Volume 24 Number 6/7 June/July 2015

NEXT ISSUE: Clinical Trial Management

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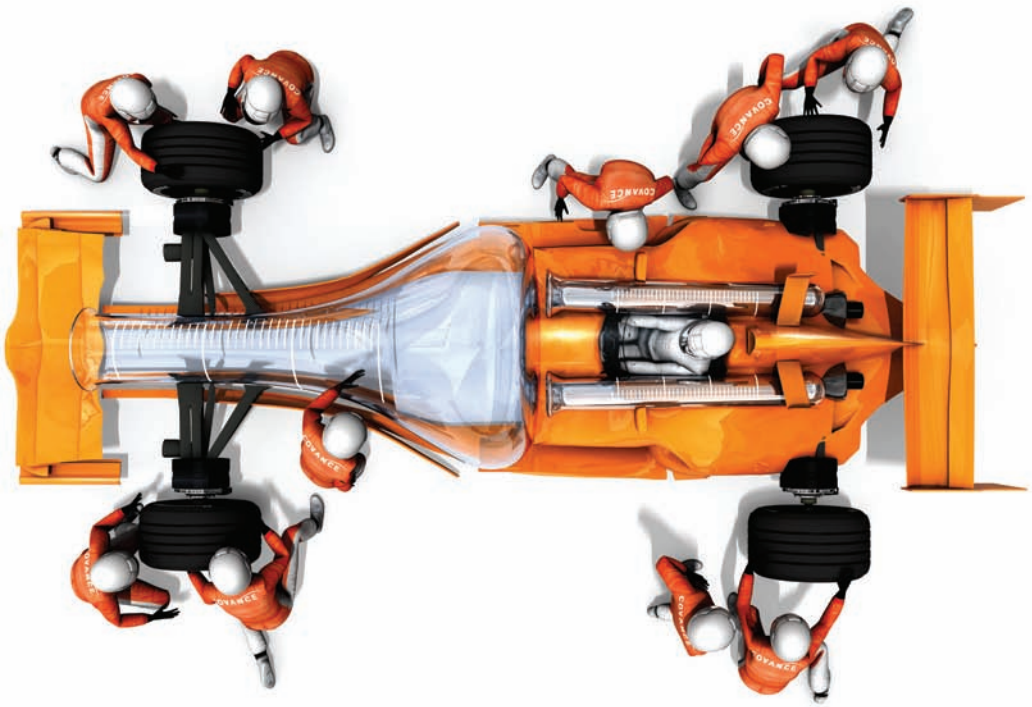

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APPLIED CLINICAL TRIALS (Print ISSN: 1064-8542, Digital ISSN: 2150-623X) is published 6 times a year as combined issues in Feb/March, Apr/May, Jun/July, Aug/Sept, Oct/Nov, Dec/Jan by UBM Life Sciences 131 West 1st Street, Duluth, MN 55802-2065. Subscription rates: $70 for 1 year (12 issues), $120 for 2 years (24 issues) in the United States and possessions; $90 for 1 year, $140 for 2 years in Canada and Mexico; all other countries $130 for 1 year, $235 for 2 years. Single copies (prepaid only): $9 in the United States and possessions; $11 in all other countries. Add $6.50 per order for shipping and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to *APPLIED CLINICAL TRIALS*, P.O. Box 6115, Duluth, MN 55806-6115. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A.

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APPLIED CLINICAL TRIALS

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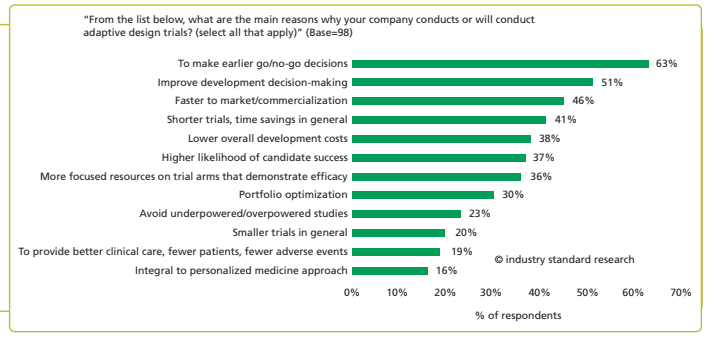

Source: ISR's 2015 Adaptive Trials: Market Dynamics and Service Provider Benchmarking report.

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Wearable Tech Boom Advances to the Brain

The boom in wearable devices has been facilitated by technological advances enabling the miniaturization of sensors and circuitry. Processors and sensors have become smaller, faster, and smarter, which has enabled huge growth in the production of affordable consumer devices aimed at the health and wellness market. An interesting aspect of the use of devices such as activity monitors is the recording of continuous monitoring data, and the associated complexity this brings in terms of the receipt, cleaning, interpretation, and summary of the data. Unlike a glucose meter or spirometer, which provide simple point data, continuous monitoring falls into the class of complex wearables due to the additional rigor needed in managing and interpreting the data recorded.

Consumer products that measure brain activity are essentially devices worn around the head to measure EEG signals. Firmware within the device interprets the signals from a series of dry electrodes contained within a headset to provide continuous EEG signal traces. In health and wellness, one main area of developing application in mobile EEG monitoring is using measured brain activity output to control a product to produce a physical action or enable communication. A compelling example of this is the use of live brain monitoring to enable paraplegic patients to communicate via a computer.

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VIEW FROM WASHINGTON

FDA Seeks Resources to Support New Research Initiatives

There seems to be a general agreement among policy makers and in the research community that the FDA has done about as much as it can to speedily review and approve important new therapies, and that efforts to facilitate patient access to needed medical products now should focus on accelerating drug development and clinical testing. Thus, the 21st Century Cures legislation developed by the House Energy & Commerce Committee (E&C) backs a number of strategies for modernizing and simplifying clinical trials, incorporating patients' voices into product development, encouraging collaboration on biomarker qualification, and reducing waste and redundancy in the clinical research process.

As the legislation moved through final negotiations in the House, E&C chairman Fred Upton (R-Mich) issued a statement highlighting how modernizing clinical trials is "essential in achieving our health innovation goals." He noted that clinical trials are "slow and expensive," loaded down with unnecessary paperwork, and an obstacle to realizing the potential of personalized medicine. Upton highlighted how the Cures legislation can make research "faster, safer, and more personalized," citing provisions that help sponsors identify suitable participants for pediatric studies and that offer flexibility in assessing new treatments through use of biomarkers, biostatistics and adaptive trial designs.

To realize these goals, the legislators propose to standardize data and formats in the ClinicalTrials.gov website as one way to facilitate patient recruitment to clinical trials.

There's support for greater use of central, or "lead," institutional review boards (IRBs) to oversee multi-site human subject research. Under the heading of clinical research "streamlining" are two potentially important provisions. One authorizes greater use of "clinical experience" to help support FDA approval of certain new indications, namely by tapping into data from registries and from FDA's Sentinel System. Another gives FDA flexibility to approve certain "qualified indications" based on clinical data summaries, as opposed to full clinical reports.

The Cures bill also includes a range of drug development proposals with broad appeal. There's an initiative to spur development of new antibiotics, utilizing a modified approval pathway for therapies targeted to limited populations. The measure reauthorizes a program providing priority review vouchers for rare pediatric diseases, which is set to expire. And it encourages more sharing of research and clinical data to support development of new cures by removing barriers to national interoperability of health technology and records. There's support for telemedicine, for faster coverage decisions on new vaccines, and for development of more orphan drugs.

More mandates, limited resources

As the legislators rolled out their bipartisan proposal last month, though, FDA officials voiced concern about just how these initiatives would be crafted and implemented, and where the agency would get the resources needed to carry out its many requirements. House leaders authorized a significant budget increase for the National Institutes of Health (NIH), but gave FDA less than $100 million a year to modernize trial design and evidence development. More important is a provision exempting FDA user fees from budget sequestration.

Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), stated at a hearing before the E&C health subcommittee in April that a new law requiring new programs and multiple guidances could undermine her ability to meet review and approval commitments. This latest E&C proposal has "significant resource implications for FDA," she said, noting that CDER's new drug review process is now "going at full speed, and we'd like to keep it that way." Getting new therapies developed efficiently is helped by timely advice from the agency, and that "would be the first to go," she warned, if the agency gets further stretched on resources.

What FDA sorely needs, Woodcock and other agency officials emphasized, is to cut some of the red tape and obstacles to bringing in the experts able to address complex scientific and regulatory issues. Too-low salaries prompt experienced staffers to leave for more lucrative jobs in industry and academia, and complex government employment requirements make it hard to recruit top talent.

Although Upton and his colleagues are looking for full House approval of the Cures legislation this summer, the Senate is moving at a slower pace. Members of the Senate Health, Education, Labor and Pensions (HELP) Committee are crafting their own biomedical innovation legislation—not just a modified version of the House "Cures" bill, they insist—and don't expect legislative action until this fall. Senate Democrats talk about an even bigger boost in NIH funding than the $2-billion-a-year increase proposed by the House. That raises questions about whether Congressional appropriators will support such outlays, as well as added funding for FDA. In the end, the key determinant will be who and how to cover the costs.

— Jill Wechsler

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GLOBAL REPORT

Experts Call for Urgent Action on Antibiotics Research

A new report has urged the global pharmaceutical industry to support an innovation fund to boost research into antibiotics. In return, companies that develop new antibiotics would receive guaranteed payments of between $2 billion and $3 billion.

The document, "Securing New Drugs for Future Generations: The Pipeline of Antibiotics," was put together by the Antimicrobial Review (AMR) Committee, a U.K. government-appointed review team headed by Jim O'Neill, the economist and former chair of Goldman Sachs Asset Management. The AMR Committee assessed the development pipeline for new antibiotics, and has made initial proposals for the global action needed to kick-start antibiotic drug discovery efforts. This includes proposals for ways of channeling new money into early-stage research relevant to tackle AMR and for major global interventions to ensure that drug developers can be sure of a predictable and viable market for new antibiotics that can successfully tackle society's most acute unmet needs.

"Drug-resistant infections could kill an extra 10 million people across the world every year by 2050 if they are not tackled. By this date they could also cost the world around $100 trillion in lost output, which is more than the size of the current world economy," noted the authors.

At the launch of the report, O'Neill stated that a fund worth between $16 billion and $37 billion per decade would be enough to incentivize drug companies to turn their attentions to antibiotics. In an article published by the Guardian newspaper in mid-May, he said it was possible the global taxpayer would have to foot the bill for the fund.

"I'd say, averaged out over 7.2 billion people, it is not that much compared to one million people dying a year in China or India in 2050," he pointed out. "We need to kick-start drug development to make sure the world has the drugs it needs, to treat infections and to enable modern medicine and surgery to continue as we know it."

Resistant strains of bacteria are spreading across the world, threatening to make existing drugs ineffective, and because the empty pipeline for antibiotics is a matter of great importance for every country, O'Neill intends to raise the finance issue at the next G20 meeting. Furthermore, if the pharmaceutical industry is to avoid a damaged reputation from the looming crisis, it must show 'enlightened self-interest' by contributing to the scheme, he continued.

Companies would be rewarded with payments if they successfully launch a new antibiotic, as long as they do not seek to sell the drug at a profit. It would be sold on a not-for-profit basis, or made by a generic company with low overheads at a cheap price instead, as happens in developing countries with drugs for HIV. The global market for antibiotics is currently worth around $40 billion a year, and the prize fund would cost about 10% of that sum, according to the Guardian report.

The authors think resistance breakers are a promising area of research. These compounds can boost the effectiveness of existing antibiotics, and this approach is cheaper than attempting to discover totally new drugs. For instance, Helperby Therapeutics in the U.K. has created a resistance breaker that acts against the superbug methicillin-resistant *Staphylococcus aureus* (MRSA). Known as HT61, the compound is due to enter clinical trials in India, where it is being developed under licence by Cadila Pharmaceuticals India. This kind of research could benefit from the innovation fund and may prove vital to making existing drugs last longer, the authors believe.

It has been nearly 30 years since a new class of antibiotics (i.e., a group of drugs with an entirely novel action) was introduced, according to a recent report by

BBC News. But the drought may soon be over as a result of a breakthrough recently announced by U.S. scientists. A team at Northeastern University in Boston has discovered 25 potential new antibiotics, all of them derived from soil microbes. One of them, teixobactin, is effective against both tuberculosis and MRSA. The drug is being developed by NovoBiotic Pharmaceuticals and should go into patient trials within two years.

"We have to respond to the challenge of antimicrobial resistance by making sure we secure the necessary antibiotics for generations to come, in order to save millions of lives and billions of pounds," Prof. Dame Sally Davies, chief medical adviser to the U.K. government, told BBC News.

The AMR Committee's final report with global solutions is scheduled for publication in the summer of 2016. It is considering how improvements in the following areas can help tackle antimicrobial resistance: the supply of new drugs, rapid diagnostics, surveillance, infection control, alternative treatments, and the use of antibiotics in agriculture.

"AMR is a complex global issue which cannot be solved by any one country acting in isolation. In this regard we think that China has a great opportunity to bring the world together in the fight against AMR when it hosts the G20 in 2016," wrote the authors.

The report can be downloaded free of charge from the AMR's website, http://amr-review.org.

— *Philip Ward*

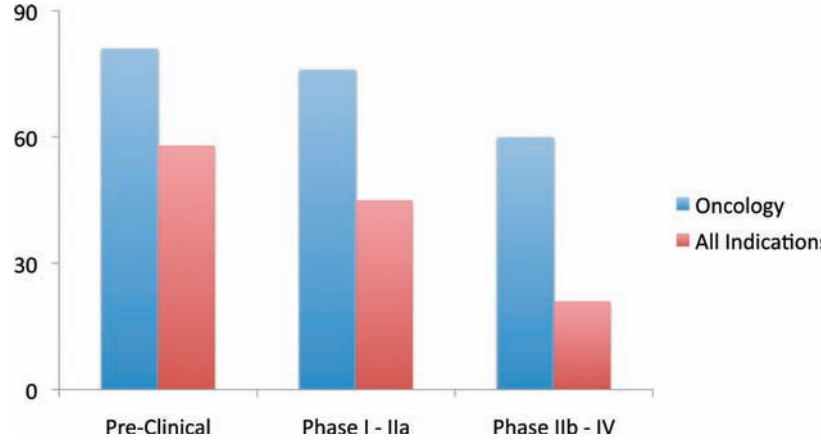
Data Analysis

Oncology Dominates Personalized Medicines Development

The opportunity to more precisely target and to personalize medical treatments based on biomarker data has attracted growing interest from biopharmaceutical companies. A recent study by the Tufts Center for the Study of Drug Development (Tufts CSDD) finds that oncology dominates personalized medicine product development in part because cancer-related illnesses are extremely complex and they receive the highest level of R&D activity. Companies involved in developing personalized medicines report that across all phases, 73% of oncology drugs now rely on biomarker data. This compares with 42% of compounds in all indications.

— *Tufts* CSDD

Number of Compounds in R&D that Rely on Biomarker Data



Source: Tufts CSDD, 2015. <csdd.tufts.edu>

Front & Center

Removing Barriers to Affordable, Accessible, and Effective Electronic Data Capture

Emerging cloud-based platforms are helping organizations of all sizes reap the benefits of EDC and streamline their clinical trial operations

Electronic data capture (EDC) platforms enable efficient management of clinical trials regardless of study size and complexity. In the past, this technology was utilized exclusively by larger companies with bigger budgets. Today, due to the introduction of modular, cloud-based EDC platforms with flexible pricing models, organizations of all sizes can experience the benefits of EDC. To further rein in rising study costs and trial times, providers of cloud-based solutions must be committed to the continuous development of more effective and efficient tools for data management and communication across sites and between various interested parties.

Fortunately, there are solutions available to the industry that can streamline operations across all clinical trial processes, leading to savings of both time and money. In particular, EDC systems are recognized by the US Food and Drug Administration (FDA) as effective for improving data accuracy and reporting and estimated to help reduce clinical trial costs by as much as 24%.

Transforming trial management with cloud-based EDC

With cloud-based EDC systems like Merge eClinicalOS (eCOS), all data, including electronic case report forms (eCRFs), electronic patient-reported outcomes (ePROs), images, PDF source documents, protocols, assignments, and more, are stored in a central EDC system owned and managed by the software provider. Not only is the data centrally located, easier to monitor and control and accessible from any Web-based device, much less time and money must be spent maintaining and operating the IT system. In addition, cloud-based EDC systems on the market today offer much more than data capture and, therefore, have an even bigger impact on productivity. For example, Merge eClinical has added improved tracking of the global drug supply, image management, reporting, endpoint adjudication, budget forecasting, and other features to eCOS.

Zaher El-Assi

EDC benefits no longer exclusive to big players

Even though the benefits of EDC are widely recognized throughout the pharmaceutical industry, users tend to be limited to larger sponsors, contract research organizations (CROs) and universities. Smaller organizations with limited budgets continue to stick with paper- or spreadsheet-based approaches, typically because they believe they can't afford and/or don't have the resources to implement new IT solutions. That is a shame, because all clinical trials can benefit from the overall enhanced productivity and cost reductions that digital management systems can provide.

At Merge eClinical, we recognize the crucial importance of making cloud-based EDC affordable for all clinical trials so that the real end goal—getting new, effective medicines to the patients that need them—can be achieved as efficiently as possible. We believe that all research efforts deserve to benefit from advanced IT solutions. As a result, we have designed our modular, cloud-based eCOS platform with a more flexible pricing model. In fact, eCOS is customizable and can be built to meet the needs of any clinical trial, with pay-as-you-go pricing rather than multi-year contracts and large upfront capital expenditures.

Greater functionality through the modular approach

Study designs can be quickly established from the outset using modular, scalable, cloud-based EDC platforms like eCOS that can be custom configured and allow the selection of only the tools that are needed. In fact, the eCOS system is specifically designed to streamline the clinical research process; with its easy-to-use build tools, trials can be up and running in days, rather than weeks or months. The Clinical Configurator™ simplifies the build process and makes it easy to choose the features that are required for a given study without the need to be a programmer. The choice of optional modules is constantly growing, too, and that means clinical trial managers have the ability to incorporate

> To further rein in rising study costs and trial times, providers of cloud-based solutions must be committed to the continuous development of more effective and efficient tools for data management and communication across sites and between various interested parties.

all types of functionality into their cloud-based EDC solutions. For example, more than a dozen modules are currently available with eCOS, such as randomization, safety reporting, translation, and endpoint adjudication, and we are always developing additional capabilities in response to customer requests.

Cloud-based systems like eCOS offer real-time access to centralized data and greater opportunities for increased communication and collaboration between everyone involved. In addition, newer modular, software-as-a-service (SaaS) systems such as eCOS allow study builders to incorporate only the tools they need (and pay as they go) for any given study. This means that small to large organizations can now realize the benefits of cloud-based EDC regardless of trial size and complexity.

Advantages of advanced forecasting capabilities

One of the main challenges in budgeting for clinical trials is the need to have an accurate forecast of the study requirements, including the number of sites, enrollment numbers, patient characteristics, length of the study, use of contractors vs. full-time employees, and more. Such difficulties were reflected in an industry survey conducted in 2011, which found that the disparity between actual and forecast budgets was as much as 16% for 20% of the respondents, and that development of these inaccurate budgets took three weeks or more for 50% of the survey participants. Budget reviews were also lengthy, taking five weeks or more for 65% of the respondents. The most often cited cause? The lack of software designed for clinical trial forecasting and budgeting.

Often, data is manually collected, with enrollment information at various sites stored in different spreadsheet programs. This generally means time must be spent reconciling the information before the budgeting process can even begin. Most EDC systems for clinical trial management do not include the financial forecasting or scenario modeling capabilities that are necessary for resource estimation, resource planning, forecasting and budget development. With eCOS and the Clinical Configurator™, all of the data is centrally located and collated, and it is possible to clearly identify the cost of each component in a study from the beginning. As a result, the time for both the budgeting process and budget reviews can be dramatically reduced.

Importance of continuous IT improvement

Clinical trials are continually changing to meet the testing demands of the new classes and types of drugs that are under development. More and more frequently, multiple study sites around the globe and larger numbers of patients are needed. Under these circumstances, cloud-based EDC systems provide the greatest advantages when appropriately implemented and utilized.

At Merge eClinical, we recognize the need to constantly build upon existing platforms in response to changes in the clinical trial field and are strongly committed to supporting the expanding global industry. Our robust R&D team is focused on continually improving the eClinical operating system and broadening the choice of optional modules. We do this to keep pace with unique client needs, industry requirements, and growing clinical trial regions, with the ultimate goal of allowing for true flexibility and transparency. The development of more effective and efficient tools for data management and communication across sites and between various interested parties is necessary to help reduce lengthening trial times and rising study costs.

Meeting industry needs

The ultimate goal of all clinical trials is the development of safe and efficacious new medicines that can improve the lives of patients around the world. We at Merge eClinical are committed to collaborating with our customers across the clinical trial value chain to develop software solutions that enable clinical trials to be implemented more rapidly and managed more efficiently.

EXPANDED ACCESS

Compassionate Use Debate Heats Up

Patient access to critical experimental medicines continues to grab public attention, as states enact "Right-to-Try" laws and Congress eyes establishing a national policy to provide not-yet-approved therapies to terminally ill patients. The FDA and biopharmaceutical companies are busy explaining how existing expanded access programs (EAPs) operate and the risks and difficulties of broader use of experimental medicines.

State compassionate use measures do little to actually provide unapproved medicines to seriously ill patients; the main thrust is to encourage physicians to seek expanded access approval from FDA. The bill approved by Arizona voters in November, for example, allows a patient's physician to recommend an experimental therapy and permits manufacturers to make a drug available without going through FDA's expanded access process. But it does not require biopharma companies to do so, and FDA policies are not considered an obstacle for manufacturers willing and able to provide test therapies to patients. This latest bill from Arizona is similar to others enacted in Colorado, Louisiana, Michigan, and Missouri and to newer ones proposed in Texas and Wyoming.

In response to state initiatives that threaten to nullify or override FDA laws and regulations, some members of Congress are proposing a national policy to facilitate early access to critical therapies. The Compassionate Use Reform and Enhancement (CURE) Act, sponsored by Rep. Michael McCaul (R-Tx), would require FDA to clarify the process for patients and physicians to request early access and for manufacturers of "covered breakthrough drugs" to inform FDA of their own expanded use programs, including company procedures for approving or denying requests. The Government Accountability Office (GAO) would analyze FDA's EAP and a Congressionally appointed Expanded Access Task Force would develop recommendations for program improvement. FDA will incorporate all these proposals into EAP guidance.

— *Jill Wechsler*

Expanded Access Implications for Clinical Trials

I recently attended CBI's Expanded Access Programs conference in Philadelphia. and the first thing to note early on was a discussion among the experts in the field about the terminology of expanded access. It emphasized that when talking about expanded access, early access, managed access, pre-approval access, or compassionate use, one should be very clear on what their definition is. Even the FDA representative Richard Klein acknowledged he didn't realize there was a terminology issue.

Clinical trials and expanded access (which is the terminology I'm going with) are very different. The investigational new drug (IND) application is held by a physician. The data requirements are nowhere near the rigor of a clinical trial. And patients comprise a wide swath outside of inclusion and exclusion criteria. But based on observations at the conference, this list comprises why clinical trials professionals need to know about expanded access:

- Many of the now-dedicated EA managers were former clinical trial professionals.
- The questions of investigational drug supply need to be closely calculated with the clinical trial investigational drug supply.
- Operationally, clinical trials and expanded access programs are the same.
- Is there a potential to derail a clinical trial if expanded access is allowed? Klein said no, however, in November a patient died in a CytRx compassionate use program, and the FDA put the program on hold. That hold was lifted in January. The definition of derail could be debated, as to some any delay in a trial can cost a lot of money.
- Planning for an expanded access program requires deep communication with others who know of the clinical successes of an investigational medicine in Phase I or II.

The rules of expanded access programs are quite clear. The FDA even launched a dedicated expanded access (compassionate use) website on Day 2 of the conference. The bottom line is that the sponsor has the ultimate decision if they are going to provide the drugs for expanded access programs or not. But with social media and internet transparency, coupled with the understandably heavy emotions that go along with life-threatening diseases, and the general mistrust of the biopharm industry, make a clearly defined regulatory guidance appear gray.

Which is exactly what happened to biotech Chimerix in April 2014. Chimerix was inundated with far-flung social media support for Josh Hardy, a seven-year-old whose life-threatening disease could be treated with Chimerix's drug in development. The whole saga illustrated both sides of the compassionate use debate, and brought the ethical decisions out to light. In the end, Josh received the drug, with a positive response, and CEO Kenneth Moch was forced out of his job.

But the message was clear: biotechs need to develop a clear policy on expanded access and have it in place to address just these types of instances.

— *Lisa Henderson*

CLINICAL RESEARCH REFORM

Califf Seeks New 'Ecosystem' for Clinical Studies

Current clinical trials are regarded as "too slow, too expensive, not reliable, and not designed to answer the important questions," according to FDA's new deputy commissioner for medical products &tobacco, Robert Califf. A veteran of multiple initiatives to modernize the biomedical clinical research enterprise, Califf emphasized the importance of improving the quality and efficiency of clinical trials as key to improving public health and to encouraging biomedical innovation.

Califf has long advocated for building a "learning health care system," where information from individual health records can be accessed to inform treatment decisions and support medical product development. Now we're "on the verge of a tipping point" in clinical trial reform, Califf predicated at a Washington seminar on "Re-Engineering Clinical Trials" organized by the Tufts Center for the Study of Drug Development and ICON. Multiple efforts so far have realized "incremental improvements" in research operations, many negotiated as part of drug user fee agreements, Califf observed; he sees real change on the horizon due to important advances in data systems, integration of healthcare delivery operations, plus greater public attention to the flaws in the clinical research enterprise.

FDA staff is implementing initiatives designed to achieve more efficiencies in clinical research, such as electronic informed consent, adoption of mobile technologies to measure clinical response, use of e-health records in designing research protocols, and adoption of common data standards, and terminologies in research studies to support applications filed with FDA. Further development of research networks at the National Institutes of Health (NIH) and the Patient-Centered Outcomes Research Institute (PCORI), along with expansion of FDA's Sentinel System, will provide added infrastructure for conducting more efficient clinical research.

— *Jill Wechsler*

VIEW FROM BRUSSELS

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Putting the EMA House in Order

The tone of agency's annual report contrasts its recent candid stance on regulatory vision for Europe

There is plenty to read in the European Medicines Agency's (EMA) just-published annual report for last year. But much of the attention of the clinical trials community will be directed to checking just how far this rather routine publication reflects a very new and very recent trend towards candor in the agency.

The sheer volume of the information in the annual report is, itself, remarkable, because the agency now has so many tasks reaching into so many corners of the world of pharmaceuticals. The report covers the core activity of recommending human-use medicines for European Union (EU) marketing authorization (82 in 2014)—and not all of these were routine, either. The year saw the first recommendation of a medicine for the treatment of Duchenne muscular dystrophy, the first treatment for erythropoietic protoporphyria, and the first therapy based on stem cells. Overall, 17 of the medicines that got the green light from the EMA were intended for the treatment of a rare disease—a new record.

It also covers the currently contentious subject of early EMA scientific support for companies developing medicines (health campaigners are claiming that it carries a risk of conflicts of interest), where the number of requests in 2014 set a new record, with three-quarters of applicants benefiting. The report notes the use of accelerated assessment procedures for medicines expected to be of major benefit for public health (seven positive opinions were granted through this route, including for four new-generation medicines for treating chronic hepatitis C virus (HCV) infection, led by Sovaldi). And it covers the equally contentious subject of transparency—with the EMA's adoption of its new policy on the publication of clinical data, the widening of the European database of suspected adverse reactions, its publication of agendas and minutes for the meetings of all its scientific committees.

New responsibilities are also reported on—with additional tasks imposed by the implementation of new EU legislation on pharmacovigilance (and, in 2014, new fees charged to industry for this increased monitoring)—falsified medicines (including producing new guidance for good manufacturing practice and good distribution practice inspections), and on clinical trials (creating the portal and database to be used for submitting applications for trial authorization).

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Quality of work

So much for the routine. But of greater interest is the tone adopted for discussion of the quality of the agency's work.

"The European medicines regulatory network is the cornerstone of the work and success of the agency," it says, pointing to the "experts from national authorities carrying out the assessment of medicines on behalf of EMA." It goes on to comment that "to be able to carry out the work to a high level of quality, it is essential that more and more national authorities participate in the assessment of medicines."

The urgency in the expression of this ambition coincides with the message at the heart of a major strategy document that EMA published shortly before its annual report. "Regulatory capability varies across the network. Some national competent authorities have more expertise in certain areas than others," says "Network Strategy to 2020," a 25-page consultation document that clearly recognizes weak links among the member states. This document—which is open for comment until June 30, and describes itself as a "draft strategic vision"—insists: "The network must ensure that all national competent authorities that participate in a specific type of regulatory activity continue to have the capability to do so. A critical success factor for the network will be to have available and at its disposal sustainable high-quality scientific and regulatory expertise able to address progress in regulatory science."

In other words, right now, there isn't enough capacity, and what there is, is not always adequate to the task. The need exists, continues this consultation document, for "a clear identification of any gaps in scientific and regulatory expertise based on current and future needs, and a corresponding competence development program," as well as for "common standards of scientific quality across the EU regulatory network," and for strengthened output, "in particular the scientific quality of regulatory

processes," to "mitigate discrepancies within the network."

Varying expertise

The point was made very tersely by Professor Sir Alan Breckenridge, who told this columnist during the reception to celebrate the 20th birthday of the EMA: "The problem with the EMA is that there are 28 members but the contributors are about six. This is something that's got to be worked on, because there's huge variability in expertise across the whole of Europe. This is a real problem—because when it comes to a decision, all of the agencies have a vote, but about 20 of them don't have an idea of what they are voting on."

The problems—in many cases longstanding—have come to the surface because of the new challenges that drug regulators and drug innovators are facing. As EMA puts it, a new framework is needed to tackle new science and new economic constraints, and to find radical new responses to cater adequately for the health of Europe's citizens. New technologies, the changing nature of pharmaceutical innovation, new advanced therapies, new licensing pathways and product life-span approaches, greater use of real-world databases, the increasing globalization of the pharmaceutical industry, and new and emerging health threats—whether in the form of antimicrobial resistance or emerging epidemics, as demonstrated by the outbreak of Ebola, or through criminal activity such as falsification of medicines. It is important, EMA believes, that the network keeps abreast of these advances to ensure that novel products can be developed optimally for the benefit of the health of the citizens of Europe.

A more modest tone

The annual report takes a more modest approach to this challenge than does the EMA strategic vision—or Sir Alastair. It says there is "an important positive trend for the EU system," in that "efforts undertaken during the last few years are paying off." One positive factor is that more national authorities are becoming involved in EMA procedures as rapporteurs or co-rapporteurs (up from 16 in 2010 to 24 in 2014). But even the moderately-worded annual report does tacitly admit that more is necessary, and describes how the agency has tried during 2014 "to ensure its continuation," with the launch of initiatives that "aim to better support the assessment work of the many thousands of EU experts involved in the regulation of medicines."

> "The problem with the EMA is that there are 28 members but the contributors are about six. This is something that's got to be worked on, because there's huge variability in expertise across the whole of Europe."

One of these is the EU Network Training Centre, jointly operated by the EMA and the less formal group of heads of national medicines agencies in the EU. This is building "a training strategy for continuous professional development of staff from national competent authorities and EMA, in order to improve the quality, consistency, and efficiency of the work of the network and promote harmonized application of the regulatory framework and guidelines." Another is a new scheme in which the agency supports the creation of multinational co-rapporteur teams to assess initial marketing authorizations for medicines for human use, "to make use of the best expertise across the EU for the assessment of a marketing authorization application." It follows a successful pilot scheme.

The pilot involved Denmark, Estonia, Finland, Latvia, Lithuania, Poland, and Sweden, as well as Iceland and Norway (which are closely associated with EMA, even if they are not EU member states). EMA has found it so useful, it is now exploring how the scheme can be extended.

So two tones are evident as the 20-year-old EMA experiences its epiphany. One is candid to the point of being undiplomatic. The other is more measured. But it is striking that the moderate tone in the annual report belongs to things of the past. The more assertive tone, as in the "draft strategic vision," is very much geared to the future.

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Characterizing the Real Cost of Site Regulatory Compliance

Study takes rare look at the financial and resource burden for sites in managing regulatory compliance

It is widely acknowledged by professionals involved with conducting clinical studies, as well as by those who oversee and manage clinical trials, that investigative sites face a heavy regulatory compliance burden. Yet, until recently, only anecdotal evidence existed to support this belief.

CenterWatch, in collaboration with Complion—a Cleveland-based firm that develops regulatory documentation solutions for investigative sites—have completed a new study that begins to quantify this regulatory compliance burden.

The study was conducted online between October and December 2014. A total of 164 U.S. sites completed the survey questionnaire. The majority of respondents (60%) are study coordinators; 20% are principal investigators. The remainder of respondents includes administrative support and regulatory staff, among other site personnel.

Nearly four out of 10 (38%) of the respondents work in independent, dedicated, and part-time community based sites. One-third (35%) are based within academic medical centers (AMCs) and 27% are within community hospitals.

The results suggest that investigative sites are dedicating substantial capacity, infrastructure, and resources to manage regulatory compliance. And the expense to do so dramatically reduces site operating profit. Most sites are handling regulatory compliance tasks in a relatively unsophisticated manner, using a combination of paper and electronic solutions. And sites expect the regulatory burden to increase. What follows are highlights from this recent study.

Perceived burden and its causes

The majority (85%) of investigative sites perceive that the burden and cost associated with regulatory compliance has increased "significantly" (41%) or "somewhat" (44%) during the past two years.

None of the respondents from independent investigative sites and community hospitals perceive that their regulatory compliance burden has diminished compared to two years ago. Less than 10% of respondents from clinical research functions within academic medical centers perceive that their regulatory burden has decreased.

Investigative sites mention a variety of factors that are contributing to increased compliance burden. Top factors include increased regulatory requirements (73% mention) and more complex protocols (66% mention). Increased reporting requirements for adverse events and protocol deviations are mentioned by 53% of investigative sites.

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Staffing and capacity

Independent investigative sites report that two staff members are typically involved in managing regulatory compliance tasks. Each member manages a mix of clerical, regulatory, and sponsor/CRO related compliance tasks for an average of six studies at any given time. AMCs and community hospitals report that an average of three staff is involved with regulatory compliance tasks. But whereas each dedicated staff member manages tasks for an average of seven studies at community hospitals, within AMCs, each staff member manages regulatory compliance tasks for an average of 3.3 studies. Compliance burden per study is likely higher within academic centers, given additional institutional reporting and compliance requirements.

Half of investigative sites report that study coordinators are typically the primary individuals involved with managing regulatory compliance tasks. Less than 20% of sites indicate that the principal investigator primarily handles these tasks. Approximately 30% of sites report that a dedicated regulatory specialist is primarily involved with managing compliance tasks.

In all, respondents provided workload—as measured by hours of time—for 25 regulatory compliance tasks on the survey. Clerical tasks assessed include handling study compliance documentation and correspondences, obtaining signatures, and general communication and reporting. Regulatory tasks include good clinical practice and protocol-specific training and document creation and editing. Sponsor/CRO tasks assessed include preparing for audit and monitoring visits, reviewing material with the study monitor or auditor and post visit follow-up.

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The most time-consuming regulatory compliance tasks are associated with learning sponsor/CRO's investigator or regulatory web portals and protocol-specific training. Sites report that 20 hours per study is devoted to these specific tasks. Reviewing regulatory documentation with the study monitor or auditor, following up with monitors and auditors after visits, reviewing correspondences and documentation, and filing staff credentials are also cited as the most time-consuming tasks. On a weekly basis, half of a staff member's time is devoted to preparing for, meeting with, following up with, and reviewing correspondences with study monitors and auditors.

Staff involved with managing regulatory compliance tasks appears overloaded. Less than half—46%—of investigative sites report that they are on schedule with their management of regulatory compliance tasks. One-quarter (28%) are approximately one week behind and 26% report being at least two weeks behind on their compliance-related tasks.

Space and storage

Regulatory compliance requires sites to physically store records and absorb most of the archiving costs, often for 11 years or longer. The predominant storage format across all types of clinical study documentation is a combination of paper and electronic. Of all respondents (i.e., combined independent, AMCs, and community hospitals), eight out of 10 report storing their regulatory and clinical data documents using a combination of paper and electronic formats. An eye-opening 25% of independent investigative sites stores their documents in paper format only.

Half of respondents indicate that their research center dedicates approximately 20% of their physical office space or more to store paper regulatory documents, including printouts of emails and electronic file attachments. About half (54%) of respondents report that four or more binders are used to store regulatory documents for a single study and most said that each document typically exceeded 250 pages in length. A majority of sites indicate that they contract with outside companies to augment their limited in-house storage space.

> **Most sites are handling regulatory compliance tasks in a relatively unsophisticated manner, using a combination of paper and electronic solutions. And sites expect the regulatory burden to increase.**

Four out of 10 (44%) respondents exchange ethical review submission documents with their institutional review board (IRB) using electronic formats, compared to about half (48%) that use a combination of paper and electronic formats. The most commonly used method for the exchange of regulatory documents is email, followed by a sponsor/CRO web portal and fax.

Estimated and actual cost

The majority (79%) of investigative sites report that sponsors are not sufficiently compensating sites for all of their regulatory compliance expenses. The results of this study support this claim.

Respondents were asked to estimate total site-operating costs—staff time plus infrastructure required—to cover regulatory compliance tasks associated with a single study. The median estimate came to $6,550. Based on itemized costs (including paper, folders, binders, storage boxes, document storage, and regulatory software) and specific staff hours per regulatory compliance task per study, the total average aggregate cost is $13,901, more than double the median per study estimate from sites.

Sites are reimbursed a median $3,000 per study, about 80% of the median estimated regulatory start-up cost of $3,750 but less than 50% of the estimated regulatory compliance cost and only one-quarter of the actual per-study cost burden. Given the average number of active studies conducted annually, overall site operating profits would nearly triple if sites were remunerated 80% of their total actual study-specific regulatory compliance cost.

Engagement through easing burden

Investigative site regulatory compliance is mission critical. Still, the results of this new study suggest that this burden may be requiring an inordinate amount of staff capacity and infrastructure that is significantly diminishing site operating profit, and may be harming operating efficiency and performance.

For less established and less sophisticated investigative sites, the burden of regulatory compliance may be hurting their long-term viability. Indeed, nearly 60% of novice investigators drop out of the clinical research enterprise, choosing not to conduct another FDA-regulated clinical trial. The No. 1 reason given: the heavy burden of regulatory compliance.

The results of this study help quantify how sites are managing regulatory compliance. The results suggest opportunities for electronic technology solutions to help streamline regulatory document storage and exchange capabilities and to reduce infrastructure requirements. The results also suggest the need for regulatory professionals, sponsors, and CROs to scrutinize regulatory compliance tasks and identify ways to simplify the compliance burden. Focusing attention and implementing steps to ease the regulatory compliance burden may go far in helping to improve site performance and sponsor-site and CRO-site relationship quality.

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Using 505(b)(2) to Solve Shortfall from Generic Cliff

Ken Phelps

Understanding the benefits of this application route in helping companies withstand the hit of patent expiries.

The patent cliff that rocked big pharma is now starting to reverberate in companies developing generic alternatives. As the slate of top-selling pharmaceuticals going off-patent declines, competition is heating up in generics to find new ways to remain profitable after the financial hits they expect to take starting as early as 2016.

Generic drugmakers are responding to the situation in a variety of ways. Some generic companies such as Watson, which acquired European competitor Actavis in October 2012, are counting on economies of scale to remain profitable, while others are redefining themselves by specializing in hard-to-make products or by seeking to make their own branded products.[1]

Manufacturers may seek approval for their products through three possible types of applications under section 505 of the Federal Food, Drug and Cosmetic Act. Section 505(b)(1) is the traditional route of approval, which can require years of clinical trials and millions of dollars in development cost, but offers owners years of market exclusivity in which to recoup their investment. Once a product has gone "off-patent," application can be made under 505(j) to produce an exact copy or generic version of the drug, but in this case, market exclusivity is only available to the first company to file, and then only for 180 days.

A third way to seek FDA approval is through the 505(b)(2) application process, which allows companies to file new drug applications (NDAs) utilizing some pivotal data already existing in the public domain. Using this pathway as outlined in the official "FDA Guidance for Industry: Applications Covered by Section 505(b)(2)," drugs can be developed and achieve FDA approval in as little as 30 months, with only a fraction of the number of required clinical trials and with a return on investment higher than many generic drugs.

Additionally, unlike generic drug applicants, the 505(b)(2) applicant may qualify for three, five, or even seven years of market exclusivity depending on the extent of the change to the previously approved drug and the type of clinical data included in the NDA.

Given these advantages, it's no wonder that generic companies might find 505(b)(2) appealing. But 505(b)(2) isn't just another regulatory pathway, it's a whole different process that requires its own understanding.

The foundation of 505(b)(2)

Prior to 1984, the FDA had an informal policy to review and approve NDAs based solely on literature. These "paper NDAs" were also used for exact copies of approved drugs—generics—which, at the time, lacked formal approval requirements.

Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act was established by the Hatch-Waxman Amendments of 1984 to allow sponsors to obtain approval of NDAs containing investigations of safety and effectiveness that were not conducted by or for the applicant, but for which the FDA has issued an approval. The section was

added to avoid unnecessary duplication of studies already performed on the reference drug.

However, sponsors must still provide any additional data necessary to ensure that the differences from the reference drug and other existing information do not compromise safety and effectiveness. Today, 505(b)(2) can provide relatively fast-track approval for a wide range of products, especially for those that represent a limited change from a previously approved drug. Thus, an essential difference between an NDA filed for an innovator drug under 505(b)(1) and the NDA filed under 505(b)(2) is the reliance by the sponsors on the use of public information in lieu of conducting the studies themselves.

Because of the way they typically bring products to market, generic companies may lack the scientific staff required for sourcing the scientific literature, evaluating its utility, and presenting it to the FDA, and they often need to utilize external resources. However, whether an NDA is filed under 505(b)(1) or 505(b)(2), the FDA standards for the demonstration of efficacy and safety are the same. This underscores the necessity of a sponsor to be able to determine what constitutes sufficient evidence and to determine which specific studies can be replaced by existing information in order to gain approval of the investigational drug product under 505(b)(2).

When existing information may suffice

When published data provides a way to apply the known effectiveness of a drug to a new population or to a different dose, regimen or dosage form, the effectiveness of a new product may be adequately demonstrated without any additional clinical efficacy trials. These situations include:

- **Pediatric.** The FDA must conclude that the course of the disease and the effects of the drug are sufficiently similar to permit extrapolation from adult efficacy data to pediatric patients. Evidence may include common pathophysiology of the disease, common drug metabolism, and/or experience with other drugs in its therapeutic class.
- **Bioequivalence.** Alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.
- **Modified-release dosage forms**. In some cases, modified-release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to an approved immediate-release dosage form.
- **Different doses, regimens, or dosage forms.** Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone.

In addition, a single clinical study of a new use, when combined with independent substantiation from published study data in related uses, can often provide adequate evidence of effectiveness in, for example, different doses, regimens or dosage forms; in other phases of the disease or closely related diseases; or in other populations.

The approval of FOSAMAX PLUS D illustrates the use of existing publicly available data. FOSAMAX demonstrated reduced risk of both hip and spine fractures in postmenopausal women with osteoporosis. In the clinical trials used for the original approval, Vitamin D was a required supplement. In 2005, the FDA approved a new product, FOSAMAX PLUS D, which added the benefit of a weekly dose of Vitamin D. Using 505(b)(2), only published data supporting the independent efficacy of Vitamin D and a single pharmacokinetic study were required.[2]

> **505(b)(2) isn't just another regulatory pathway, it's a whole different process that requires its own understanding.**

Unlocking profit potential

Significant value can result from the 505(b)(2) pathway. The following examples demonstrate the potential return on investment (ROI) from a strategic 505(b)(2) development program.

Pentamidine

Although Pentamidine had been approved for sleeping sickness, research uncovered a new indication as a treatment and prophylaxis for AIDS-related Pneumocystis pneumonia (PCP)—an orphan indication eligible for seven years of market exclusivity. In addition, Pentamidine was reformulated through the 505(b)(2) into an aerosolized dosage form that reduced side effects. The company was sold for more than $1 billion.

Amphotericin B

Amphotericin B is a polyene antifungal drug, often used intravenously for systemic fungal infections. Administered orally or intravenously, it is well known for its severe and potentially lethal side effects, including high fever, shaking, chills, hypotension, vomiting, headache, dyspnea, and tachypnea. Reformulated as a liposome through 505(b)(2), the new product discourages generic competition because it is difficult to copy and manufacture, yet it dramatically reduces side effects and improves efficacy. More than $300 million in sales have been made with only a small hospital-based sales force.

Glycopyrrolate

Originally approved for reducing gastric and other secretions intravenously before surgery as well as for use during anesthesia and intubation, a glycopyrrolate tablet formulation was approved for peptic ulcers. Research into new indications and formulations led to the development under 505(b)(2) of a liquid formulation for cerebral palsy patients to reduce drooling. The new drug was granted orphan-drug

status for new indications. It is also currently being developed as a long-acting muscarinic antagonist (LAMA) for COPD patients in multiple-dose inhaler, dry powder inhaler and nebulized dosage forms. The estimated market potential for these new indications exceeds $1 billion.

The key factor behind these successes is the strategic planning that occurred first. Because generic companies have historically produced only copies of other products, they often lack the background to evaluate the scientific, medical, regulatory, and commercial feasibility of proposed differentiated drug products—and all are vital to market success and ROI.

The 505(b)(2) process is ideal for reformulations of existing products that address different indications, populations, or routes of administration. However, being able to technically prepare a new formula based on an existing drug is not enough on which to base a go/no-go decision to pursue a 505(b)(2) development program. Before deciding on a product to pursue, sponsors should know details of key factors influencing the pharmaceutical marketplace and regulatory status, as well as the nonclinical and clinical strategy that would be involved in the development of a specific drug, in order to avoid potentially destructive financial risks.

How to identify viable candidates

There are two distinct approaches companies are taking to identify candidates for possible development. Larger pharmaceutical and biotech companies often have a proprietary list of candidates and seek assistance in evaluating which candidates hold the greatest promise. Instead of a list of products, other companies are seeking assistance to identify viable products using selection criteria unique to their business.

In either situation, it is important to evaluate candidates against four interrelated criteria to determine if they can be successfully developed under 505(b)(2). It's a process similar to Camargo Pharmaceutical Services' proprietary Ready 4 Action process. This four-step process addresses:

- **Scientific viability:** Does the science make sense? For instance, is the formulation or chemistry practically and pragmatically achievable? Is it scalable? Are API ingredients available and affordable?
- **Medical viability:** Does the product have a clear niche in the medical specialty? Is it effective for solving a unique problem or solving a problem in a unique way? Does it present acceptable risk/benefit? Is it appealing to the proposed patient population?
- **Regulatory viability:** What clinical trials or other data will be required to gain approval? Can development be expedited? What distinguishing information can be presented on the labeling for eventual promotional activity?
- **Commercial viability:** Is there a viable market for the product? What is the potential for future competition or substitution? What is needed to ensure reimbursement? What is the optimal pricing?

Evaluating candidates on all four of these criteria is critical. For example, assessing whether a product can be effectively marketed at a profit and verifying market requirements before development begins helps inform the design of studies to meet various objectives, such as gaining essential labeling language.

One essential tool now being used in the development and strategic management of new or modified drugs/biologics/devices is the Target Product Profile (TPP). Basically, it is a summary of the proposed drug development program described in terms of the labeling concepts. Its purpose is to focus discussions and aid in the understanding between sponsors and the FDA.

As the FDA itself says in its guidance, "The TPP embodies the notion of beginning with the goal in mind."[3] Utilizing this methodology, the sponsor must envision the end product, including the target population, the formulation, the dosage form and strength, etc., as a means of expressing the goals of the product along with the specific studies needed to support the labeling concepts.

> **The 505(b)(2) process is ideal for reformulations of existing products that address different indications, populations, or routes of administration.**

By evaluating candidates on these four criteria, sponsors can identify candidates with sound scientific footing to meet the requirements of a 505(b)(2), and those that also have enough differentiation to be commercially viable. A comprehensive drug development plan must be provided that includes testing, formulation, and manufacturing, along with a plan for conducting any needed preclinical and clinical studies. With this plan in hand, it is advisable to gain FDA's concurrence, usually by requesting a pre-investigational new drug (IND) meeting.

Choosing viable candidates

Furthermore, before choosing a product to develop, it's important to have an assessment of the sponsor's assets, specific goals, and business needs. The criteria that are germane to this are many and may include everything from existing products or APIs the client holds, to market areas it wishes to enter or targeted populations/therapeutic segments it wishes to address.

Identifying viable candidates is essential, but deciding whether a company should pursue development is also critical. There are four steps to deciding what product to

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Assessment Chart	
CRITERION	**ACCEPTABLE RANGE**
Unmet medical need exists	Yes/No
Regulatory pathway	505(b)(2)/505(j) Suitability Petition/505(j)
Indication	Chronic/Acute/Cyclic
Dosage form	Tablet/Liquid solution/Liquid suspension/ Other
Patent	Paragraph 1 or 2 (expired), Paragraph 3 (will expire by approval), Paragraph 4
Clinical evidence of efficacy/safety exists	None/Some/Robust
Ability to show positive pharmacoeconomic date	Already exists/Likely/Possible/Unlikely
Clinical requirements	Phase 1 pharmacokinetics or similar ~$700k Phase 1 & 2 & 3 >$1.5 <$5MM Phase 1 & 2 & 3 >$5MM
Approval date	Month/Year
Preclinical requirements	Yes/No
Exclusivity	How long?
Competition	High/Medium/Low

Source: Phelps

Table 1. The typical criteria and value range when choosing a drug candidate.

pursue: criteria selection, criteria evaluation, candidate narrowing, and candidate selection. Although every company will utilize a unique set of criteria, a typical chart and range of values may look something like what is illustrated in Table 1.

Once the criteria are established, potential products are evaluated against the criteria as part of the second step. In the third step, candidate narrowing, the object is to refine the list by choosing the most important criteria and investigating in sufficient detail to clearly identify the most attractive options. If, for example, conducting Phase III trials in order to gain market exclusivity is a key goal of the sponsor, candidates that didn't meet that criterion would be deleted from the list.

This narrowing of focus is essential to get beyond broad and unmanageable marketing segments, such as indications or diseases, in order to pinpoint highly specific definitions of unique products and discrete market segments. The research effort required will span the scientific, medical, regulatory, and commercial space because all these elements must work in tandem to create a product that can be defined, differentiated from what else is available, and effectively marketed at a profit.

In the final stage, candidate selection, detailed research is undertaken. Consideration should be given to a broad range of research concerning the market, the product, manufacturing, and regulatory affairs, as well as marketing and investor strategy.

To gain the depth of understanding required, research may begin with a detailed overview of the disease or condition under consideration, including analyses of the current standards of care and a market-needs assessment. This, along with a strengths-weaknesses-opportunities-threats (SWOT) analysis of the product's potential to strategically address market needs, helps develop product positioning and the target product profile.

Additionally, sponsors must evaluate the regulatory issues that must be addressed and establish the physicochemical properties of the product, including its chemical makeup, stability, and solubility, as well as the specific route of administration. Determining whether the product may be made available as a capsule, tablet, aerosol, liquid, or as a subcutaneous, intramuscular, or intravenous injection will also have a bearing on the suitability of a 505(b)(2) approach to approval.

Finally, because maximizing ROI is the ultimate goal, it's important to have a firm grasp on the market you'll be entering, including the competitive landscape and the issues that may impact your distribution plan. Having developed answers to these questions in addition to having a pricing and payer reimbursement plan in place will put you in a much stronger position to identify potential partners and negotiate with investors.

With this research, a company can ascertain the viability of a product and also whether the product is a good fit for their particular business. And, with these results in hand, companies can begin to devise a comprehensive development plan with confidence.

Understanding market dynamics

The traditional dynamics of the generic market allow for all the competing generic manufacturers to calculate the potential value of the total market for a drug once it loses patent protection. What they don't know is how many rivals are likely to enter the same market and what impact that number of competitors will have on their profits.

A study of generic drug industry dynamics showed that generic drug prices fall with a significant increase in the number of competitors, but remain above long-run marginal cost until there are eight or more.[4] However, because a generic version of an off-patent drug still requires FDA approval, firms must make a significant application investment before knowing when or how much competition they will face, or when or if they will make a profit.

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The same cannot be said for the differentiated products developed under 505(b)(2). By partnering with companies that specialize in 505(b)(2) development, generic companies can acquire the specialized expertise they need to gain market approval. However, to determine true product viability, generic companies should seek help from companies not just experienced in the 505(b)(2) pathway, but from companies that can also demonstrate expertise in a variety of areas, including clinical development, intellectual property, and product revenue forecasting.

To effectively develop products under 505(b)(2), it's vital to have a robust relationship with the FDA, as well as a firm understanding of the types and sufficiency of product patents that are acceptable with this strategy. Generic companies can also benefit from specialized knowledge in developing sales and marketing strategies, as well as cogent advice on compendia positioning, pricing, distribution, product liability, and risk management.

Given the cost of drug development today, the time and money involved in planning represent a prudent investment to move forward with development of a successfully marketable product.

Facing the future

In the future, pharmaceutical and biotech companies of all sizes are going to have to adjust their strategies to remain competitive. Some big pharma companies still have their sights set on blockbusters coming from biologics. For example, Johnson & Johnson's and Pharmacyclics' ibrutinib was approved by the FDA as Imbruvica in November 2013 for the treatment of mantle cell lymphoma and in February 2014 for the treatment of chronic lymphocytic leukemia. Ibrutinib had been designated a breakthrough therapy by the FDA, granting it an accelerated approval process, and is one of the most promising late-stage cancer treatments on the market, with a potential to earn $1.3 billion a year.

But these biologic drugs cost several-fold more to develop than small molecules, and are out of reach financially for most generics companies. The patent cliff will shrink the opportunities for making generics and cause big pharma to consider means of extending the value of existing products. Thus, both generics and big pharma companies will need to find additional sources of revenue. The 505(b)(2) pathway can provide a useful mechanism for the industry to replace or augment revenues.

Research-based companies with products facing patent expiration may find that the 505(b)(2) pathway can provide a useful mechanism to extend market exclusivity. For generics companies, the 505(b)(2) pathway can be a powerful tool to improve the revenue stream by identifying niche branded products and marching in a different direction than competitors.

As previously stated, products approved through the 505(b)(2) pathway may qualify for three, five, or even seven years of market exclusivity, depending on the extent of the change to the previously approved drug and the type of clinical data included in the NDA. 505(b)(2) success hinges on identifying products that have documented market differentiation, low development risk, and high profit potential. Moreover, the 505(b)(2) pathway comes with unique and demanding requirements that are difficult to navigate. Sponsors benefit from employing a deliberative, step-by-step approach led by a team of experts with the commercialization, drug development, and regulatory expertise to synthesize a viable 505(b)(2) development plan.

From 2010 to 2013, 43% of all NDAs approved have been 505(b)(2) drugs.[5] In 2014, this number was 50%, with 41 new 505(b)(2) drugs approved compared to the same number of new molecular entities (NMEs).[6,7] This percentage is expected to rise to more than 80% over the next few years.[8] In the final analysis, 505(b)(2) development is more than just a regulatory pathway, it is a unique strategy that can often result in product approval with lower risk, reduced development cost, and faster speed to market.

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Ken Phelps *is President and* CEO, *Camargo Pharmaceutical Services.*

Demystifying genomics for drug developers

On-demand webinar | Originally aired May 19, 2015

Register for free at
www.appliedclinicaltrialsonline.com/act/quintiles-demystifying

Event overview

There has been an interesting shift in the reasons why pipeline drugs fail. While lack of efficacy in clinical trials has stayed about the same, 20 years ago most drugs failed because of problems related to drug metabolism and pharmacokinetics. Fast forward 10 years and now most failures are related to problems with non-clinical toxicity or clinical safety. Can genomics help solve this critical issue?

This webinar will focus on how genomics lays the foundation for precision medicine & developing the safer, more efficacious precision medicines of tomorrow. Our talk will review genomics & precision medicine foundations covering:

- Biomarkers
- Toxicogenomics
- Bioinformatics

By the end of this webinar you will be able to

- Understand expression analysis and heat maps well enough to be able to make sense of genomics experiments as reported in major medical journals
- Appreciate that biomarkers need to be defined in the context of their use, know what a genomic biomarker signature is and be able to name at least one commercial genomic biomarker
- Be able to remember toxicogenomics as 'pathway based toxicology' and understand the promise it shows in early drug development
- Recognize the primary of bioinformatics in genomics research and biomarker development

Who should attend

- Clinical development programs—leaders and team members
- R&D directors, managers in biotech or pharma
- Clinical program managers or project managers
- Companion diagnostic Specialists
- Patient recruitment specialists
- VP, Director of clinical operations
- Medical science liaisons
- Chief medical and scientific officers
- CEO/President of pharma business unit or organization

Presenter

Klaus Gottlieb, MD, MBA
Senior Medical Director
Quintiles

Clinical Professor of Medicine
George Washington University

Questions

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QUINTILES

Lifecycle Modeling and Simulation in Clinical Trials

Andrew Garrett, Michael O'Kelly, Davis Walp, N. Seth Berry

How the application of evolving M&S models are transforming full-research design strategies.

Computer-based modeling and simulation has advanced numerous industries, from aeronautics and engineering to meteorology and finance. Its potential benefits in drug discovery and development have been recognized for decades, but full realization of modeling and simulation in the health sciences has been limited by the vast complexity of biological systems, lack of understanding of disease, lack of large-population data on real-world health outcomes, and uncertainty regarding regulatory acceptance of modeling and simulation applications in clinical drug evaluation. These barriers are gradually being overcome, and modeling and simulation is now poised to transform the entire drug development lifecycle, from discovery to commercialization.[1]

Modeling and simulation (M&S) practice has evolved to solve complex problems that could not be addressed using direct observation and measurement. Models are built using historical observations to describe behaviors observed within systems. Models are commonly used to predict a future outcome and can be either deterministic or probabilistic (stochastic). Simulations use models to test how variability within a system can impact outcomes. Simulations can use more extreme model inputs than have been observed to help characterize the range of potential outcomes. In this way, simulation can be used to better understand risk and identify opportunities to improve outcomes.

In clinical drug development, M&S is used to quantified problems and test assumptions as a means to improve decision-making and increase predictability. Emerging applications are now being used to predict drug safety and efficacy, to plan individual trials and Phase I to III development programs, and to better manage research portfolios.[2] These applications offer a glimpse of the biopharmaceutical industry's modeling and simulation-informed future—more focused communication among development experts, greater efficiencies, and higher success rates. M&S will foster a knowledge-based drug development process that creates more value for patients, payers, and healthcare providers.[1]

Benefits: More predictability, better decisions

Predictability is the fundamental challenge of drug development. In the Food and Drug Administration's (FDA) 2004 report on Critical Path needs and opportunities, regulators called for an aggressive, collaborative effort to create a new generation of predictive tools that could reduce costly development failures: "As biomedical knowledge increases and bioinformatics capability likewise grows, there is hope that greater predictive power may be obtained from in silico (computer modeling) analyses."[3]

Computer-based predictive models are essential tools to increase clinical trial efficiencies and probability of success in what FDA envisions as "model-based drug development." In model-based development, pharmaco-statistical models of drug

Optimize Clinical Trial Results Through Reliable Adherence Measurement

ON-DEMAND WEBCAST

(Originally aired June 9, 2015)

Register for free at www.appliedclinicaltrialsonline.com/act/adherence

EVENT OVERVIEW

This webinar will address the impact of medication non-adherence in clinical trials. It is widely assumed that adherence is nearly ideal in clinical trials. In fact, the opposite is true.

- Non-adherence is the largest source of variability in drug response.
- When non-adherent patients can't be distinguished from non-responders early on, drug developers can face costly phase III failures, jeopardizing entire programs.
- Adherence must be accurately measured in order to evaluate a compound's true potential and increase the likelihood of a successful trial outcome, leading to faster speed to commercialization.

The webinar references data reported in the state of the art article entitled "Methods for Measuring, Enhancing and Accounting for Medication Adherence in Clinical Trials," published in Clinical Pharmacology & Therapeutics in 2014.

Key Learning Objectives

- Understanding the impact of medication non-adherence across therapeutic categories during trials, both for patient health and the pharmaceutical development process
- Understanding the pros and cons of available measurement methodologies such as MEMSCaps & newer innovative technologies, and delving into the proven benefit of electronic adherence measurement and analysis
- Understanding the impact of accurate measurement on trial design, patient behavior, and trial outcomes

Who Should Attend

- Clinical trial program and therapeutic leaders
- Pharmacometricians, modeling and simulation scientists
- Clinical operations
- Clinical packaging

Presenter

BERNARD VRIJENS
Chief Science Officer
MWV Healthcare
Associate Professor of Biostatistics
University of Liège, Belgium

Moderator
LISA HENDERSON
Editor
Applied Clinical Trials

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efficacy and safety are built from available preclinical and clinical data with expert opinion to determine M&S objectives and inputs for simulation. Models are used to simulate scenarios of predicted relationships between drug exposure, drug response, and patient outcomes.

M&S informs decision-making by leveraging early data to guide downstream decisions and strategies. When practiced across the full development lifecycle, M&S drives more efficient ways of working based on wider applications of data and on communication across disciplines and operations. It places greater reliance on evidence rather than on assumptions; where assumptions are necessary, M&S predicts their implications across a range of assumptions.

To implement well-informed modeling and simulation, it is necessary to eliminate traditional research silos that inhibit information sharing. M&S practice encourages closer collaboration among development experts from different disciplines. Their combined knowledge ensures that M&S assumptions are reasonable and results are interpreted correctly. By fostering collaboration, M&S adds value by leveraging knowledge across the full drug innovation lifecycle.

Benefits in PK/PD dose modeling. The most mature practice and best current example of the value of M&S in drug development is pharmacokinetic/pharmacodynamic (PK/PD) dose modeling.[4] This M&S application, which is heavily dependent on cross-functional collaboration, has dramatically improved dose determination—increasing predictability and reducing time and cost by leveraging data as it accrues, from preclinical to Phase III studies.

By clarifying a drug's exposure-response relationship, PK/PD models can be used to predict optimal dosing regimens for patient testing, to provide insight on endpoints, and to test a range of assumptions about clinical outcomes. Population PK/PD analyses help identify dose adjustments for special populations such as children, the elderly, ethnic groups, patients with impaired renal/hepatic function, and patients likely to experience drug-drug interactions. They do so by better understanding patterns in the exposure-response relationship and their variability.

Enabling knowledge-based decisions: Trial design simulations. M&S facilitates knowledge-based decision-making by quantifying problems and providing a basis for discussion and assessment in a multifunctional team, particularly when there is uncertainty about the safety or efficacy profile of a therapy. For example, one of the authors modeled a number of different strategies that might be used to gain regulatory approval for a treatment indication pertaining to the central nervous system. Each strategy included interdependent Phase IIa, IIb, and Phase III studies. Success or failure at each stage was simulated for a range of plausible assumptions about safety and efficacy, based on evidence from preclinical and early clinical results. The simulated "what if" scenarios helped experts to evaluate each possible strategy. These simulations gave rise to fruitful interdisciplinary discussions about the assumptions that should be used, both pessimistic and optimistic. In addition, they provided an easily shared basis for clinicians, statisticians, regulatory affairs experts, and health economists to work together to make informed, knowledge-based choices for the development plan. Here, the value of M&S was in fostering informed discussion about the risks and benefits of each strategy among diverse experts, rather than in identifying the "best" design.

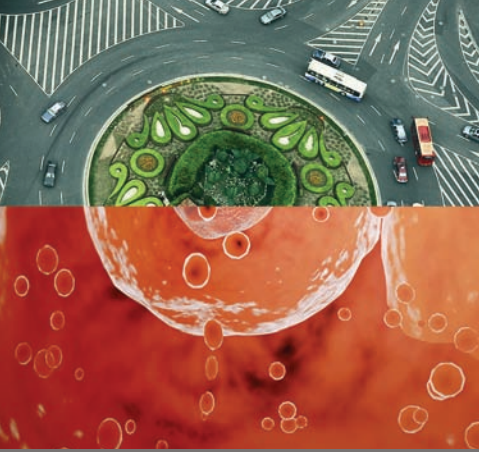
> **To implement well-informed modeling and simulation, it is necessary to eliminate traditional research silos that inhibit information sharing.**

Managing complexity: Predicting market performance. Modeling and simulation can improve commercial decision-making by taking into account more of the complex variables inherent in the post-marketing landscape. Effective management of a biopharma company's development portfolio requires assessment of therapeutic benefit, safety, commercial competitiveness, and cost-effectiveness—assessments that change as each drug candidate advances through development. Unpredictable development timelines and costs, regulatory changes, and evolving market conditions pose additional uncertainties. M&S can provide more reliable predictions of a product's market potential by addressing complex commercial questions. For example, compared to existing products, how much better do therapeutic outcomes have to be for a drug to gain formulary acceptance?[5]

Creating a statistical model of a portfolio allows developers to simulate various changes to the portfolio and their resulting impact on the likelihood that the portfolio will support business objectives. Simulations can be used to evaluate portfolio tradeoffs through the probabilistic representation of key performance metrics, such as time in development phase and development costs. M&S applications in portfolio management are now being used to understand the impact of tradeoffs (i.e., whether or not to add a risky development project to an existing portfolio) in the context of total portfolio risk and return. "What if" scenarios can help developers consider the probability that a company will meet a specific revenue threshold in a given year, or launch a target number of new products in a given timeframe. Figure 1 (see page 34) shows an analysis of varying development timelines on commercial impact.[6]

Drivers and barriers

Regulatory endorsement is a major driver of the expanding use of pharmacometric (quantitative pharmacology) models to simulate relationships between drug exposure, drug response, and individual patient characteristics. FDA's 2009



Reducing the Risk of Phase III Failures

On-Demand Webcast

(Originally aired June 4, 2015)

Register for free at www.appliedclinicaltrialsonline.com/act/phase3

EVENT OVERVIEW

It is well documented that 50 percent of Late Phase clinical trials fail due to efficacy and/or safety reasons. The result is a tremendous financial burden to biopharmaceutical companies, the engagement of tens of thousands of patients participating in clinical studies to no avail, and significant time lost for patients looking for viable treatment options in numerous therapeutic areas.

This major industry-wide problem prompted PAREXEL colleagues Dr. Sy Pretorius, Chief Scientific Officer, and Dr. Alberto Grignolo, Corporate Vice President, PAREXEL® Consulting to dig deeper and examine Phase III study failures – to better understand and categorize why the failure rate is so high and, most importantly, to identify solutions to help reduce the risk of failure in this, the most expensive and labor-intensive phase of drug development.

Key Learning Objectives

- Illustrate and document the reasons for Phase III failures.
- Present and discuss solutions such as risk-based monitoring, data surveillance, adaptive trial design, modeling and simulations, innovation and pre-competitive alliances, and more.
- Document the solutions through case studies and other examples.

Who Should Attend

- Pharmaceutical C-suite visionaries and senior R&D and Market Access executives
- Clinical Research professionals spanning a variety of backgrounds and areas of expertise
- Regulatory professionals who depend on Phase III clinical trial data to win regulatory approval
- Commercialization and Market Access professionals who depend on Phase III clinical trial data to demonstrate product value to payers and achieve reimbursement

Presenters

DR. ALBERTO GRIGNOLO
Corporate Vice President, Consulting
PAREXEL

DR. SY PRETORIUS
Chief Scientific Officer
PAREXEL

Moderator
LISA HENDERSON
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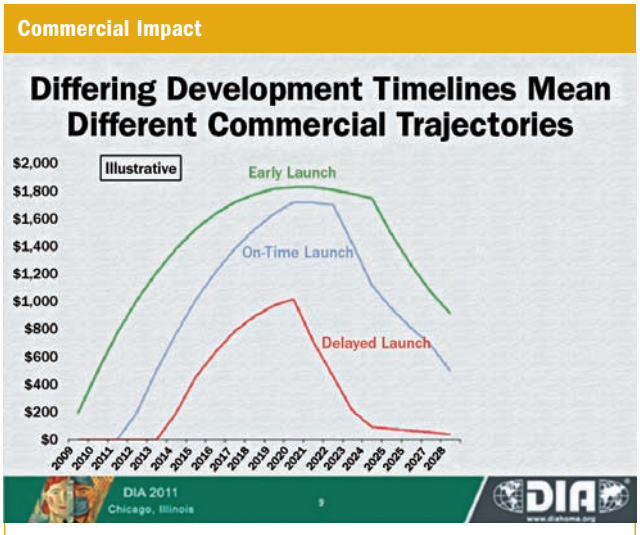

Source: Garrett et al.

Figure 1. M&S application in portfolio optimization.

"Guidance for Industry: End-of-Phase 2A Meetings" encourages sponsors to seek regulatory meetings to discuss quantitative modeling and trial simulations to improve dose selection.[7] In cardiovascular safety evaluation, the FDA's Office of Clinical Pharmacology often recommends concentration-QT (C-QT) modeling as a means of better evaluating drug potential for QT interval disturbance.[8]

Impact on approvals and labeling. A 2011 review conducted by FDA's Division of Pharmacometrics found a dramatic increase in both the number of reviews with pharmacometric analyses and their impact on FDA's drug approval and labeling decisions.[9] For 198 applications submitted between 2000 and 2008, pharmacometric analyses contributed to approval decisions in 126 applications. In 50% of these applications, M&S provided either pivotal or supportive insights into effectiveness; in 43%, M&S provided pivotal or supportive insights into safety. Pharmacometric analyses impacted labeling decisions in 133 applications. In 41% of those, M&S informed dosage and administration labeling, and in 14%, M&S contributed to safety labeling.

The review points to additional uses of pharmacometric models. FDA is using M&S to select pediatric dosing regimens and to approve drug dosages not studied in Phase III trials. There is also "an increasing trend toward use of model-based primary endpoints in pivotal trials, such as slope in a dose (exposure)-response model."[4] The report notes that five of the 198 new drug application (NDA) submissions just discussed used such model-based endpoints. Two of these submissions were indicated for pediatric epilepsy, and the primary endpoints used were slopes of the dose-response relationship and exposure-response relationship in the reduction of seizure frequency.

Another notable trend is toward the application of M&S as a pathway to regulatory acceptance of a single Phase III trial, plus a causal evidence model for demonstration of drug safety and efficacy. A provision of FDA's Modernization Act of 1997 (section 115a) allows new drug approval based on data from one adequate and well-controlled investigation, plus confirmatory evidence.[10] This model has received increasing attention as a more rational, efficient, and informative approach to clinical development.[11]

Barriers: Time, cost, expertise. There are a number of barriers to the broader application of lifecycle M&S. Despite the compelling value of M&S in clinical research and regulatory review, newer M&S applications still pose uncertainties and industry has been slow to adopt applications that go beyond PK/PD modeling. Organizations tend to accept widely understood approaches, and M&S is still unfamiliar in many applications. Thorough and careful pre-specification is often required by regulators, especially for game-changing uses of M&S in new drug applications.

M&S also requires special expertise and new ways of working. There are economic barriers as well. M&S takes time to develop and adds cost to lean research budgets.[12] The bottom line for industry is: Will an investment in M&S pay off in terms of greater predictability? The following discussion provides examples of emerging M&S development applications and their benefits.

> Testing various trial designs *in silico* before running the actual study is a very efficient method to improve the likelihood of a successful study and to reduce risk to patients.

Applications in clinical trial design

There is growing acceptance of M&S to inform clinical trial design. Simulated trials are used to "test-run" various designs; results predict likely outcomes for a range of assumptions pertaining to dose, trial size, and operational considerations.

Creating virtual patients. Virtual patients can be created at the individual level using health records, PK/PD data, and historic data. Patient attributes also can be added to virtual patients to describe behaviors, such as adherence to treatment and other study procedures. These virtual patients can then be enrolled based on inclusion/exclusion criteria for clinical trial simulations.

Example: Informing enrollment criteria. Archimedes Inc. recently conducted a simulated trial to help researchers define inclusion/exclusion criteria and gain information for powering a diabetes study.[13] FDA regulations for evaluation of new type 2 diabetes treatments require that Phase II and III trials include

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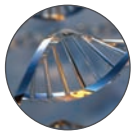

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Clinical Trial Disclosures

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Patient Engagement in Benefit-Risk Assessment throughout the Life Cycle of Medical Products

Tutorial: September 16
Conference: September 17-18
North Bethesda, MD

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Drug and Device Combination Products - Current Topics

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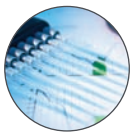

Study Endpoints

October 5-6 | Bethesda, MD

US Conference on Rare Diseases and Orphan Products

October 7 | Bethesda, MD

Biosimilars

October 18-20 | Bethesda, MD
DIAGlobal.org/Biosimilars

DIA Annual Canadian Meeting 2015

Tutorial: October 26
Meeting: October 27-28
Ottawa, ON, Canada
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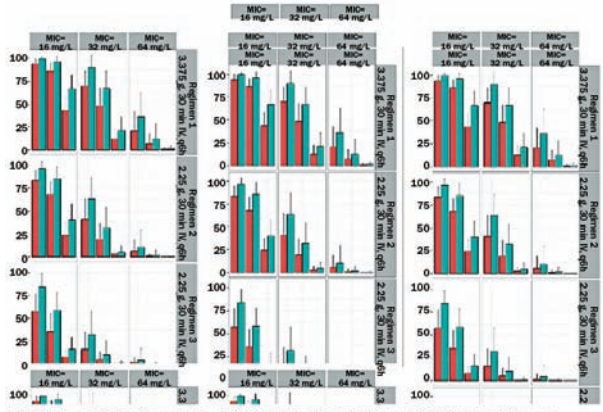
Dose-Determination Benefits



MIC: Minimum Inhibitory Concentration; PTA: Probability of Target Attainment; CrCl: Creatinine Clearance.

Source: Garrett et al.

Figure 2. Simulations used to assess dosing regimen adjustments of piperacillin/tazobactam in obese patients with varying degrees of renal function and antimicrobial susceptibility.

patients at higher cardiovascular risk. The drug developer needed to know the expected cardiovascular event rates in various patient populations being considered for enrollment in the intervention and control arms of the trial. Archimedes modeled 25,000 type 2 diabetes patients, including subpopulations of interest, and simulated a five-year trial that predicted cardiac events in control and intervention study arms. The simulated trial generated actionable information on expected trial outcomes, relative contribution of criteria to expected cardiac event rates, identification of optimal subpopulations, and effects of variations in the trial's protocol on outcomes.

Modeling disease progression. Models of disease progression describe the untreated effect on patients over time. Once disease progression models are established, they can be used to tailor therapy, to evaluate and compare the action of various treatments, and to make more sophisticated tests of equivalence between treatments.

Example: Disease progression model in biosimilar development. One example comes from a study conducted by Novartis and presented at a joint EMA-industry workshop in London in November 2011.[14] The aim was to test for the equivalence between a biologic treatment for rheumatoid arthritis and their candidate biosimilar. The usual test for equivalence is conducted at a single time point. Instead, the Novartis team used historic data to build a model of disease progression over 24 weeks in patients treated with the biologic. Novartis has proposed a new test of equivalence that, in the final assessment of equivalence at 24 weeks, uses the modeled progression over the entire study. Their simulations suggest that this new test of equivalence has better sensitivity than the traditional test, which results in savings of 40% in sample size for the planned study.

Clinical trial execution models. Operational models also are important in helping to optimize the drug development process. Statistical models have significantly improved efficiencies with accurate predictions of likely recruitment[15] and risk-based scheduling of the distribution of study treatments. Operational models also help to predict workflow peaks and, in the case of event-driven studies, to predict time to the end of the study.[16]

> **Although M&S testing and analysis add work at each developmental step, the resulting improvement in incremental decisions can lead to more efficient allocation of resources and greater likelihood of successful outcomes.**

Clinical trial simulation. Testing various trial designs *in silico* before running the actual study is a very efficient method to improve the likelihood of a successful study and to reduce risk to patients. Many of the aforementioned models are included in clinical trial simulation to help answer study design questions and investigate various assumptions. Clinical trial simulation provides the means to test multiple scenarios, to predict the potential study outcomes for each, and to quantify the risks and benefits of each design.

Example: Dose determination in trial design. An interesting example of M&S utility in trial design comes from a recent Quintiles project aimed at developing a pain treatment. As various designs were being considered, it became clear that pain tolerability would be a critical factor in whether patients would remain in the study. Unless the experimental drug relieved pain early in the course of treatment, a high dropout rate could make the study unfeasible. Early development PK/PD models were used to design a dosing regimen that included a loading dose to achieve pain relief on day one, as opposed to day seven as the sponsor had anticipated with the traditional dosing. In the actual trial, patients experienced early pain relief consistent with simulation results.

In another example of M&S utility in dose determination, simulations were used to assess dosing regimen adjustments of piperacillin/tazobactam in obese patients with varying degrees of renal function (categorized via creatinine clearance) and antimicrobial susceptibility (categorized via minimum inhibitory concentration). Population PK models, based on data from previous studies in normal patients, were used to simulate clinical trials in the obese population with differing degrees of renal function to evaluate proposed new dosing regimens. Obese patient demographics used in the simula-

eSource—
Easier than you think

On-Demand Webcast (Originally aired June 11, 2015)

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EVENT OVERVIEW

This webinar will provide summary results from a comprehensive survey on eSource conducted by Applied Clinical Trials (in collaboration with OmniComm Systems). The presenters will highlight opportunities for adoption in the light of current regulatory guidance, the exciting confluence of eSource and Risk Based Monitoring initiatives, and specific technical approaches for gathering and managing eSource data. The presentation will include examples of direct data capture for laboratory data, direct instrument capture and ePRO.

Key Learning Objectives

- Understand the current regulatory guidance and adoption rate for eSource initiatives
- Learn what your industry colleagues are saying about their plans
- See specific implementation techniques, both generally and for OmniComm's EDC products

Who Should Attend

- Clinical Operations
- Clinical Data Management
- Site Management
- Biostatistics

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tion were sampled, with replacement, out of a healthy obese study dataset to maintain realistic demographic correlations within the simulated patients. Results of the clinical trial simulation, as illustrated in Figure 2 (see page 36), showed that the probability of attaining the target minimum inhibitory concentrations were similar in normal and obese patients, taking renal function into account, across all regimens (in both 30-minute infusion and extended 4-hour infusion regimens), and across categories of antimicrobial susceptibility (minimum inhibitory concentration from 16 mg/L to 64 mg/L). From the simulations, it was also possible to conclude that no weight-based dosing adjustment was necessary in the obese population. The simulations also confirmed that extended-infusion regimens could be used, and potentially preferred, in both normal-weight and obese individuals.[17]

Applications in program design and trial strategy

M&S is now being used to design strategies for full research programs. M&S can help sponsors improve success rates by predicting and comparing the likely consequences of various strategies. These data-driven scenarios are used to guide research choices and go/no-go decisions at critical development stages.

Example: Improving go/no-go decisions. In a recent Quintiles project, a sponsor was considering development of a compound that had shown benefit in protecting animals against damaging biochemical effects resulting from traumatic brain injury, but where the benefit and side effects for humans were uncertain. The question was: Should the sponsor proceed with clinical development, given what was known about drug safety? A model was developed using all available toxicity data. Simulations assumed different levels of risk at different doses. Clinicians and statisticians considered seven scenarios, four in which no dose was viable, and three in which at least one dose was both safe and effective. Studies were simulated to find trial designs that could identify a viable (safe and efficacious) dose for approval, but that could also be stopped early for those scenarios in which no viable dose existed. The sponsor decided the risk was too high and halted development before risking patient safety and scarce research dollars.

Modeling and simulation practice is advancing. A 2010 industry survey of model-based development in 10 biopharma companies found broad application of modeling and simulation in both early- and late-stage development.[18] Dose determination remains the primary focus of M&S in development. Survey responders indicated that M&S is having the most positive impact on the rationale for dose selection, on facilitating the work of scientific and strategic project teams, on making early go/no-go decisions, and on facilitating regulatory interactions. They also cited important emerging applications in study design, disease progression, human PK and PK/PD prediction, comparator models, and decision models. Companies expected increasing use of M&S in nearly all areas of development.

The biopharmaceutical industry is clearly gaining experience with M&S, and the practice is advancing. This report proposes the adoption of a lifecycle approach in which M&S is included at each step of the development process. Although M&S testing and analysis add work at each developmental step, the resulting improvement in incremental decisions can lead to more efficient allocation of resources and greater likelihood of successful outcomes. According to one estimate, a 10% improvement in predicting failures before clinical trials could save $100 million in development costs per drug: "A mere 10% improvement in accuracy of decisions at any stage would confer disproportionately large benefits."[19] M&S practice supports knowledge-based approaches that can make clinical research processes more efficient and informative and enhance return on investment for drug developers in a challenging market environment. M&S will continue to gain ground as methodologies advance and new applications demonstrate their value.[4]

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The U.S. Biosimilar Pathway: Policy Precedes Science

David Shoemaker, PhD

A regulatory perspective on the current state of protein science and the implications for biosimilar approval.

With the passage of the Biosimilar Price Competition and Innovation Act (BPCIA) in 2009, the U.S. created new pathways for development and approval of biosimilar and interchangeable products [Section 351(k) of the Public Health Service (PHS) Act (42 U.S.C. 262)], in the hopes of creating a low-cost alternative to expensive, innovator-marketed biologics whose patent terms were expiring. The BPCIA was intended to be a major cost-containment mechanism of the Patient Protection and Affordable Care Act of 2010. The origin of the BPCIA had its roots in the Drug Price Competition and Patent Restoration Act (DPCPRA) of 1984 championed by Senators Waxman and Hatch, which has provided low-cost generic alternatives to prescription brand-name drugs for the three subsequent decades. What Congress failed to appreciate at the time was the current state of protein characterization science and, consequently, whether interchangeability could in fact be obtained or what level of biosimilarity was acceptable.

The major differences between small therapeutic molecules that are subject to the DPCPRA and biological therapeutic molecules that are the subject of the BPCIA are detailed in Table 1 (see page 42).

FDA guidances

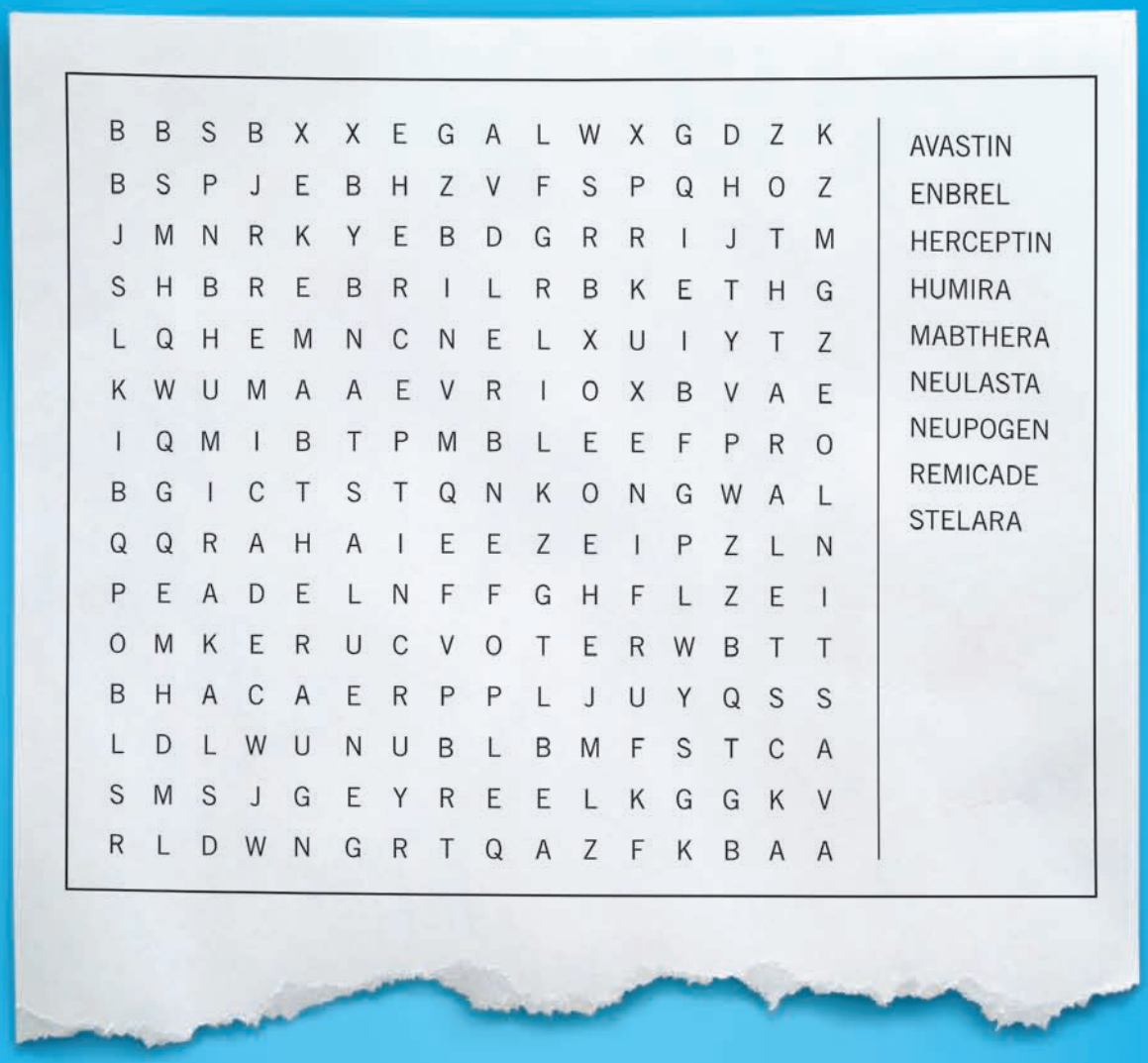
As has been well documented in the years prior and subsequent to the passing of the BPCIA, the analogy of "generic" does not transfer well from the realm of small-molecule drugs to that of biologics, due primarily to biologics' considerably larger molecular size and complexity of manufacturing that may affect the final product in terms of tertiary structure or post-translational modifications.[1] The Food and Drug Administration (FDA) recently finalized three guidance documents to help clarify expectations regarding the concept of "biosimilarity" and thereby to assist manufacturers in the development and approval of biosimilars.

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
- Q&As Regarding Implementation of the BPCI Act of 2009

FDA's document "Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants" is still in draft form.

Despite the earlier availability of the guidances in draft version, no biosimilars were approved by the FDA until this year. In March, the agency approved the first-ever biosimilar therapy in the U.S., clearing Zarxio (filgrastim-sndz), a biosimilar to Amgen's Neupogen (filgrastim), which is used to increase white blood cell counts in cancer and bone marrow transplant patients. Sandoz, a unit of Novartis, is the maker of Zarxio.

While more approvals are likely to follow, as the initial dearth of activity illustrated, biosimilar developers in the U.S. will remain challenged to advance their products to market. The primary reason is that the additional work required to demonstrate similarity of the efficacy and safety



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Drug Comparison: Small vs. Large Molecules

	SMALL THERAPEUTIC MOLECULES (DRUGS)	BIOLOGICAL THERAPEUTIC MOLECULES
Size of molecule	- Small (single molecule) - Low molecular weight	- Large (mixture of related molecules) - High molecular weight
Complexity of molecule	Drugs generally have well-defined chemical structures, and a finished drug can usually be analyzed to determine all its various components.	It is difficult, and sometimes impossible, to characterize a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown.
Source/Origin	Chemicals	Living organisms to include plant or animal cells, microorganisms, biological fluids (e.g., plasma).
Manufacturing Processes	Typically manufactured through chemical synthesis by combining specific chemicals in a controlled environment in an ordered process producing an extremely pure product.	Typically manufactured in biological systems such as a microorganisms, plant or animal cells. Most biologics are very large, complex molecules or mixtures of molecules of acceptable purity. Many biologics are produced using recombinant DNA technology.
Characterization	Easy to characterize completely using standard analytical assays.	Cannot be characterized completely due to the complex molecular composition and heterogeneity.
Stability	Usually stable at room temperature	Usually unstable at room temperature necessitating storage under refrigerated conditions
Immunogenicity	Usually non-immunogenic	Usually immunogenic

Source: Shoemaker

Table 1. The major differences between traditional pharmaceuticals and biological therapies.

of the biosimilar molecule to the original approved biologic is sufficiently burdensome to make approval via the original approval pathway for biologics (351(a)) equally attractive to biosimilar manufacturers. Also, by choosing the 351(a) biologics license application (BLA) innovator biologic pathway, the company is entitled to a 12-year marketing exclusivity period associated with this development pathway versus as little as 12 months of marketing exclusivity if it was approved as a biosimilar (351(a)(6)).

The FDA espouses that clinical and nonclinical work will be abbreviated for biosimilar approval and that approval will be granted on the basis of the "body of evidence" provided by the manufacturer, but that each application will have to be handled on a case-by-case basis. However, this is potentially much more labor intensive than the traditional biologic development process familiar to pharmaceutical and biotechnology companies. Development of a biosimilar currently requires significant comparability work be agreed upon a priori with FDA and this work must be "front-loaded" in the development program. Depending upon the results of this comparability nonclinical and manufacturing work, additional work most likely will be required.

The FDA recently released another guidance relating to its evolving standards for satisfying the biosimilarity requirements of the Biologics Price Competition and Innovation Act (BPCIA) that focused on clinical pharmacology study requirements: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.[6]

This guidance details the recommendations for the design and conduct of pharmacokinetic and pharmacodynamic studies, which will provide data for only one element in the eventual evaluation by FDA of the biosimililarity of a newly submitted biosimilar product to the approved reference product. In addition to the clinical pharmacology study or studies needed for an approval of a biosimilar product, additional clinical studies may be required along with the requisite bioanalytical molecular comparisons between the biosimilar and the reference product.

Success in Europe

There are several companies that have successfully gained marketing approval for biosimilars in Europe who have assisting FDA in determining the data package required for approval of a biosimilar in the U.S. The difficulties stem to some degree from the division of the FDA into the Center for Biologics Evaluation and Research (CBER) and the Center for Drugs Evaluation and Research (CDER) due to evolutionary organizational reasons. The European Medicines Agency (EMA) is able to bring to bear the same scientists to evaluate small molecules and biologics and, as a result, there is not the same degree of separation of opinions about how each type of molecule is regulated within one agency. Consequently, the EMA was able to foresee this biosimilar pathway's emergence much earlier and issue a number of class specific guidances that contain specific recommendations for development.

Efficacy vs. safety

Also, achieving an FDA determination of true interchangeability of a biosimilar versus an original biologic product as exists for generic and innovator small-molecule drugs will not be accomplished until a great deal more is understood about the biochemical processes generating these molecules

Considerations for formally validating software in laboratories supporting of CLIA genomic assays

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Event overview

During this webinar we will discuss practices and iÜortant learnings from a system validation for a large-content oncology-based genomic assay that meets CLIA requirements. In addition to extensive wet lab analytical validation, this assay also received extensive review of validation materials that included confirmed coÜlex variants as well as thorough system development, review, and testing of the bioinformatic software and systeÙ that coÜrise the assay and transform its data.

The field of bioinformatics, once research-focused, is now being used as a game-changing clinical tool signifying a need to integrate molecular biology, statistics, coÜuter science, and software/systeÙ engineering. In this move from research to clinical, a number of key issues arise that need to be addressed:

- What are the special clinical validation considerations from the viewpoints of overall design, wet lab performance, suitable reference material, and utilizing software-intensive systeÙ?
- Best approaches to evolve the assay as more saÜles are process and limits are more thoroughly tested?
- How is patient risk affected for broad-spectrum genomic profiling assays?
- Expected iÜact on timelines from concept to formally validated system (lab and software)

Webinar attendees will learn:

- The iÜortance of determining and iÜlementing proper validation design
- The iÜortance of software processes and allotting adequate time for system validation execution and documentation, including Part 11 solutions
- IÜortant considerations for reference material that are a key aspect of the validation to determine accuracy, along with reproducibility
- Prudence measures for use of 3rd party groups who format and/or consume the test information

Who should attend

Lab Directors or Assoc Directors, Key Stakeholders in CLIA labs, Bioinformatics managers and professional, IT Directors and associated professionals associated with molecular laboratories, Medical Directors, Research MDs, Primary Investigators, genomics-oriented professionals, consumers of genomic tests, patient advocacy groups

Presenter

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and the contributions of the various regions of the molecules to efficacy and safety concerns. Of primary concern is the contribution of the various structural elements of the biosimilar molecule to the safety concerns in clinical studies. Efficacy can more easily be demonstrated in a reasonably sized clinical development program, but it is safety that regulators struggle to define the minimum number of subjects that represent a sufficient safety data base to warrant marketing approval.

The scientific methods that are used to determine molecular similarity are currently insufficient to specifically identify the relationship between differences between a biosimilar and an original biologic. For example, assigning an adverse event observed in a clinical study to a specific peak in a mass spectrometry profile is imprecise at best, but we are nowhere near this level of precision at the current time. Consequently, the regulatory authorities emphasize that the "body of evidence" will determine their judgment as to the biosimilarity of a molecule. The FDA has championed the need to consider the safety of pharmaceuticals and biotechnology products as a science, but the integrated effort required to produce these types of results has been slowly embraced by industry, academia, and governmental agencies. Until much more work is done defining the relationship between structural elements of a biological molecule and the adverse events observed in the clinic, the determination of biosimilarity with regard to safety remains largely subjective.

Biosuperiors

Consequently, while many large pharma companies have announced their intention to develop biosimilars, many manufacturers have chosen to develop alternative products designed to be more than just biosimilar—biosuperiors or biobetters.[2] These are products similar to the original approved biologics, but with some measurable superiority such as extended therapeutic effect time or a reduced adverse event profile. These products are being developed and approved via the traditional 301(a) BLA pathway for biologics and are required to demonstrate efficacy and safety without the necessity of comparability studies designed to demonstrate their similarity to the originator molecule.

This approach has several advantages. First, it relieves the product sponsor from conducting a large Phase III active-control clinical study versus the innovator biologic demonstrating equivalence. These types of studies are larger and less scientifically rigorous than clinical studies versus placebo, and carry all the vagaries of generating meaningful data from a clinical study.[3] Of course, the efficacy of the biosuperior product has to generate efficacy and safety data demonstrating a benefit/risk ratio of the same approximate magnitude as the innovator product, but not in a head-to-head comparison. The biosuperior developer will be measured against the results obtained by the innovator in their current package insert. Consequently, the work required for approval of a biosuperior would more closely resemble the 505(b)(2) new drug approval (NDA) regulatory pathway for "improved" approved drugs leveraging FDA's knowledge of previously approved innovator products as opposed to the 505(j) NDA pathway for generic drugs with its expectations of interchangeability.

Until much more work is done defining the relationship between structural elements of a biological molecule and the adverse events observed in the clinic, the determination of biosimilarity with regard to safety remains largely subjective.

In fact, the 505(b)(2) pathway has already been utilized in the approval of biosimilar molecules that fall under the purview of the CDER as opposed to those which fall under the CBER. For historical reasons, hormones are regulated by the Food Drug and Cosmetics Act of 1938 and not the PHS Act. Consequently, well-characterized hormone molecules such as insulin and somatropin have several products competing for the market and undoubtedly put pressure on the original innovator price of these products. In Europe, where there is no distinction between the approval pathways for drugs and biologics, several molecule-specific guidances have been issued to assist product sponsors with the development of these well-characterized molecules (i.e., insulin, somatropin, erythropoietin, granulocyte-stimulating hormone, follicle-stimulating hormone, and interferon).

One might argue that focusing on biosuperiors defeats the original purpose of legislation for development of biosimilar products, i.e., the reduced sales cost to the consumer that has been well documented in the generic drug market. However, due to the complexity of development of biologics, the expected sales price of biosimilars was anticipated to originally be in the range of 70% to 80% of the originator molecule as opposed to the about 30% of the originator drug that has been documented for generic drugs.[4] Consequently, the price competition that might result from the presence of viable biosimilars on the market was never expected to be game-changing for consumers the way that small-molecule generics have been. For biosuperiors, the degree of superiority represented by the biosuperior competitor may alter this dynamic significantly, perhaps leading to a premium price for the biosuperior relative to the innovator product. In general, it is safe to assume biosimilars and biosuperiors will not realize anywhere near the degree of price discount seen with small-molecule generics.

Debate around INN

Aside from questions around how to prove "biosimilarity" or the likely effects on product pricing, the current debate raging between the companies manufacturing biosimilars and innovators revolves around the International Nonproprietary Names (INN) convention for biosimilars.[5,6] The companies manufacturing biosimilars, reasoning along the same lines as the intent of Hatch-Waxman for generic drugs, argue that all derivatives of an innovator molecule must possess the same INN name. However, the manufacturers of the innovator molecules argue that while similar, the subsequently approved biosimilar molecules will likely possess significant differences in glycosylation and tertiary structure and, consequently, should be examined separately for adverse events that may not be affiliated with the safety profile of their innovator molecules. With a bona fide biosimilar approved now in the U.S., this discussion around regulatory protein science should continue to advance and hopefully evolve to the point where detailed molecular structural information can definitively be matched with the safety and efficacy events a biological product demonstrates.

Biosuperiors advantage

Was it possible to see the evolution of biosimilars and biosuperiors prior to the passage of the BPCIA? Much of the prior debate focused on whether it was even possible to manufacture a biosimilar to the exacting standards required to mimic the efficacy and safety of an approved biologic. Large pharma emphasized the inability of biosimilar manufacturers to replicate the complex structure of biologics and, hence, predicted the introduction of unknown safety concerns attributed to the changes in structure. Nonetheless, many large pharma companies stated their intent to refocus some of their efforts on biosimilars while others steadfastly avoided this commitment or expressed their intent to pursue biosuperiors. The development of biosuperiors will no doubt also encounter some regulatory hurdles not experienced during the development of innovator molecules. For one, it will be of critical importance for the developers of biosuperiors to convincingly demonstrate to FDA their advantage over the innovator molecule if they intend to advertise that distinction. Hence, the current state of protein science seems to augur approval decisions and court battles focused on the clinical relevance of the superiority rather than the similarity of biosimilar compounds to innovator molecules.

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Managing Portfolios to Deliver Economic and Clinical Value

Rita E. Numerof, PhD, Jill E. Sackman, DVM, PhD, Michael J. Kuchenreuther, PhD

The importance of focusing on both outcomes as early as possible in the product development cycle.

The global pharmaceutical industry is in the midst of a redefining transformation. Costs of product innovation are rising as increased regulatory scrutiny is raising internal development costs, risks, and time requirements for clinical trials, while licensing and acquisition markets have become more competitive. At the same time, revenue and market share growth have stagnated for most manufacturers due to commoditization, increasing competition, patent expiration, and problems related to product differentiation.

Markets are becoming fragmented as physicians, providers, patients, and payers look for focused solutions that have optimal efficacy and safety profiles for narrower patient populations. As healthcare consolidation continues, the role of payer organizations is increasing as the complexity of decision-making moves further from the physician. There is also much greater skepticism among regulators, payers, physicians, patients, and other key stakeholders in the integrity and soundness of the industry.

In addition, demands for affordable healthcare are challenging the economics and traditional business assumptions of the pharmaceutical industry. For instance, regulatory approval has historically been thought of as the main barrier to market access, and obtaining satisfactory reimbursement was a routine consideration. However, manufacturers are now beginning to realize they can no longer successfully operate under this longstanding business assumption.

The recent boom in biologics and personalized medicine promises new levels of clinical effectiveness, but has also contributed to soaring drug costs. Taken together with record public debt and shrinking budgets, payers across the globe are increasingly saying "no" to new treatments and therapies where value can't be appropriately demonstrated to justify a premium price. This trend can even be seen in markets such as the U.K. and Germany, which have had more stringent pricing and reimbursement policies in place for a number of years.[1,2]

In the U.S., hospitals and physician groups are becoming increasingly focused on costs as well—a trend that is largely driven by declining reimbursement rates, the enforcement of financial penalties related to clinical quality metrics, and increased regulation. A sequence of events, including the Centers for Medicare & Medicaid Services' (CMS) focus on value-based purchasing, never events (medical problems that providers created or should have been avoided), and readmission rates, as well as the Affordable Care Act's endorsement of accountable care organizations (ACOs), has led to an increasing focus on moving risk associated with the quality and costs of healthcare to the provider. Recent announcements by CMS and a group of major commercial payers suggest that this trend toward value-based healthcare is not only here, but will quickly accelerate in the next few years.[3,4]

In short, economic and clinical value has become the basis for both differentiation and main-

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taining premium pricing, and the importance of the economic and clinical value case is likely only to increase. This trend is truly global in scope, applies to multiple key stakeholder groups (payers, physicians, and patients), and is particularly apparent in high-cost therapeutic areas where large numbers of new and costly therapies are being introduced for treatment of chronic diseases. Moving forward, economic and clinical value must serve as the foundation for all portfolio management decisions. Companies must also have processes and capabilities in place to focus on economic and clinical value as early as possible in the product development cycle. These include how clinical trials are shaped and conducted, and the duration and content of post-launch monitoring required.

The strategy table

Some of the most critical decisions a business makes are about its lifeblood: the stream of products it develops to generate a revenue stream. This portfolio decision-making has traditionally been the purview of the R&D and marketing functions in most companies. R&D introduces new product opportunities in terms of what is potentially possible from a technological perspective. Then marketing helps decide on the best projects by dimensioning the size of the potential for the new product concepts.

This decision-making approach worked in stable markets lacking any disruptive new technology or new buying decision variables. However, it is not sufficient in more turbulent markets, such as the ones manufacturers find themselves in today. The biggest flaw is the operating assumption that the market would continue to operate as it always had. Sales projections are based on expectations that demand for the company's products will remain the same, disregarding the potential of non-traditional competitors or "watchful waiting" as an alternative treatment option. There is also the assumption that payers will continue to pay what they did the year before. The demographics of the market are then used to extrapolate business cases and financial *pro formas* for new products, which themselves are often just an extension of technology as we know it. As a result, under this traditional approach, reaching product portfolio decisions has become a fictional exercise completely disconnected from today's market.

Regulatory approval has historically been the key for successfully bringing a new product to market, just as subsequent reimbursement at the price demanded has typically been largely safely assumed. Consequently, manufacturers have often emphasized clinical efficacy and safety criteria in determining which therapies to develop rather than criteria such as total product value and quality of life outcomes. In today's environment, however, manufacturers are increasingly required to demonstrate the economic and clinical value of new products to key stakeholders in order to justify market access and pricing.[5] Payers want hard evidence that new products are worth a premium over comparative, older products. Hospitals are standardizing on those products that best enhance the economic and clinical value of their service line offerings. Even consumers are demanding value and price information as they take on an increasing share of healthcare costs. This trend can only be expected to accelerate.

Recently, there has also been a greater need for manufacturers to provide real-world evidence (RWE) such as patient reported outcomes to meet regulatory and reimbursement requirements and to support the value propositions for new and existing products.[6] For example, global regulatory agencies are requiring additional data about the long-term safety and efficacy of new products when they are used by broader patient populations in real-world settings. At the same time, healthcare providers—and those who pay for healthcare—are demanding that new therapies provide better outcomes or greater value than existing standards of care, and are expecting real-world clinical evidence to support these claims. Effective RWE study design requires cross-organizational collaboration that RCTs do not offer. Managed markets teams, health and economic outcomes research (HEOR) scientists, clinical research, and medical affairs will all need to have input moving forward, which can be a challenge where this level of collaboration hasn't existed before.

This is the world within which manufacturers now have to compete. To make their best bets in portfolio decision-making, they will need greater insight into this world and the implications for their products. One way to achieve this is by nurturing a global, cross-functional focus on economic and clinical value.

Invite non-traditional roles

Because the basis for competition in the market has shifted, manufacturers need to challenge the base assumptions on which product portfolio decisions are being made. Economic and clinical value management is an operating model grounded in cross-functional collaboration and incorporating the input of outside stakeholders to proactively identify and demonstrate the different value drivers of a product. Successful implementation requires generating buy-in across the organization and all levels of R&D and commercial senior leadership, as well as the managed markets and payer relations teams.

There are three functions which potentially can provide invaluable insight into the shifting needs and demands of the healthcare market and the implications for manufacturers' portfolio of products: clinical affairs/medical affairs, regulatory affairs, and health economics & reimbursement.

These functions have traditionally been seen as tactical resources engaged to ensure regulatory endpoints are met during the development and launch of new products. Their

work is understood as shaping and conducting the clinical research necessary to get regulatory approval. They should also be actively engaged in portfolio decision-making where their insights can serve as a source of strategic value for market access and commercial success. Specifically, these functions can provide invaluable insight into shifting needs, new buying decision considerations, new evidence expectations, or hidden costs that would lead to very different portfolio decisions.

Market access and reimbursement decisions have become more technical in nature and less subject to influence by marketing and relationship management. Scientific and technical staff can serve as a healthy reality check here, ensuring sufficient consideration to key issues such as:

- Payers' growing price resistance to existing products, or their willingness to reject new technology in favor of older, less expensive therapies in the absence of compelling economic and clinical evidence to the contrary.
- The need to operate within an overall clinical strategy that manages predictable cost, leverages a collective body of disease state and technology research, and ensures that the evidence needed for commercial success can be feasibly generated.
- New product business case anticipation and consideration of realistic regulatory paths, timeframes, and comparative evidence expectations beyond traditional efficacy and safety requirements.

In addition to ensuring decision-making consistent with shifting market demands, there is another reason for including these functional perspectives upfront in your portfolio strategy discussions. In this market, no company can afford sub-optimal use of its resources. Considerable infrastructure, resources, and expense go into the work of clinical/medical and regulatory affairs and health economics & reimbursement. These efforts must be efficiently leveraged over the entire product portfolio.

Regulators and payers have long been in a position to dictate the structure and objectives of Phase IV and other post-market trials, which in turn increases trial costs. The creation of a more collaborative, value-based environment across the global organization will allow for proactive shaping of trial endpoints that can generate the data needed to demonstrate economic and clinical value. Such collaboration will also enable commercial functions to plan ahead to best support new products' value profiles throughout market launch.

Spectra Clinical Research

Nicholas Brownlee, PhD, President

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In the absence of an integrated view of needs across the portfolio, companies are likely to overextend one-off new product projects that seemingly are justified on their own, but in fact collectively require resources beyond the company's capacity to provide.

Capabilities to reflect change

It is not enough to give clinical/medical and regulatory affairs and health economics & reimbursement a seat at the strategy table. Without changes in capabilities, these functions are unlikely to be able to deliver the value they're expected to provide.

Having been typically utilized as tactical implementation resources, the capabilities of these functions have been developed accordingly. In order to contribute to up-front strategic market analysis and define implications for portfolio decision-making, these functions will need to build new capabilities… or "infrastructure."

For example, global companies have traditionally had people assets on the ground in their chosen markets with little structure in place for these assets to proactively and consistently capture important information capable of influencing a product's level of success (e.g., most relevant economic and clinical unmet needs, shifts in regulatory policies, and changes in market access requirements). Companies are now increasingly relying on registries and building global information systems to systematically define and capture data relative to the constantly changing clinical, regulatory, and economic evidence requirements across established and emerging markets.

However, to utilize this information to inform business strategy and portfolio-related decisions, companies will also need to develop more strategic capabilities in these key scientific and technical functions. Performance in this role will require people with the ability to discern trends in the data and infer strategic implications for the company's portfolio management. For instance, these individuals will need to be able to look at RWE and clearly define how that data can be used to inform clinical study design (e.g., endpoints, choice of comparator, etc.).

These global strategists will also require a high level of business acumen, with a capability to articulate implications in the context of the company's business and to influence portfolio strategy accordingly. Here, internal consultative capabilities are critical.

To be successful, clinical, regulatory, and health economics & reimbursement teams must effectively engage internal clients and share joint accountability for outcomes. Specifically, these scientific and technical functions will need to demonstrate their ability to diagnose problems; provide input into the framework for market research and business intelligence activities; contribute to business plan development; align processes with organizational strategy; guide implementation; and evaluate results. In order to optimize their value, technical associates will need to effectively identify and prioritize their work against broader organizational strategy and objectives.

Finally, scientific and technical strategists must be able to lead their own functions in the development of an integrated, overall strategy that efficiently and effectively addresses clinical, regulatory, and reimbursement needs for commercial success.

Definition of these roles, development of people to perform in them, and development of supportive processes is the "infrastructure" necessary to enhance strategic portfolio management with critical guidance from these functions.

New levels of competition

In our experience, there are three requirements to step up your ability to compete in a market demanding better outcomes at lower cost.

The first is to establish a truly strategic product portfolio management process—one that can optimize the use of limited resources to produce a stream of products that can serve as competitive growth platforms with demonstrated economic and clinical value. This is the strategy table.

The second requirement is putting all the right resources at that table, including clinical, regulatory, and reimbursement perspectives that can ensure decisions are made in light of a comprehensive understanding of the market's requirements.

And the third requirement is building right the capabilities in these functions so they can provide their important perspectives as intended.

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Safety Considerations for Follow-On Non-Biologic Complex Drugs

A follow-on NBCD may have difficult-to-detect differences from the original drug that cause serious safety problems that only come to light after the drug is marketed.

Scott Kolodny, MD
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Biologic drugs and non-biologic complex drugs (NBCDs) have revolutionized the treatment of many difficult-to-treat diseases, including cancer, multiple sclerosis, and chronic iron deficiency. Biologic drugs are derived from living sources, such as microorganisms. NBCDs are produced by chemical synthesis, rather than from a living source; however, like many biologic drugs, the active ingredients in NBCDs typically comprise complex heterogeneous (but closely related) nanomolecular components that cannot be isolated, fully quantitated, or completely characterized—even when using state-of-the-art physicochemical analytical tools. Additionally, NBCDs may have multiple or unknown modes of therapeutic activity.

Patents for many biologics and NBCDs are soon expiring and drug manufacturers are actively working toward producing biosimilar drugs and follow-on versions of NBCDs. The FDA has issued three final guidances for development of biosimilars based on feedback from pharmaceutical and biotech companies, researchers, and patient and physician groups. On March 6, Zarxio (filgrastim-sndz) became the first biosimilar product to receive marketing approval from FDA. Currently, no FDA guidance is available regarding regulatory requirements to ensure the safety and effectiveness of follow-on versions of NBCDs. While non-biologic, small-molecule, generic drug approval is based on long-established, clearly-defined regulatory requirements, regulators must carefully consider the applicability of "pharmaceutical sameness" to follow-on NBCDs as their regulatory approval pathway is defined.

Generic drugs cost less than branded drugs because their approval does not require clinical testing. In the classic approach, a generic drug must be shown to have an active ingredient that is identical to that of the reference drug and to have the same mechanism of action. However, in the case of NBCDs, two drugs cannot be shown to have identical active substances if the active substance has not been fully identified, nor can they demonstrate the same mechanism of action if it remains unknown or not fully elucidated. Importantly, the identity and quality of NBCDs are contingent on their well-controlled (often proprietary) manufacturing process. Follow-on NBCDs that are manufactured differently from the original branded product could have minute structural or compositional differences from the original product that are undetectable but might compromise product safety.

Despite these caveats, the FDA has accepted abbreviated new drug applications for follow-on NBCD products. This concerns many physicians and other medical experts because a follow-on NBCD may have difficult-to-detect differences from the original drug that cause serious safety problems that only come to light after the drug is marketed. Concern is amplified for physicians who treat patients with chronic autoimmune diseases such as multiple sclerosis, in which a slight change to a previously successful immunogenic therapy could prompt serious adverse events or compromise long-term effectiveness.

To ensure the safety and quality of follow-on versions of NBCDs, FDA should require Phase III clinical trials with relevant safety and efficacy endpoints. Further, once follow-on NBCDs are available, comprehensive post-marketing surveillance and risk-assessment programs should be in place to capture drug side effects that may not be evident in one- or two-year clinical trials.

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