which can be privately labeled to the CRO partner. Langford said with the software, CROs can perform the services they would normally do as a paper data management function. “EDC is just capturing data differently. We want to be able to provide CROs tools so they can do all the things that they would do within a paper trial—design the forms, building the edit checks—by using EDC. It allows them to capture the revenue that they would normally capture from data management and not have to pass that through to a third-party EDC partner or vendor.”

Whatever decision CROs make about implementing EDC systems, they recognize the technology can no longer be ignored. “Virtually everyone realizes EDC is inevitable,” said DataTrak’s Green. “The question now is which technology, which company, how do I change my current process to convert to EDC and take maximum advantage of it.”

—Karyn Korieth and Steve Zisson

Microdosing

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failures sooner and cut study costs. These early human microdose studies aim to weed out drug candidates with inappropriate metabolism, such as too short a half-life or poor bioavailability, before significant amounts are spent advancing the drugs into clinical trials.

While some pharmaceutical companies in the United States have done pre-phase I exploratory studies in humans for years, during the past 18 months the industry has seen acceptance of microdose studies grow more quickly in Europe, where a recent guidance defines abbreviated animal toxicology requirements to allow microdose studies of drugs in humans.

However, many expect the number of microdose studies, also called human phase 0, to increase in the United States once the U.S. Food and Drug Administration (FDA) issues a draft guidance in March that will ease preclinical safety data requirements for microdose studies, making it easier to conduct them as exploratory studies rather than traditional phase I programs.

Since the FDA began developing its guidelines for early human microdose studies, interest in the concept has heightened. Microdosing has become a hot topic at industry conferences; analysts at Frost & Sullivan included the concept of microdosing in a recent report discussing technologies that can accelerate early phase drug discovery efforts. And the top 20 pharmaceutical companies are exploring the possibility of using first-in-human microdosing studies in order to select drug candidates that offer a greater likelihood of success in later-phase clinical trials; while today sponsors use data from microdose studies mainly for in-house decision making rather than regulatory submission, a few major pharmaceu-

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tical companies have had microdose studies approved by the FDA through the traditional IND process.

At the same time, CROs have stepped up efforts in the United States to offer services for microdose studies and accelerator mass spectrometry (AMS), the technology most often used to analyze trace drug doses in the human body. Accium BioSciences, a Seattle-based contract clinical and analytical facility that specializes in phase 0/I technology and clinical trials, will open a dedicated clinical trials facility in April designed for the low-radiation dose delivery and sample collection required for AMS microdose studies. Vitalea Sciences Inc., a niche-CRO based in Davis, Calif., recently opened a commercial AMS facility in Woodland, Calif. Meanwhile, two U.K. companies that have completed many successful microdosing studies in Europe, Xceleron and Pharmaceutical Profiles, have established bases in the United States and plan to grow these activities substantially.

Microdose studies allow for more efficient, faster drug development by providing early information about pharmacokinetics (PK) and a drug's absorption, distribution, metabolism and excretion (ADME) characteristics in humans before investment is made in the resources needed for traditional phase I clinical development. The data help sponsors not only identify drug candidates that are

likely to succeed in later-phase clinical trials, but also to kill no-go drug candidates earlier, which saves time, money and resources during preclinical and clinical development.

While some believe microdosing has the potential to transform the drug development process, others are more cautious about embracing this new concept. Microdose testing can have negative effects on the scheduling of drug development since scale-up of chemical synthesis must be put on hold for six months or more pending results of the microdose study, and many remain unconvinced about the value of data from these studies, which only test PK and not safety and efficacy. Others, meanwhile, are waiting for data to answer the fundamental question about whether a correlation exists between the PK of microdoses and the PK of therapeutic doses.

New FDA Guidance

Momentum for microdose studies has built in Europe during the past 18 months since the European Medicines Agency (EMA) issued guidance on the nonclinical safety package to support human microdosing studies. At Xceleron, for example, which pioneered AMS microdosing studies in Europe, researchers have studied 10 molecules during the past 12 months. Three years ago, just one molecule was studied during the year. And some European drug sponsors have begun to incorporate microdosing

techniques into their early studies; Tripep, for example, a Swedish biotech research company, recently used microdosing for the development of alphaHGA, an HIV-inhibiting drug.

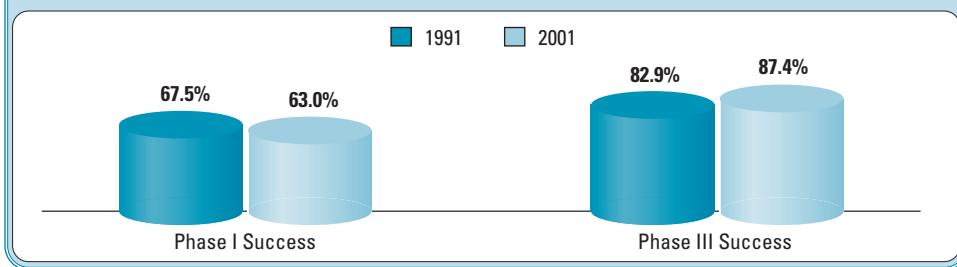
The FDA expects that the number of microdosing studies and exploratory IND studies will grow in the United States as well once the preclinical safety testing guidelines for microdosing studies are issued. "Sponsors start off with hundreds or thousands of chemical structures. Using a series of assays, for both efficacy and safety, they wean them down to a single drug, which they then synthesize—often in kilogram quantities—and take into the clinic. In some instances, you find out very quickly once you introduce it into humans that it doesn't have the characteristics of a successful drug," said David Jacobson-Kram, the FDA's associate director for pharmacology and toxicology, Office of New Drugs, Center for Drug Evaluation and Research. "This guidance will give sponsors the opportunity to not have to choose a single molecular entity—they will be able to choose between a number of molecular entities based on human data. Our hope is that we can really facilitate the drug development process."

The FDA will release its document, called "Guidance for Industry Investigators and Reviewers: Exploratory IND Studies," as a draft before the end of March. The draft guidance will be open for comment for 90 days; the FDA then will respond to the comments, make appropriate changes and publish the document as a final guidance.

The guidance addresses requirements for many types of exploratory IND studies; microdose studies are a subset of studies included in the guidance. "The whole notion behind this guidance is it enables sponsors to do clinical trials for different reasons. In some cases it would be to do imaging studies, in some cases they may have a handful of

Increases in Phase I Spending Improve Phase III Success

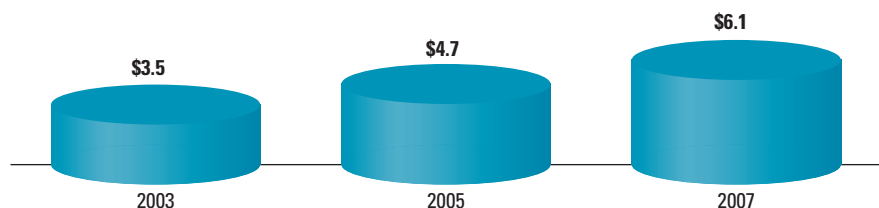
% chance of completing phase



Source: Thomson CenterWatch analysis, 2004; DiMasi, et. al., 2003.

Growth in Phase I R&D Spending

U.S.\$ in billions



Source: Thomson CenterWatch analysis, 2004; Goldman Sachs, 2003; Parexel Sourcebook, 2004–2005.

potential lead compounds that they want to choose between based on human data. This guidance provides a vehicle for doing those studies. It also provides the preclinical safety testing requirements for the various kinds of exploratory INDs,” said Jacobson-Kram.

With the new guidance, microdose studies will require fewer tests than conventional phase I trials. “The premise is that the amount of preclinical safety testing that a sponsor has to do will be gauged to what they want to do clinically,” Jacobson-Kram said. “Microdose studies are an extreme case here. Typically these are going to be single dose studies in very small numbers of people with doses that are sub-pharmacologic. Because of the very limited nature of those clinical trials, the amount of preclinical safety data that we would ask is really quite minimal and much less than a sponsor would be expected to submit for a traditional IND.”

The guidance has been prioritized as supporting the FDA’s Critical Path initiative, which includes developing tools that could allow sponsors to identify unsuccessful drug candidates earlier in the development process. “We see this guidance as an important tool for sponsors to make very early decisions in drug development,” said Jacobson-Kram. “We see it as an important piece in the Critical Path in enabling sponsors to make good decisions and not waste time and resources on drugs that will ultimately fail.”

Until the FDA issues its guidance, which could allow sponsor companies to expedite the microdose process, sponsor companies that submit microdosing INDs usually must meet requirements for traditional phase I studies, including IRB approval and two-species toxicology studies. “We’re in kind of a gray area since the guidance hasn’t been issued,” said Jacobson-Kram. “In some instances, what sponsors might find until this guidance is available is that some divisions would adhere to traditional requirements, which this guidance suggests is probably overkill for these kinds of studies. This guidance would hone down that battery of tests to a much more minimal level.”

Industry leaders remain cautious about endorsing the FDA’s guidance until they can review the document, including preclinical work requirements and submission standards, yet most welcome efforts to address regulatory obstacles to microdosing studies. “One of our significant limitations under 21 CFR 361.1 is that we are restricted to

radioactive drugs that have been previously evaluated in humans,” said Dennis Swanson, director of the University of Pittsburgh Research Conduct and Compliance Office. “First-in-humans, under a microdosing concept, certainly would allow us to do more types of studies and significantly expand our research efforts under the current regulations. That would be a big benefit.”

The new guidance could address these restrictions on studying radioactive drugs first-in-humans since the exploratory IND process allows FDA staff to evaluate each study on a case-by-case basis.

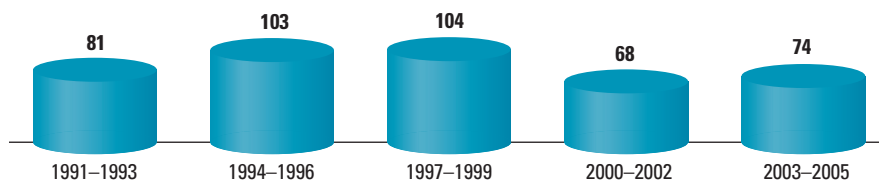
Microdosing Benefits

During the past two decades, advances in genomics and proteomics, along with high-throughput screening and combinatorial chemistry, have resulted in thousands of new drug leads, yet drug developers often struggle to identify the molecules that can become useful drugs. In fact, while the amount pharmaceutical companies spend on research and development has increased to an estimated \$59.2 billion last year, according to a Goldman Sachs report, only 23 new molecular entities were registered by the FDA in 2004. “There are a lot of new technologies that have focused primarily on the discovery portion of drug development,” said Michael Chansler, vice president of business development at Accium BioSciences. “The problem is that we’re still doing clinical trials the same

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Declines in Innovation and Productivity

Number of NMEs approved



Source: Thomson CenterWatch analysis, 2004; PhRMA Industry Profile, 2004; FDA, 2004.

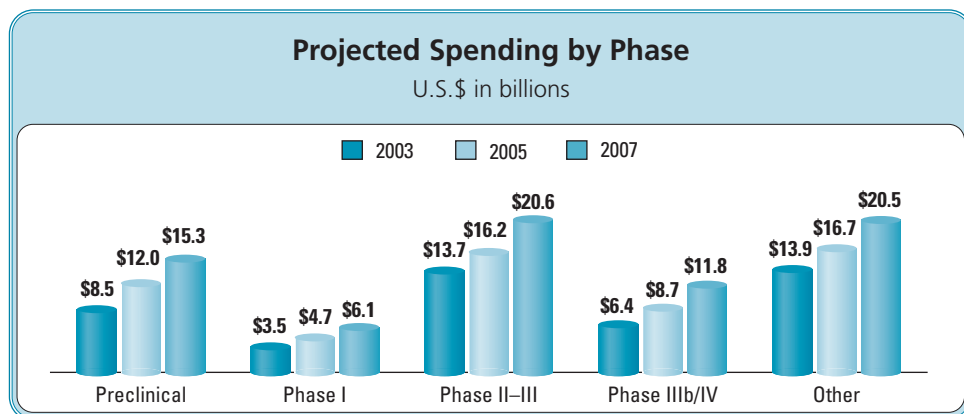
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way we've always done clinical trials. We're following the same regimen. There haven't been any new technologies adapted. Microdosing is a new technology that changes the way people are thinking. The goal is to bring some new technologies to the second half of the discovery chain; microdosing is one of those technologies."

Ian Wilding, executive chairman of Pharmaceutical Profiles, a Nottingham, U.K.-based CRO that specializes in early clinical development capabilities, added, "With so many drug candidates exiting discovery and entering development, the task of choosing and then advancing the right molecules into the clinic has become more and more difficult. In the future, for pharmaceutical companies to be successful, it will be necessary for them to determine, at a very early stage, which of their drug candidates is the most likely to pass the necessary safety and efficacy hurdles to become approved medications. Chemists and development scientists need to be confident that only the compounds with the best chance of success are taken forward, a task that is becoming increasingly difficult as the biopharmaceutical properties of molecules gain in complexity. Human microdosing studies can provide this key decision-making information."

At present, up to 40% of compounds entering clinical development fail because of inappropriate drug metabolism and pharmacokinetics, despite extensive preclinical screening of drug candidates with a broad range of *in silico*, *in vitro*, *ex vivo* and animal models. Animal models, in particular, can be problematic in predicting PK for humans since different types of animals, such as rats, dogs and monkeys, can metabolize the same drug in different ways. "Each animal species could handle the drug differently—sometimes we get contradictory results. The so-



Source: Thomson CenterWatch analysis, 2004; Goldman Sachs, 2003.

called allometric scaling from animals to humans is very difficult even if these results are not confounding or contradictory," said Nenad Sarapa, M.D., director of clinical pharmacology at Pfizer Global Research & Development. "Sometimes the whole process doesn't work very well because of the nature of the breakdown of the compound in animals versus humans. That is why, at some point very early on, microdosing in humans can reveal information which wouldn't have been apparent from any preclinical species."

Human microdosing studies involve the administration of microgram quantities of drug candidates in a very small number of healthy volunteers in order to gain pharmacokinetic and pharmacodynamic information. Because of the low doses of drugs used in microdose studies, usually 100 micrograms or less, ultrasensitive methods are needed for PK measurement; most microdosing studies rely on AMS, an isotopic measurement tool, although positron emission tomography (PET) also has the sensitivity to measure compounds administered in the low microgram range. PET provides real-time data on drug disposition, whereas AMS is used to analyze drug and metabolite concentrations in body fluids withdrawn after dosing. Both methods require radioactive labeling of the drug being studied.

While microdosing studies can't provide safety or efficacy data, since the drug doses

used are sub-pharmacological, they do provide PK and ADME information, which can allow sponsors to select drugs with appropriate PK parameters for further development. "The main purpose of microdosing is really de-selecting of the compound," said Pfizer's Sarapa. "People usually speak of speeding up drug development or making it more innovative, but taking off the table a compound that would eventually prove to be unsuccessful based on properties that can be gleaned out of microdosing much earlier than would have been the case in classical, conventional data is an important benefit. It can be translated to de-selecting the compound; if you have two or three compounds which are different between themselves, doing microdosing with all three of them early will enable you to park one, kill another and possibly develop the third."

Sponsor companies often use microdose testing on a compound that has shown issues in preclinical development. But Sarapa believes the most efficient, productive use of microdosing is testing similar compounds that are difficult to distinguish. "Pre-phase I studies are best used in cases in which several drug candidates target a novel therapeutic principle from which one wants to select one for further development," Sarapa said.

Microdose studies also hold potential use in other phases of drug development.

“One could consider microdosing in pediatric studies, where you are administering sub-pharmacological doses so you are not putting babies at risk in any way. It could be used in patient studies as well, where you want to study the metabolism of your drug in patients, but not put the patient at any risk,” said R. Colin Garner, CEO of Xceleron, a York, U.K.-based company that is the world leader in biomedical applications of AMS. “Microdosing probably will broaden in terms of groups that are studied using the approach.”

Significant Cost Savings

Drug sponsors are interested in microdosing studies because of their potential to reduce development costs. Microdosing doesn't provide shortcuts to drug development, but rather can help improve the attrition rate of compounds in later-phase clinical trials by allowing sponsors to choose the best candidates for further development. “Microdosing appears to be a promising new, safe and rapid methodology to derive human PK data as an aid in candidate selection prior to committing large resources to a full-scale phase I study,” said Carl Peck, M.D., founder and director of the Center for Drug Development Science at Georgetown University Medical Center, Washington and former director of the FDA's CDER.

“The main reason companies are looking at microdosing is to help decrease failure rates in later clinical development,” Accium's Chansler added. “If you could save just one year, you could save a lot of money in the development process. Hopefully, these types of technologies will be able to decrease the overall cost of drugs in the market.”

At Xceleron, Garner estimates microdose studies cost one-tenth of a conventional phase I study, not only in the amount spent on toxicology studies, but also in costs to synthesize chemical compounds since

microdose studies use very low amounts of the pharmaceutical ingredient or bulk drug. “The low amount of bulk drug clearly translates to a low cost. It also means low usage of experimental animals, and low environmental and human exposure risk. But most importantly for drug companies is the aspect of low costs,” said Pfizer's Sarapa. “If we can kill the compound at an early stage based on human microdosing, before the very costly business of pharmaceutical scale-up has been initiated, it translates into savings anywhere between \$500,000 and \$2.5 million, depending on how expensive the compound is to make. There are very direct, very real savings.

“Otherwise, if you continue the development of this compound,” Sarapa added, “you would have to scale up the manufacturing to a point where you would be utilizing raw materials and chemical plants and numerous outsourced partners. Equally important, you would start utilizing this newly synthesized compound for new tests that eventually prove to have poor PK properties in humans. If you do microdosing and realize those poor properties sooner, then all of that subsequent cost and subsequent studies will be unnecessary and you can save both in human resource and the cost.”

Microdosing studies also can be completed more quickly than traditional phase I studies. For example, Xceleron recently worked with a company that carried out three human microdose studies on a compound within a 12-month period. “They did the studies in sequence, rather than in parallel,” Garner said. “They got the microdose data, decided that the molecule could be improved in some way, improved it, repeated the process, got some more microdose data and then improved the molecule a little more. They ultimately got a molecule which they think has the optimum pharmacokinetic characteristics. If you were to do classi-

cal phase I studies for three molecules, they would take two to three years.”

In another example, a recent microdosing study Pharmaceutical Profiles carried out for the Swedish biotech research company Tripep took less than six months from inception to completion. The study examined the PK of an HIV-inhibiting molecule in healthy subjects. The microdosing study, according to Anders Vahlne, Tripep's acting CEO and head of research, gave the company early human PK data on the performance of their candidate drug more quickly than would have been possible using conventional development strategies.

However, microdose testing has drawbacks. In and of itself, microdosing won't speed up drug development. “While you prepare radio-label compounds and while you evaluate microdosing, everything else to do with this compound must be stopped,” said Sarapa. “Drug companies do what's called advanced scheduling or scale up of chemical synthesis—while I'm doing a set of preclinical experiments, I'm already scaling up synthesis of the chemical compound for human studies. Synthesis, to be made more efficient, must account for larger quantities than those that are required for microdosing. But if I want to do microdosing, I do not want to scale up chemical synthesis of the compound for later phases because I don't know what the microdosing study will reveal. Therefore, there will be a period between three and six months that my chemical synthesis will be stalled and that is not really favorable for most compounds.”

Adoption Slow in the U.S.

In the United States, microdosing techniques have not been widely adopted by pharmaceutical researchers. Some estimates show that microdosing studies are done

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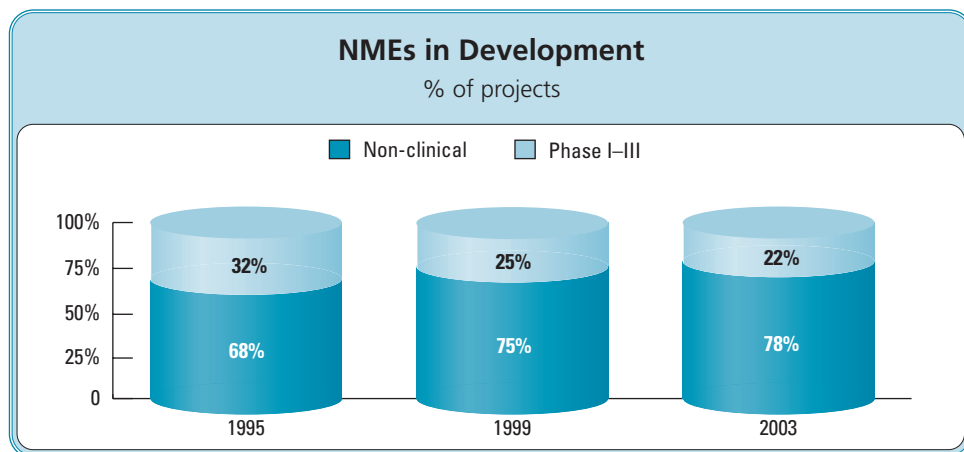
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before formal phase I studies less than 5% of the time.

Chansler said there are three main reasons that microdosing techniques and AMS technology have lagged in the United States. First, companies have little or no access to specialized AMS equipment since currently there are about 50 AMS centers in the world and only two analyze biological samples. The United States also lacks dedicated clinical trials facilities designed for the low 14C dose delivery and sample collection required for AMS microdosing studies. The third obstacle has been an FDA regulation that states no radioactive drugs may be studied first in humans because investigators must first provide pharmacological dose calculations based on published literature or other human data.

Yet for many in the industry, the main obstacle to wider acceptance of microdosing remains the fundamental question about whether a correlation exists between metabolism at a microdose and at a pharmacological dose. At Xceleron, which has been the principal advocate in driving the microdosing debate since its inception in 1997, Garner said data from AMS microdosing studies has begun to establish a link between microdose and full dose. "Certainly the pharmacokinetic data that you obtain from these microdose studies on whole does seem to reflect that which you would obtain at pharmacological doses," said Garner.

An ongoing clinical program, called Consortium for Resourcing and Evaluating AMS Microdosing (CREAM) has begun to build a database to compare PK parameters at micro and pharmaceutical doses; data collected by the consortium may help validate the microdosing concept. Sponsor companies in the consortium, which include Eli



Source: Thomson CenterWatch, 2004; IMS Life Cycle.

Lilly and Company from the United States along with three European pharmaceutical companies, F. Hoffmann-La Roche, Servier Laboratories and Schering AG, recently participated in a trial conducted by Xceleron to compare the metabolism of five drugs at pharmacological doses and microdoses. Results of the study will be announced at a drug symposium on microdosing to be held at the American Society for Clinical Pharmacology and Therapeutics' annual meeting in March. After the meeting, study results also will be written as a peer-reviewed scientific paper.

In the study, which was completed last year, five 14C-labelled drugs were examined in a crossover study design in which human volunteers received both a microdose and a pharmacological dose of the respective drug. The drugs were all fully commercialized, but had complex metabolism properties in which animal models or *in vitro* studies failed to predict human PK; the drugs had specific issues associated with their development, such as a long half-life. The CREAM trial was designed to determine whether AMS microdosing could have predicted the problems. "The idea behind the consortium was to take a number of drugs with known metabolism at pharmacological doses and compare metabolism at microdoses with the metabolism at the high dose," Garner said.

"The results are still bound by confidentiality agreements. But the bottom line is that the CREAM trial seems to support the microdose concept."

But even positive results from the CREAM trial may not convince some skeptics about the value of microdosing. P. David Mozley, M.D., senior medical director, Department of Imaging at Merck, formerly a medical fellow at Eli Lilly, believes the field should introduce some "harsh reality testing" into the microdosing conversation. Mozley said that any microdosing paradigm, including both PET techniques and AMS, will fail to produce data of value unless issues of cost-effectiveness and the variability in approaches can be addressed.

"The effectiveness of weaving molecular imaging into new drug development seems to be directly related to how well the study conditions reflect the actual circumstances in which the therapeutic drug candidate will be administered. The validity of some results can appear to be questionable when some conditions, such as the dose administered, vary too much, said Mozley." Although Mozley's comments mainly reflect concerns with the microdosing paradigm that uses PET techniques, which involves an imaging modality, he believes AMS models also will fail to produce data of value unless these issues he raised are addressed.

The FDA's Jacobson-Kram added, "If you talk to the pharmaceutical industry in the United States, they are not that excited about microdose studies. It seems to be more of a European kind of initiative; my sense is that there is more enthusiasm across the pond for these kinds of studies than there is in this country," he said. "You basically only can get PK information from these studies. Sponsors feel that to really understand and be able to make decisions about a compound, you need pharmacologic data. There is not unanimity about how valuable the data from these studies are."

Moving Forward With Caution

Will human phase 0 studies ever become a routine part of late-stage drug discovery?

"That's the question which is hotly debated," said Garner. "My view is that it should become routine. I would envisage, ultimately, that microdosing would become the first-in-human study. We take the view that getting early information about human metabolism must be good for developing drugs. We also think there is an ethical aspect to this—is it ethical to expose humans to higher doses, then subsequently kill a compound for metabolism reasons when the same information could have been found out with a safe microdose?" he asks.

Yet others hold a more modest view. Pfizer's Sarapa believes microdosing can be a valuable tool in making development decisions based on ADME/PK data, yet he cautions it can't be used in every drug develop-

ment program. Sarapa said, "I hope to see microdosing being used more, but in a meaningful way. It's not a panacea. One needs to be very selective in using it because it has some negative repercussions on scheduling of drug development."

"It also has some very clear advantages," Sarapa concluded. "If it is used meaningfully in appropriately chosen cases, I see great potential that it contributes to resolving issues in picking out compounds that will reach human testing with a greater likelihood of success. A greater likelihood of success in phase I will translate directly into greater speed and greater ability of these compounds to help patients that need them."

—Karyn Korieth

Eye On: Parkinson's Disease

Parkinson's disease is a progressive degenerative disorder of brain cells controlling muscle movement, leading to symptoms including tremor, muscle rigidity and problems with gait, balance and coordination. The characteristic hand tremor is known as "pill rolling" because the thumb and forefinger rub back and forth. Tremors may also involve the head, lips or feet, and they tend to disappear during sleep.

Other typical symptoms include slowed movement (bradykinesia), slow and shuffling gait, stooped posture, "freezing" of gait and of other movement (akinesia), "masked" expressionless face, and softer voice volume. Disturbances of autonomic function include slowed digestion, swallowing problems, constipation, increased salivation and decreased sweating.

If dementia develops, it may be heralded by slowed thought processes and difficulty

concentrating. Nearly half of patients with Parkinson's disease develop depression, which is thought to result from the neuropathology rather than being situational in response to disability. Sleep disturbances and sexual dysfunction are not unusual.

Onset is typically after age 50, with very low prevalence under age 40 and increasing prevalence over age 70. In the United States, approximately 500,000 people have Parkinson's disease, with about 50,000 new cases reported each year.

In Parkinson's disease, decreased control over movement results from loss of brain cells in the substantia nigra. These neurons normally use the neurotransmitter dopamine to communicate with other brain cells in the corpus striatum.

Although the cause of Parkinson's disease is poorly understood, it most likely is a combination of genetic and environmental fac-

tors. Some drugs, diseases and toxins are associated with parkinsonism, lending credence to this theory. Other risk factors include male sex, reduced estrogen levels and reduced folate levels.

Involvement of dopaminergic neurons in the substantia nigra suggests the possibility of treatment with levodopa (L-dopa), which has long been the therapeutic standard. However, this drug is limited by adverse effects, by decreased efficacy as the disease worsens and by less predictable response over time. Combining levodopa with carbidopa (Sinemet) allows more levodopa to cross the blood-brain barrier and reduces adverse effects.

Other available drugs include dopamine agonists, which are used both as adjuncts to levodopa therapy and as initial treatment in early Parkinson's disease, especially in

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