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Earlier DMPK Studies Improve Pipeline Attrition Rates

p. 44

Emerging Market Lessons From Novartis Clinical Development

"Shortening drug development processes in frontier markets is a long-term investment. It's about building for the future." p. 16

Debra Barker, M.D.,
chief science officer,
Novartis group emerging markets (GEM)

Solving Sterile Manufacturing Capacity Issues

p. 10

Not-For-Profits Fill The R&D Gap

p. 26

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16 FEATURE: NOVARTIS

Debra Barker, M.D., chief science officer, Novartis group emerging markets (GEM), explains why Africa is the next target for Novartis Clinical Development.

August 2012

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DEPARTMENTS

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CONTENTS

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EDITOR'S NOTE

Diversity In Clinical Trials – A Best Business Practice

In June, I had the opportunity to moderate a panel discussion at the Diversity & Clinical Trials Symposium in Chicago. Prior to introducing my distinguished panel, which included Karen Brooks, senior director with Pfizer, Dr. Vince Bufalino, SVP with Advocate Healthcare, and Dr. James Powell, principal investigator at Project IMPACT, I looked out at the audience and stated, "Diversity in clinical trials is NOT a race issue." It was fairly clear that I was in the minority at this event in both my race and with this opinion. So I clarified by reiterating my previous statement along with my opinion that diversity in clinical trials is a best business practice. If you are developing a drug for a disease which has an affinity to manifest itself in a particular race or gender, then it makes sense to have that race or gender well-represented in your clinical trial. Panel member Dr. Powell pointed out that diversity in clinical trials is best represented by genetic diversity, not necessarily racial diversity. I echo his sentiment.

Unfortunately, many of the genetic traits we possess, such as skin, eye, and hair color, are some of the superficial traits which clinicians often use to determine whether or not to enroll or offer enrollment in a clinical trial. Dr. Augustus White III, M.D., Ph.D., describes this as unconscious bias. According to White, coauthor of "Seeing Patients: Unconscious Bias in Healthcare," there are 13 groups in the United States which receive disparate medical treatment (African-Americans, Native Americans, Asian-Americans, Latinos, prisoners, Appalachian poor, immigrants, disabled individuals, certain religious groups, gays, obese, elderly, and women). We know that the risk of inheriting certain diseases comes down to genetics. For example, sickle cell anemia is more common in families from Africa, India, the Mediterranean, Saudi Arabia, and South and Central America. In the United States, it most commonly affects African-Americans and Hispanics. Though diversity in clinical trials should be a best business practice, it seems to remain an issue driven by race, or perhaps bigotry.

After this event, I attended two very large industry shows — BIO International and DIA. I had the opportunity to interact with executives and key opinion leaders from vendors, pharma/bio companies, and academia. Having recently attended the diversity summit, I was curious to get their take on the diversity issue. I was surprised to find that many executives either don't see diversity in clinical trials as being an issue, or is an issue which they believe has already been adequately addressed. Personally, I think that if you want more diversity in clinical trials in the United States, you need to get more minorities like me involved.

Rob Wright
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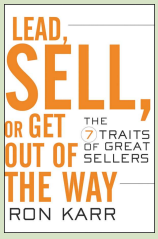

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ASK THE BOARD

Have a response to our experts' answers? Send us an email to atb@lifescienceconnect.com.

Q: How can companies build flexibility in product supply and manufacturing so they can better respond to volatile manufacturing capacity requirements?

Let's look at this from two perspectives — the company's external customer and the company's manufacturing capability. The need for accurate forecasting at the customer level is more critical than ever, and having this data accessible by product management, operations, and manufacturing allows for more flexibility. Sales trends are easily identified and forecasted, so planning for now and in the future becomes predictable. From the manufacturing perspective, some of the current trends indicate that companies are focused on being more responsive to customer and market needs. These include increased budgets with investment in upstream and downstream technology, cost-savings (e.g. the use of single-use equipment), and the utilization of contract manufacturing as a more strategic, targeted approach to flexibility of product supply. Incorporating these perspectives into the manufacturing strategy ensures external customer satisfaction and the company's success.

Ann Willmoth, M.Ed.
Willmoth is the general manager of Blue Standard Consulting, a healthcare management consultancy, advising companies on business strategy and commercial approaches to the market.

Q: What are some of the biggest mistakes you have seen companies make when revamping their leadership/ mentoring program, and how can these be avoided?

One of the biggest mistakes companies make is focusing development efforts solely on those classified as high potentials. Succession must occur at all levels of an organization – not just at the executive level. The classic nine-box methodology is great for diagnostics, but not necessarily so great for creating development road maps. The goal of development programs should be to free people from boxes, not place them in boxes. But perhaps the biggest problem most organizations face in their leadership development programs is not being outcome-based. Programs must translate into measurable performance gains. If the curriculum isn't aligned with the people, culture, and business objectives, it will fail.

Mike Myatt
Myatt is a noted leadership expert, author, and widely regarded top CEO coach in America. As a thought leader and columnist on topics of leadership and innovation, his theories and practices have been taught at many of the nation's top business schools.

Q: What keeps many R&D transformation programs from meeting their potential, and what advice do you have for improvement?

The simple response is trust and execution. Transformation programs have two goals: getting to market in less time and at less cost. Perhaps choosing the wrong partner impedes these goals. Beyond the analysis of the partner's experience and capabilities, you must consider each partner's goals and competencies. Can the goals of each partner be achieved? Is the leadership present to assure goals are fully aligned throughout each organization? This is difficult on the strategic level; tactical considerations require accommodation of constant change. Trust is both given and earned at each company interface. Do individual teams bring trust to the table, or do they demand performance first? Both partners must execute in a transparent manner, or the alliance suffers.

Tim Krupa
Tim Krupa is president of TSK Clinical Development, LLC, a consulting firm providing leadership and solutions in clinical planning, project management, clinical operations, and outsourcing.

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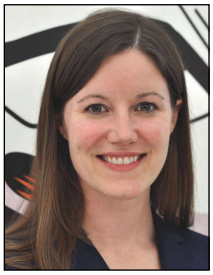

OUTSOURCING INSIGHTS

Capacity Issues And The Question: To Insource Or Outsource?

By Kate Hammeke, Director of Marketing Intelligence, Nice Insight

Sterile manufacturing of injectables has been at the forefront of both industry news and drug developers' minds recently for a variety of reasons influenced by capacity. An increase in demand for parenteral drugs, driven by growth in biologics R&D, has created greater demands for capacity. However, the financial investment needed to establish an aseptic fill-finish operation — in addition to the challenges in achieving and maintaining compliance — presents a significant barrier to any obvious short-term solution for increased capacity. A higher number of sterile manufacturers and increased scrutiny by the FDA has also amplified capacity issues, as unsuccessful inspections have led to temporary shutdowns in order to address compliance concerns.

The increase in demand for sterile injectable drugs still presents complexities and costs that must be evaluated when considering whether to insource or outsource production.

BALANCING CONTROL AND THE ECONOMICS

Outsourcing is the alternative route, but the increase in demand for sterile injectable drugs still presents complexities and costs that must be evaluated when considering whether to insource or outsource production. Striking a balance between having a comfortable level of control over the process, while still making an economically sound decision for the business, adds to the question of whether to do the work in-house or engage a CMO. Results from Nice Insight's 2011 and 2012 pharmaceutical and biotechnology outsourcing surveys indicate a five-percentage-point rise among sponsors who outsource the manufacture of steriles (6% in 2011 vs 11% in 2012). When looking at specific sponsor segments, it becomes clear that Big Pharma is driving this increase, with growth from 7% in 2011 to 14% in 2012, followed by Biotechs, which showed an increase from 7% in 2011 to 10% in 2012. This outsourcing trend suggests a few possibilities — a level of "comfort in control" has been found, the costs and time associated with establishing new sterile facilities have forced a compromise, or a loss of confidence in sponsors' own ability to maintain compliance has encouraged decisions to outsource.

Considering that some of the big names that have received 483s come from both the sponsor side and contract manufacturer side of drug development, a combination of factors potentially influence the insourcing vs. outsourcing decision. Once a decision has been made to outsource, it is important to gain an understanding of how the CMO ranks with respect to quality, reliability, regulatory track record, and productivity — the top four drivers influencing sterile fill-finish outsourcing in order of importance to sponsors. To see if the FDA's increased vigilance has had any impact on how sponsors rate these manufacturers, we reviewed historical Nice Insight survey data for several of the major players in this sector. Surprisingly, the overall net changes across each driver indicated positives in selecting CMOs, with the largest gains in reliability. Interestingly, Patheon experienced a 4% drop in customer perception of quality, but a 6% increase in productivity perception and a 5% increase in regulatory perception. DSM demonstrated smaller (2% to 3%), yet steady improvements in each category, with the exception of a 1% drop in regulatory perception. The clear standout among the CMOs included was Vetter Pharma, with a 6% increase in perception of quality, a 7% increase in perception of reliability, and a 3% increase in regulatory perception.

THE NEED FOR GMP-COMPLIANT FACILITIES

One facet of this capacity conundrum that deserves more attention is the increasing need for good, affordable, GMP-compliant facilities that can provide smaller batch runs for Phase 1 testing of cytotoxic products. At present, many facilities capable of manufacturing sterile injectable drugs were designed for substantial-size runs, using one or more manufacturing lines. When it comes to cytotoxic drugs, which can only be produced on certain types of lines and in certain facilities, the options among manufacturers drop, and costs rise. The rumor is that India's contract manufacturing industry has noticed this anomaly — creating a niche for flexible facilities and modular capacity for cytotoxic injectable production — and intends to use the opportunity to enter the market.

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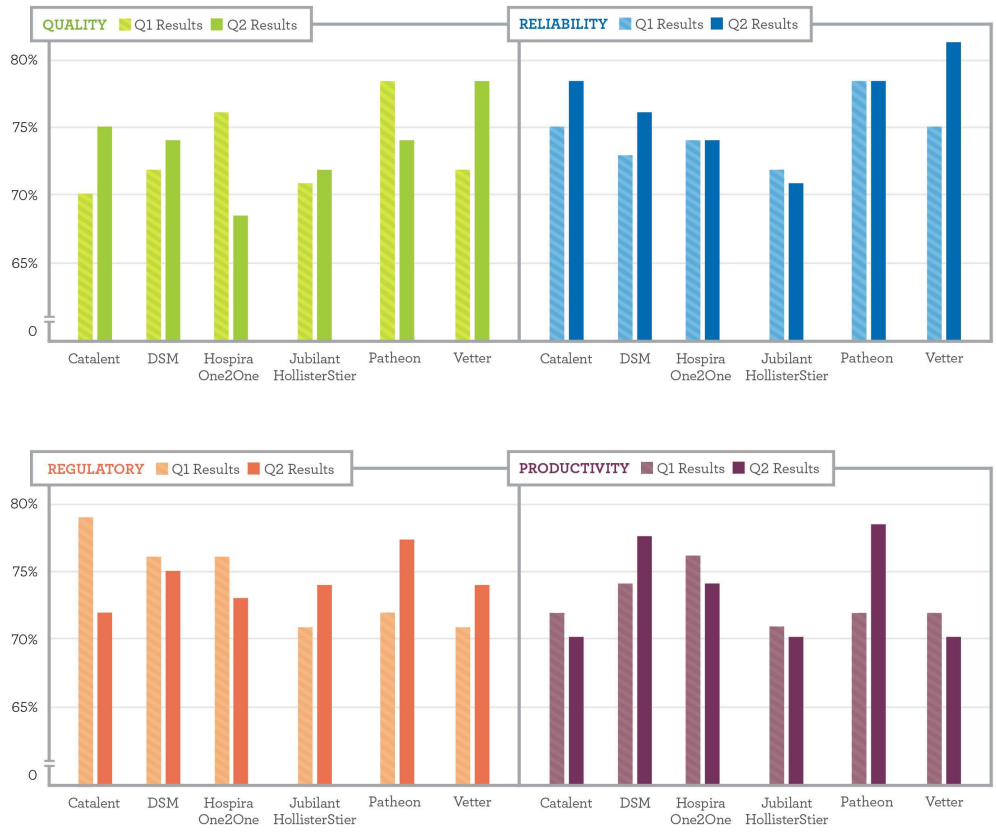

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis/four times per year [Q2 2012 sample size 2,402]. The survey is composed of 750+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 300 companies that service the drug development cycle. More than 1,200 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability, which are ranked by our respondents to determine the weighting applied to the overall score.


Walker

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, or Salvatore Fazzolari, director of client services, at Nice Insight by sending an email to niceinsight.survey@thatsnice.com.

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BIO DATA POINTS

Biopharma Outsourcing Leveling Out

By Eric Langer, president and managing partner, BioPlan Associates, Inc.

Biopharma companies have become increasingly comfortable outsourcing a variety of their manufacturing service needs over the past five years, but results from our Ninth Annual Report and Survey of Biopharmaceutical Manufacturers indicate that the extent of this outsourcing may be flattening out. This year, we asked 302 biotherapeutic developers their outsourcing strategies for production and found that there appears to be a slight downtick in levels of outsourcing when segregating by production system. This flattening also was indicated in research questions associated with budget trends for outsourcing.

In the study, we asked respondents the type and scale of services they outsource. For mammalian culture this year, 47.1% of respondents indicated they would not be outsourcing any production at any stage. This is up slightly from 44.6% last year, but still represents a drop in 100% in-house production from 2006 to 2010, when between 57% and 57.6% of respondents kept all mammalian culture production in-house. The story is much the same for microbial fermentation: This year half said they were not outsourcing any production, which is a step up from last year (43.8%), but still below levels from 2006-2010, which ranged from 58.1% to 64.2%. Similarly, for yeast systems, the percentage of respondents keeping 100% of production in-house is up from last year, which is now leveling out after five consecutive years of decline (in complete in-house operations) from a high of 86% in 2006. The study also provides capacity and outsourcing data for insect and plant systems. Overall, based on percentages of outsourced manufacturing, particularly with the most used systems (mammalian, microbial, and yeast), there appears to be slightly decreased levels of outsourcing this year, suggesting that outsourcing activity could be leveling off after a five-year period of generally increasing levels.

The industry continues to focus on lower value-added services.

MOST BIOMANUFACTURERS NOW OUTSOURCING SOME SERVICES

Beyond just biologics manufacturing, the study also evaluates outsourcing of a broad range of associated services. The study indicates that outsourcing today continues to be dominated by relatively lower value-added services, such as testing. We tested 23 different areas of outsourcing, finding that the primary outsourced activity today is analytical testing, with 83.3% of biopharmaceutical companies outsourcing at least some of this activity, up from 61% last year. The reason for this situation is related to the need for highly specialized staff to run certain assays and the need for expensive, high-maintenance equipment. This percentage outsourced will likely increase in the future, with regulatory agencies simply wanting more characterization and other data about products.

Toxicology testing (72.9%) and validation services (69.8%) were next on the list, with product characterization testing and fill/finish operations rounding out the top five. At the other end of the scale, there appears to be relatively low outsourcing activity for design of experiments, downstream/upstream process development, and QbD (quality by design) services. These tasks are often considered core corporate capabilities not suitable to being outsourced.

We compared the outsourcing activities undertaken in 2010, 2011, and 2012. We found some changes, but for the most part, the percentage of biomanufacturers outsourcing at least some of these individual activities appears to be relatively stable, with exceptions including analytical testing, toxicity testing, regulatory services, media optimization, and upstream bioprocess design services, which all showed increasing outsourcing trends.

OUTLOOK

Despite indications that certain outsourcing activities have leveled off this year, outsourcing for biologics will continue as more companies — including virtual companies — work to get their products into clinical trials. Established companies will seek partners to get established products outsourced to free up capacity for new, upcoming products from their pipelines. And as biomanufacturing becomes more globalized and offshoring becomes increasingly mainstream, newer markets will arise and establish an increasingly important footing in the industry landscape.

Figure 1: Biopharmaceutical Manufacturing Facilities Outsourcing *No* Production 2006-2012

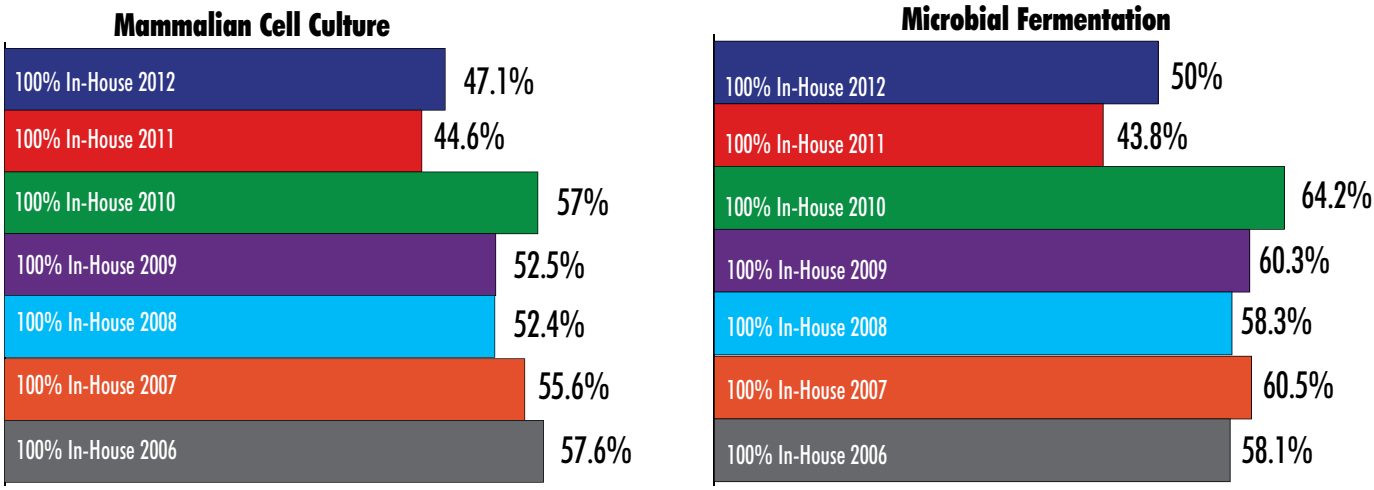

Figure 2: Selected Results — Percent Of Biomanufacturers Outsourcing At Least *Some* Production 2010-2012

Survey Methodology: The 2012 Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 302 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 29 countries. The methodology also included 185 direct suppliers of materials, services, and equipment to this industry. This year's survey covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

If you want to learn more about the report, please go to bioplanassociates.com.

Debra Barker, M.D., chief science officer, Novartis group emerging markets (GEM)

Africa – The Next Frontier For Novartis Clinical Development

By Rob Wright

Just as people distinguish between "old" and "new" Europe, the healthcare industry is beginning to distinguish between "old" and "new" emerging markets. The BRICs (Brazil, Russia, India, and China) are the "old" and have been increasingly suffering from the law of diminishing returns. A 2010 article in *The Economist* classified the "new" emerging markets into two categories — "overlooked" and "frontier." Overlooked markets can rival the BRICs in terms of prosperity, while frontier markets are poorer and riskier than their overlooked counterparts. The biggest concentration of these markets just happens to be in Africa. Though many of these markets are known for being unpredictable, prone to whims of nature, wiles of dictators, and wills of Somalia's pirates, they also represent huge growth opportunities.

With a population second only to Asia's and forecasted to grow faster than those of Europe, Latin America, and North America, it is anticipated that by 2050 Africa will have a population of around 2 billion. No wonder Novartis (NYSE: NVS), with nearly 120,000 employees worldwide and sales revenues of $58.6 billion (up 16% vs. last year), sees Africa as the next frontier in emerging markets. Debra Barker, M.D., chief science officer for Novartis group emerging markets (GEM), has spent a lot of her career in the emerging markets. Responsible for clinical development and regulatory affairs across all Novartis divisions for a number of small, dynamic emerging markets, Barker shares her insights as to why Novartis sees Africa as one of the next frontiers for clinical development, the company's approach to market entry for clinical trials, and associated lessons learned.

CLINICAL TRIALS EXPANSION IN EMERGING MARKETS

Though Novartis has been in Africa for a long time, the strategy for entering the frontier markets in Sub-Saharan Africa was advanced further with the foundation of the Region Group Emerging Markets (GEM), which includes some small, dynamic emerging markets in various continents, amongst which are a few countries in sub-Saharan Africa. As a complement to the business strategy, the company is also planning to increase its investment in clinical trials in the region to ensure that drugs developed there meet the unmet medical needs of the local communities.

Originally started as a pilot in nine countries in 2008 to help fulfill unmet medical needs in smaller emerging economies, GEM has helped Novartis accelerate year-over-year growth in selected countries across various continents. The idea behind GEM was to create a team which could quickly align efforts across the divisions of Novartis to meet the customer and patient needs and become the "local partner of choice" in some smaller emerging countries. Prior to the Novartis GEM setup, if a hospital in Kenya wanted to procure a variety of products, it would have multiple points of contact, such as Novartis Pharmaceuticals for oncology medications, or Sandoz for generics. According to Barker, the creation of the GEM team allows Novartis to be able to gain a greater understanding of emerging market medical needs and provide an integrated solution across the six different divisions. "The different divisional organizational structures don't exist in GEM," she says. "We are able to represent all the Novartis products to the healthcare professionals." This allows for a more personalized level of service to healthcare professionals

THE IMPORTANCE OF COLLABORATIONS IN CLINICAL TRIALS DEVELOPMENT

Africa consists of 54 countries — more than the EU, more than Asia, and more than North and South America combined. In such a vast and diverse continent, one of the first challenges is to determine which countries or even regions to focus on. "In Africa, like in any other region where we operate, we want to make a difference in terms of impact on healthcare," states Debra Barker, M.D., chief science officer for Novartis group emerging markets (GEM). In order to do so, clinical development efforts have been increased by establishing a significant medical presence in Kenya and Nigeria. "Africa is not just one big mass," she explains. "The countries have their own individual cultures as much as any country in Europe." Barker analogizes that trying to run operations in Kenya from an office based in Nigeria is similar to trying to run a China operation from an office in Japan.

She admits that for now, the company does not intend to have an office and run clinical trials in every African country. However, she does advise that if you want to target a market for studies, the best approach is to have people on the ground, in country, and listening so as to best understand the needs of that region. For Novartis, entering into frontier markets includes treating the markets individually, hiring locally, and providing new hires with the necessary support and training. In addition, Novartis likes to bring in expatriates so as to have a quick impact to the business unit by accelerating Novartis knowledge transfer to local talent. Expats also bring different perspectives from how trials are conducted in other markets, for example teaching the CRAs (clinical research associates) that a trial is a true partnership between the institution and the company, requiring time and effort on both parts.

Finally, the Novartis approach to frontier market clinical development includes strategic collaboration. Novartis has found that strategic collaborations with local and regional vendors help to establish and train centers more quickly and also give the company a better understanding of how clinical trials are conducted in these markets.

Being a large multinational company with a long history, Novartis likes to partner with companies with which it has a track record. This might not be possible in frontier markets. In these cases, the company uses an assessment questionnaire to make sure the vendor or local CRO can comply with international standards. Barker urges caution in selecting strategic partners. "Don't ship a huge consignment of a very expensive experimental cancer drug to a partner you have never used before," she states. "This is a sensible approach in any country. We need to be extra vigilant as we strive to ensure the safety of our products and patients at all times. It's common for samples to either be left on a quayside when the customs paperwork is not filled in properly or simply 'disappear' before they ever get to a patient." Also, ensure the partner has the equipment necessary to store the drug properly, and for Phase 4 studies with registered products, determine if your product packaging meets the climate zone requirements. For example, a majority of Africa is in climate zone 4 — high humidity and very high temperature. "Many companies that are focused solely on the West in regard to commerce will just make and package their drugs to meet the stability requirements for climate zone 2," Barker says. "Medicines which would be stable on your desk in an air-conditioned office in the United States may not be stable on a pharmacy shelf in a tropical climate zone, which may be a kiosk in the middle of the jungle or the corner of a desert."

When considering developing your company's frontier market-entry strategy for conducting clinical trials, Barker endorses thoroughly understanding disease epidemiology, unmet medical need, regulatory requirements, affordability, and genetic and disease diversity. For example, the pathogenesis of hypertension in black patients is thought to be different than in white patients. Thus, some hypertension drugs may work better in one population versus another. Dosages may vary among populations, with some needing more or less of a medicine to get the same therapeutic benefit, which is why Novartis performs global studies to ensure the "generalizability" of its data and the safe global use of its medicines. In Africa, some people may get their wages on a daily basis. So, not only do the drugs need to meet genetic and disease diversity, but also packaging may need to be such that patients can buy a two-to-three-day supply. According to Barker, the medicines Novartis studies and intends to bring to market in Africa need to be suitable for both global and local use. "We don't do studies for any drugs that we are not going to commercialize in that country. By increasing clinical trials in Africa, we want to make a difference for these patient populations by addressing their unmet medical needs."

within countries of limited resources. Barker describes having been to emerging market clinics where they see 300 patients in a morning. "If a doctor and his nurses are going to see 300 patients in a morning," she explains, "you can see the challenge for that doctor to spend half an hour to explain an informed consent document to enroll just one of the patients in a clinical trial." When entering a frontier or emerging market to perform clinical trials, Barker suggests determining how to help these overwhelmed clinicians. One way is by making things easier, i.e. having one point of contact for necessary resources. This is what Novartis tries to address through the GEM organizational structure, providing access to clinical resources across all Novartis divisions to improve health care in some of Africa's frontier markets.

"Shortening drug development processes in frontier markets is a long-term investment."

CLINICAL TRIALS LESSONS LEARNED

Novartis has historically conducted clinical trials in South Africa — the continent's biggest economy, accounting for nearly a quarter of its GDP. That being said, South Africa has nearly 25% unemployment, while another 25% live on a little over a dollar a day. Nonetheless, the country's economic strength is 10 times that of Kenya and twice that of Nigeria — two countries Barker notes where Novartis has recently begun conducting clinical trials. "But it's not easy," she admits. "You have to be willing to make an investment." The investment to which Barker is speaking involves time, money, as well as infrastructure — both physical and social. "Some hospitals might not have a fridge for storing trial drugs or blood samples properly," she explains. "Certain equipment which is often taken for granted in many countries, such as fridges, freezers, and even fax machines, are needed to support clinical trial work."

Other investments might include supporting a clinic through a grant so that a clinic seeing 300 patients in a morning can hire a nurse to help manage the patients who are study candidates. With a lighter workload, a doctor may have more time to spend on enrolling patients in clinical trials. Companies can consider providing the hospital a grant to invest in a research fellow to assist and support a clinical trial or pay a site-management organization to assist in identifying and supporting patients. "Maybe a doctor needs a separate room, as they don't have an office where they can do clinical research," says Barker. "They don't have fireproof cabinets, and patients are often two to a bed," she states. "Ask yourself how you can appropriately support the doctor to do his job." As for time, Barker advises companies to be on the ground with their own staff so as to best determine what training needs to be done. "You have to put in about 100 times more effort and time than you think you would," she affirms. Barker explains that when beginning trials in frontier markets, clinicians would describe having screened hundreds of patients, and yet, none had given informed consent. One reason is that clinicians are overburdened in their work. Another is the need for better clinician training on the informed consent process. Finally, Novartis found the importance of understanding the social and cultural infrastructure as well. "If you look at an informed consent form given to an American patient, it might be four to five pages long — fairly standard," she explains. "American patients are generally very well-informed, make decisions quite independently, and have a good standard of literacy." This same approach doesn't tend to work as well in Africa, where literacy standards may be lower and patients seek advice from tribal elders. Novartis developed an informed consent program, which utilized storyboards and pictures, and involved the patient as well as the tribal elders. The company was sure to be careful that tribal elders were helping to inform patients, but not coerce them to enroll in the clinical trial. "You have to be really culturally sensitive to what's happening," Barker confides. By implementing some of the above, Barker and Novartis saw a dramatic increase in clinical trial participation thanks to a better understanding from the patient of what clinical trial participation really means. As an example, she cites one diabetes study where, using a standard approach, only 10 patients of a needed 100 were recruited in the first six months the study was open, because people were suspicious of being used as "human guinea pigs" and thus, very reluctant to participate in the study. "In the final three months of the recruitment period, we switched to a strategy based more on discussing the consent and trial with the local community. This was successful, and the study was completed on time — much to our relief."

Many of the metrics used to measure clinical development success can apply to frontier markets as well, such as the number of patients enrolled in clinical trials and the number of approvals. However, Barker reminds those interested in entering frontier markets to be less concerned about key performance indicators and more concerned with building both relationships and capabilities. There are other lessons to be learned. For example, according to Barker, the Novartis approach in *developed* markets is changing to more closely resemble how the company conducts trials in *emerging* markets. That approach also includes larger but simpler studies being asked for by the FDA and European regulators and an increasing emphasis globally on quality of life and affordability. "Shortening drug development processes in frontier markets is a long-term investment," she states. "It's about building for the future."

Novelty, Purity, And Potency:

Three Pillars Of Biotherapeutics

Formulation Drives Innovation At The AAPS National Biotechnology Conference

by Wayne Koberstein, contributing editor

Tiny pieces of gunk — formally known as particles or "aggregates" — almost completely dominated the discussion among some 7,000 participants at the 2012 AAPS (American Association of Pharmaceutical Scientists) National Biotechnology Conference (NBC) May 21 to 23 in San Diego.

Aggregates in therapeutic proteins ultimately constrain their concentration, thus their potency and potential dosing in patients. But the work to produce the purest possible forms of new biotherapeutics begins long before they reach the first human beings. From the bench to clinical trials, and continuing even into commercial production, biotherapeutics stand or fall on their level of purity and potency.

WHAT'S IT ALL ABOUT, AGGREGATE?

Reducing an entire conference to a simple phrase — e.g. tiny pieces of gunk — is oddly appropriate. For the aim of this meeting could well be seen as an exercise in resolving extremely complex issues in living chemistry into comprehensible terms that scientists and nonscientists together can discuss.

Such issues critically inform and determine a host of decisions by companies, business executives, and investors, as well as regulators and policymakers, and of course, all the researchers, engineers, and industrial managers plodding along the path of product development. Characterization, another blanket term for the process of evaluating molecules for purity and potency, came up as a key element in virtually every session of this exhaustive and highly technical program. But a few common goals emerged from the depth of expert-level details:

- accelerating biotherapeutic development by improving the quality, e.g. pharmacokinetics/pharmacodynamics (PK/PD), of new molecules
- smoothing the regulatory path for new molecules and biosimilars
- expediting the translation of new discoveries into compounds testable in humans
- accommodating personalized medicine and novel drug delivery in the development of new drug-diagnostic or drug-device combinations.

Case in point: a roundtable with the intriguing if somewhat overpromising title, "Ask the Regulator: What Biopharma Scientists Always Wanted to Discuss with FDA and EMA Representatives." Rather than a spontaneous panel-audience exchange, the session was highly structured as a veritable work session presenting and gathering feedback on regulators' current plans for evaluating the biological effects of aggregation in biotherapeutics.

The FDA's Susan Kirshner, associate chief of the laboratory of immunology, and Laura Salazar-Fontana, staff fellow, spotlighted some of the agency's responses to the AAPS focus group on "Particle Aggregation and Biological Consequences" (PABC). They presented a set of questions and answers related to regulatory oversight and prioritization of process and product changes, comparability studies and protocols, surfactant specifications, and other aspects of product composition, from bench samples to bulk supply. Their answers gave some guidance on when and how producers must report process and composition changes with important side effects or risks.

One of the most far-reaching questions in the FDA's presentation was, "How does the FDA decide when to ask for data from new technologies in the production of biotherapeutics in development?" New technologies may arise at any step in the process, but may include single-use components, aseptic blow-fill-seal, or novel purification tools. The FDA's answer stressed the top priority of safety and the need for producers to look at the PK/PD implications of every change: "Applicants are required to demonstrate … the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as they may relate to the safety or effectiveness of the product."

An "industry view" presentation by Vicki Frydenlund, CMP compliance manager at Genentech, focused on how to structure company production operations to ensure purity, potency, and good PK/PD. She emphasized some basics, such as the need for sufficient "temporal segregation," adequate analytical methods, and careful flow design to avoid cross contamination in multiproduct facilities. Genentech is conducting a QbD (quality by design) pilot program built on the principle of extensive quality and risk management. Key elements of its approach are sterility testing, comparability, and measurement of subvisible particles.

The ask-your-regulator session ended in a brief and mainly inaudible Q&A exchange with the audience. One person asked how his company could work with FDA to decide which of several possible new production methods to adopt. The FDA reps recommended that the company first evaluate the alternatives before making a proposal to the agency, comparing each method with clear aggregation data, some measure of potential immunogenicity, and an analysis of the method's likely impact on the related "community" of producer, regulator, investigators, and patients.

ENDURING EDUCATION

Most of the sessions in this conference were more than 2 hours long and ran in several parallel tracks from early morning to evening, with some even carrying on through the lunch break. A typical afternoon saw concurrent sessions on plant-derived vaccines, preclinical immunogenicity assays, developability assessment, and biosimilars. Generally, except for FDA, no presenters shared their slides, and — because many of the speakers were from proprietary companies — recording by attendees was forbidden. So the audience became a sea of furious note-takers mottled with yellow tablets, laptops, and iPads. That setting alone characterizes the event as a whole: There was no substitute for being there.

The conference deserves high marks for sticking to the essentials of a physical meeting of people in a well-defined community. Not a second was wasted on "virtual" elements that could as well have been communicated online. Still, the event arguably suffered from a lack of networking among participants; there simply was no time left between the exhaustive sessions, other than two 1-hour receptions in the exhibition and a lunch area outside. Another drawback was poor acoustics and microphone management, which often made Q&A exchanges frustrating to follow, especially considering the admirable international mix of English speakers with sometimes challenging accents.

The opening plenary session on day one supported the conference's overarching theme: "Advancing Health Through Innovations in Biotherapeutics." Tony Coyle, head of the Pfizer-academia initiative, Centers for Therapeutic Innovation (CTI), pointed to the "perfect storm" of Big Pharma R&D shortfalls, collapse of VC funding for biotech, and growing participation of academic science in new discoveries, which he said creates a need for new ways and new partnerships for translating science into therapeutic breakthroughs. He laid out a clear rationale for the CTI model as a solution for funding and facilitating translational science for academic researchers, who now account for more than 50% of new therapeutic entities. (Note: An upcoming report on Pfizer R&D in *Life Science Leader* will share a closer look at the CTI model.)

Dr. C. Anthony Blau of the University of Washington gave a much smaller scale but no less significant view of his own initiative stemming from academic research. Called "Partners in Personal Oncology" (personaloncology.org), his open, Web-based "institute" aims to be a "network of networks" dedicated to integrating all the best possible resources and bringing them to bear as an optimally tailored treatment for every cancer patient. Blau is a hematologist, but after a trip to a large cancer meeting with his oncologist wife, saw the need for oncology to restructure itself in the way his own field refined its approaches from the early, stem-cell-transplantation-for-all philosophy to the quite different, patient-specific treatment programs of today. He issued a challenge to the cancer-research community.

"We still treat cancer as a black box," he said. "We need to deal with the heterogeneity of cancer among patients and see who responds best to which treatment. Current clinical trial design does not allow for such variability. All we can do is compare an experimental therapy against standard therapy and pick the winner."

Orphan drugs were the focus of another plenary presentation by Tim Cote, longtime rare disease advocate and chief medical officer of NORD (National Organization for Rare Disorders). Cote was an early associate of Abbey Myers, who decades ago founded NORD, which became the principal force behind the revolutionary U.S. Orphan Drug Act (ODA). ODA gave companies big incentives to develop drugs for orphan conditions and inspired similar approaches internationally.

Cote traced the amazing growth of orphan drugs since then, from zero to more than

SESSION SAMPLER: EVALUATING CANDIDATES EARLY

A seminar and roundtable on early biotherapeutic development selection at the AAPS National Biotechnology Conference yielded details of large- and small-company as well as academic initiatives to adopt new technologies, and methods to characterize new molecules and predict their effects in humans, as well as manufacturing and delivery.

Bristol-Myers Squibb (BMS) is building molecular "scaffolds" to generate "millimolecules" — essentially smaller antibodies with multiple targets, according to Sharon Cload, VP at Adnexus, a BMS R&D company. The goals are superior potency and specificity, aggregation propensity, and immunogenicity potential, all leading to in vitro selection of candidate molecules with "high affinity, selectivity, and binding." Presumably, over time, as tools improve, in vitro selection will occur earlier and earlier, and it should also yield better results as the "biophysical triage" of scaffolds and molecules more accurately reflects PK/PD (pharmacokinetics/pharmacodynamics) in patients.

Novartis has teamed with MIT in a computer-based approach to early developability assessment, reported Bernard Helk, global executive director of technology development at Novartis Biologics/Process Sciences. The aim is "biophysical profiling" of molecules based on such factors as charge distribution, self-interaction, surface hydrophilicity, and conformational stability.

George Makhatadze, professor of biology at Rensselaer Polytechnic Institute, expanded on the charge factor, specifically charge-charge interactions over the surface of a molecule, as a function or predictor of purity and potency. Molecules designed to have an "optimum" charge distribution have shown greater thermostability, protolytic degradation, and protein aggregation versus their "wild-type" precursers, he said.

Naturally, in addition to the academic and large-company efforts to improve early candidate selection, there will be plenty of small companies vying to help out. Tudor Arvinte of Therapeomic described how his company specializes in "enabling formulations" with superior stability, using a variety of technologies and assays individually "tailored" to the evaluation of specific proteins, not only for chemical and physical stability, but also easy application procedures, optimal release and delivery, optimal presentation of the molecule at the target site, minimum side effects, and manufacturability. "Companies trying proof-of-concept with poor formulations raise the risk of a failure," he maintained.

200 now on the market, with orphans gaining 38% of all FDA drug approvals last year. He gave credit to the drugs for contributing greatly to the expansion of biotech. But he noted problems such as companies' tendency to herd together around similar orphan areas and modalities. "People want to do the same thing others have done — to achieve the same success," he said. "But the government has a right to push companies toward diseases with no existing treatments."

He implied that big companies may distort the intent of ODA by using orphan status as only a starting point for a drug's development into wider indications and larger markets over time — as well as high profits from day one, considering the record-setting price tags on the more recent "orphan blockbusters." Indeed, Myers warned years ago that high prices could severely limit rare-disease patients' accessibility to the very drugs designed to treat them.

SAMPLE ANALYSIS

For any nonexpert in the given topic, attending any session was like jumping into a swift and tumbling stream. Every session was but a brief excursion down a single tributary in the grand flow of biotherapeutic discovery, characterization, and production. A good example was the session on early assessment of biological development candidates. Two large companies, one small one, and an academic researcher shared details of their short- and long-term efforts to identify optimum development candidates in the formative stages of preclinical research. (See the sidebar, "Session Sampler.")

As with most sessions, this one closed with a speaker roundtable, further exploring lessons from early candidate selection of small molecules, unique CMC (chemistry, manufacturing, and control) challenges with biomolecules, ways to build in stability, the feasibility of platform approaches, and the question of how early is early enough. Experts in the audience peppered the panel with questions about conjugated antibodies, immune response, PEG (polyethylene glycol) interference, the effects of high concentration on charge interaction, relationship of viscosity to aggregation, and other queries ranging from mystified to skeptical to prescient.

And so went this extraordinary assemblage of sessions packed into the three days of the NBC. (Additional work sessions sandwiched the main conference on the preceding weekend and following day.) There may be many other even more scientifically intensive meetings in this field, but in this one AAPS seems to have hit on a unique formula that puts the expert science in a strategic context, making it accessible to the full range of players in biotherapeutic R&D, manufacturing, and business. Thus, the conference offered both immersion in the stream of technological progress and inspiration at the headwaters of discovery.

Not-For-Profits Fill The R&D Gap For Underserved Diseases

by Wayne Koberstein, contributing editor

Some say there is market dysfunction in drug discovery and development. Large patient populations in third-world countries and patients with rare diseases are left without effective medications or therapies. Economics, regulatory oversight, and stockholder demands chain pharma to the blockbuster. But perhaps the market is working as it should. Desperation impels action. Frustrated parents, patients, and relief organizations have formed advocacy groups to support R&D in diseases where big pharma cannot. They have the advantage of focus, ingenuity, and immediacy that only limited resources and desperation can give. The sense of urgency in the nonprofit-industry business model focuses efforts on translational research and bringing cures to market.

What changes for R&D in this relationship is the goal. Advocacy and relief groups seek products, not profits. Removing the criterion of profitability from compound selection can speed the entry of candidates into research. With their increasing sophistication and financial resources, advocacy groups have the ability to partner with researchers directly to speed the discovery and commercialization of therapies.

THE NONPROFIT IN BIG SCIENCE

Rafick-Pierre Sékaly, Ph.D., co-director and scientific director at VGTI-Florida, says that nonprofits now play an increasing role in drug development, focusing on the early stages of discovery and preclinical development. As an example, he points to the work of large foundations like the Wellcome Trust or the Gates Foundation. They have the resources to put together projects of scale with multiple players and moving parts, and set the guidelines with stringent milestones, timelines, and rules regarding intellectual property. They regularly ask for research proposals to solve specific challenges. The Gates Foundation supports global health projects that can help large populations in underdeveloped nations. One of its main programs is developing treatments for AIDS/HIV, an area of expertise for VGTI.

VGTI has been a player in two international consortia funded by the Gates Foundation. One was aimed at developing novel assays to measure protective immune responses, while the second was focused on developing novel viral vectors as vaccines for HIV. Sékaly says projects that have targets of such importance require multiple institutions that bring different expertise to the table. "You can no longer work alone; the tasks are too many and the scope too big." Sékaly describes this as, "The idea of big science. You work alongside researchers you would have considered competitors 10 years ago." He says, however, that these are the kinds of projects that will make a huge difference to humanity.

ADVOCACY ADDING INCENTIVE TO R&D IN THE THIRD WORLD

At the end of the last century, more than one million people died annually from malaria. Most of these were children under 5 and pregnant women. The medicines used to fight the parasite were losing potency and there were few new drugs in development. It was a huge potential market, but poverty in the endemic areas was so great that there was no incentive to conduct R&D. It was the kind of helpless situation that drives some to action.

Dr. David Reddy, CEO of Medicines for Malaria Ventures (MMV), says, "A handful of individuals representing WHO, World Bank, IFPMA (International Federation of Pharmaceutical Manufacturers & Associations), the United Kingdom, and

Switzerland recognized something had to be done and looked for a way to share risk." The result was MMV, a public-private partnership to support the development of antimalarial drugs and therapies. Reddy says MMV-supported research has brought four new compounds to market, entered more than 65 projects in development, and identified about 2,500 compounds that have activity against the parasite.

Reddy explains that the key was creating incentives for research and development through the Product Development Partnership (PDP). MMV is supported by grants from public and private organizations and gifts and in-kind donations of expertise, personnel, and facilities from researchers and manufacturers. It uses these philanthropic donations to support the R&D of effective and affordable antimalarials, which reduces the organization's development costs to almost a quarter of the industry average.

MMV attracts research through an annual call for proposals. Reddy says, "We look for drug candidates that are truly differentiated and targeted." He explains that being very selective reduces costs, prevents overlapping efforts, and concentrates research on a small group of promising compounds rather than diluting resources over many.

Keeping manufacturing costs low is a high priority. The agreement with pharmaceutical partners is to price the medicines at marginally more than the cost of manufacturing. This keeps the price of medications low enough for underdeveloped countries and patients to afford. "We expect rigor from the manufacturer to reduce costs," says Reddy. "Industry estimates for clinical development of an anti-infective drug are $180 million. For one of our more recent antimalarials, Pyramax, developed with Shin Poong, the figure was $43 million. The numbers speak to the efficacy of the model."

RARE DISEASES — PATIENT ADVOCACY AGGREGATING NUMBERS FOR LEVERAGE

On the other end of the spectrum are parents who have a child with unusual symptoms that no physician seems able to put a name to. But when they do, it's a diagnosis that is as foreign as the name is to say. There are nearly 7,000 rare diseases and fewer than 50% have an advocacy group. Nonprofits play an important role in this area because few pharma companies will invest in development of therapies for such small numbers.

Nicole Boice is organizing the RARE Project, a nonprofit platform to aggregate their numbers. There are roughly 30 million Americans with a rare disease, making it one of the largest patient groups in the United States, but one with a fractured voice. RARE plans to link patients, information, and resources in numbers sufficient to make legislators and the public take notice.

A major objective of that effort is to increase R&D for rare diseases. Boice identifies patient activism and lobbying for legislative and regulatory reform as important steps to speed up the delivery of drugs. Currently she favors reauthorization of PDUFA (Prescription Drug User Fee Act) and passage of new orphan drug legislation, which she feels will increase incentives for R&D in rare diseases. Additionally, Boice says, "We are launching a corporate alliance with biotech and pharma to move the needle on reimbursement and physician education on rare disease."

A problem with rare diseases research is that the patients are rare as well. This poses a problem for researchers when they try to register enough patients to show significance in clinical trials. RARE has contracted with Patients Like Me to use its technology to start an open registry for rare diseases. This gives patients an opportunity to share their medical information with professionals. For researchers, the registry provides a source for recruitment and information about patients with the disease.

RESEARCH FINDS A HOME AND BACKWARD ENGINEERING

Success at promoting research requires skill. Paul and Debra Miller founded CureDuchenne when their 5-year-old son was diagnosed with Duchenne muscular dystrophy. She says, "Starting a 501(c) is easy and relatively inexpensive. Getting results is not." She says an advantage she and her husband had was the business background to organize and push activities forward. Their goal was to find a cure for Duchenne in their son's lifetime and put themselves out of business in 10 years.

Usually nonprofits find research to support, but occasionally the research finds the nonprofit. Shortly after setting up office, Debra Miller was approached by Prosensa, a Dutch company that had promising research to moderate the effects of the disease through exon skipping. She committed to supporting their research with $1.3 million, and worked arrangements to get the money. Prosensa conducted the research, and seven years later Prosensa received a commitment of up to a $650 million investment for their Duchenne programs.

Since then, CureDuchenne has supported seven projects that are now in human trials. They are the result of a science advisory board that has taken a backward engineering view of the disease. Miller and the advisory board imagine what a cure would look like. Then they work backward and imagine what research they would need to get there. Reviewing the stack of research proposals they receive, the board attempts to find a project that fits their view of the cure. "If we don't find one," Miller says, "We set out to create the project. We will put scientists together who have similar research. Other times we will push scientists along even if they don't think they're ready."

FOCUS ON TRANSLATIONAL RESEARCH AND REIMBURSEMENT

Parents often become the force behind nonprofits searching for cures. They provide family support and information and back basic research. What they don't often do is look for more immediate results through translational research. FasterCures, a nonprofit working toward accelerated access to new therapies, calls this the valley of death, the area between promising basic research and commercialization and the space where good ideas die because few organizations will take the risk to back them.

This was the case for Beth Anne Baber when her son was diagnosed with a neuroblastoma, the most common form of solid tumors in children. As a bench researcher in cancer herself, she was shocked to find that the current standard of care for pediatric cancer

was massive doses of drugs designed for adults years ago. She found many nonprofits providing family support or backing basic research, but fewer groups were going after actual pediatric therapies. So Baber founded the Nicholas Conor Institute (TNCI) to find and support translational research in childhood cancers.

She located companies developing promising products in diagnostics and theranostics that were looking for backing. Their partnerships faced an unexpected obstacle. They found childhood cancers are somewhat in-between categories. They are clearly rare diseases and just as clearly cancer. However, when Baber sought support from larger pharmaceutical companies that work with rare diseases, she was told they didn't work with cancer. When she went to cancer-oriented pharma companies, she was told they didn't work with rare diseases.

This posed a problem because it would be difficult to find backing, sell, and get reimbursement for diagnostics and therapeutics designed for children. The institute decided to expand diagnostic panels to be applicable to adult patient populations as well. This made both scientific and economic sense because there were a number of mutual targets for both adult and pediatric oncology.

Baber points out it's equally important to work with insurance companies to get coverage for the diagnostic panel. The partnership has to demonstrate the value equation of the test to payors. She says this is not something that can wait until the test has been validated and ready for clinical use. Without coverage, they may not be able to have the test ordered by the treating oncologists.

To fund the translational development research, Baber uses what she calls "hybrid" venture philanthropy. It involves forming a consortium of charities, businesses, and other interested entities that pool funding for a project. The result is shared rights to the IP and licensing, and reduces risks since the investment is split among several members of the consortium. The added benefit for investors is being able to claim they support the development of an actual product that is in clinical use.

NEW OPPORTUNITIES FOR INNOVATION

Probably no one wakes up and says, "I think I'll start a foundation today." Patient advocacy and relief organizations are the children of tragedy and frustration. In the information age, their frustration has formed communities that seek to reform regulatory bottlenecks and promote drug research and development. Their focus on solutions rather than profits has opened opportunities for researchers and biotechs to find funding to cure rare diseases and epidemics. This partnership is filling the void for neglected diseases and is an opportunity to innovate.

Direct To Data — An Electronic Solution To Patient Diaries

By Wayne Koberstein, contributing editor

Regulators have two main requirements for clinical-trials data: accuracy and data integrity from patient to investigator to regulatory review. For patient-reported outcome (PRO) information, paper diaries have long been the standard instruments for recording responses to treatment by the patients themselves.

But following a study published in the *British Medical Journal* (May 18, 2002), there has been general recognition that paper is a poor protector against patient noncompliance with diary keeping — timely and accurate entry of meaningful information — and that electronic alternatives (ePRO) can improve data accuracy and integrity by comparison. As with any technological solution in drug development, however, the use of so-called eDiaries or ePRO instruments requires especially careful design and engineering, integration with trial protocols and endpoints, and security measures.

FROM PARKING LOT TO ON THE SPOT

The 2002 study focused on patient compliance with the requirements of diary-keeping, comparing the accuracy, timeliness, and completeness of paper and electronic diary entries. Researchers traditionally used paper and pencil, but for decades researchers have grown ever more aware that patients often incorrectly entered information, and they have become more uneasy about the lack of means to verify compliance. When the key measures are patient responses to treatment, such uncertainty becomes an even more acute problem.

The study's lead author was Dr. Arthur Stone, professor at Stony Brook University and Chairman of the Scientific, Clinical, and Regulatory Advisory Panel at invivodata (now part of ERT). "One of the major issues with paper and pencil diaries had been known for a long time but hadn't really been quantified before our 2002 paper," Stone says. "Just how often were people doing it the way they were supposed to do it? Anecdotally, researchers knew people were not highly compliant; there was already a term for it: parking lot compliance."

At some point, someone on a research team looked out the window and witnessed a patient sitting in a parked car furiously catching up on neglected diary entries before turning it in. In many cases, researchers found that a patient would fill out an entire diary in that way.

Stone's study used a hybrid of electronic and paper technology to monitor diary entries. One group of patients entered its reports in a paper binder that, unbeknownst to them, was outfitted with a computer chip and a light sensor that recorded when the binder was opened and for how long.

Most patients (79%) routinely fudged their inputs, reporting entries they had not actually made. In comparison, the study gave another patient group a fully electronic diary that prompted, accepted, and confirmed all entries at the required time intervals. Compliance — reported entries matching actual ones — rose to almost 100%.

The study's revelations came at about the same time clinical research was turning to ecological momentary assessment (EMA), also called experience sampling method (ESM), based on the assumption that proper timing of

patient-reported treatment responses elicits the most accurate data. Paper diaries offered no way to verify actual compliance in time. So, clinical researchers began to adopt ePRO instruments over paper as the standard.

Meanwhile, the FDA developed the PRO Guidance, issued as final in 2009, that avoids endorsing any technology but arguably makes ePRO an obvious choice to satisfy the agency's criteria for patient-recorded outcomes data. The guidance strongly recommends short-time intervals between reports so that patients rely less on memory, and it calls for verification that patients have entered their reports at the proper times.

The agency does state some reservations about ePRO instruments, however — mainly related to security in how researchers "create, modify, maintain, archive, retrieve, or transmit clinical data to the FDA," as directed in the final rule 21 CFR part 11.7,8. The normal restrictions apply: Lead investigators, not the sponsors or CROs, should have sole access to the raw ePRO data on the developer side, yet FDA investigators must be able to inspect, verify, and copy the data at any study site. Security measures must be sufficient to ensure that data is not altered, prematurely unblinded, or otherwise compromised by bias, data loss, high error rates, or misdirection.

PRO ACHIEVEMENTS

Since the preliminary draft PRO Guidance issued in 2006, the first drug to claim FDA approval of labeling that includes ePRO symptom data was Incyte's Jakafi (ruxolitinib) for myelofibrosis. One of the two pivotal studies used eDiaries to collect patient reports on six symptoms: night sweats, itching, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone or muscle pain. Based on considerable back-and-forth with the FDA, the trial design used the PRO data to measure a "total symptom score" as the secondary endpoint, with a physical measure (spleen-volume reduction) as the primary endpoint.

Incyte CEO Paul Friedman, speaking at the 2012 JP Morgan Healthcare Conference, credited the symptom data for clinching Jakafi's FDA approval. "Looking at the change in total symptom score for each individual patient at week 24, most patients receiving Jakafi experience reductions in symptom burden, while the majority of patients receiving no treatment continued to see their symptoms worsen."

A more recent ePRO-driven approval is for Subsys, a sublingual spray form of fentanyl from specialty pharmaceutical company Insys Therapeutics. In January 2012, the FDA approved Subsys for breakthrough cancer pain. The Phase 3 efficacy trial used eDiaries to collect patient-reported response scores at

COST & COMPLEXITY

Small companies doing small studies have pioneered eDiary technology, despite the general expectation that such companies would be the last to afford it. Most reports of the Jakafi approval, for example, emphasized little Incyte's brave tradeoff of expense for the advantages patient-reported outcomes brought to the table in strengthening the approved labeling.

Even on paper, PRO (patient-reported outcomes) involve more trouble and expense than biological data collection. The "e" for electronic in ePRO typically adds the cost of equipment, software development through testing and validation, vendor services, patient and personnel training, and data security.

Once a company decides it needs PRO, however, the equation of whether or not to use ePRO or paper is simple: Given available funds and assuming a high value of symptomatic labeling for the product in development, researchers need to balance ePRO's added cost against its relative efficiency and verifiability. Despite the high cost of clinical trials in general, or maybe because of them, buying the extra confidence in patient compliance, data accuracy, and regulatory conformance may be money well-spent.

Some evidence exists that, despite higher initial costs, eDiaries save money in execution through the reduced cost of data cleaning and the efficiencies of well-designed ePRO instruments. Obviously, having PRO data with the high compliance factor of ePRO is much more efficient than finding and correcting large-scale corruption from noncompliant paper reports. Researchers at the Department of Psychosomatic Medicine Charite, Humbolt University, Berlin found that, when compared with paper methods, ePRO methods reduced trial preparation time by 67% and data management time by 78% (Hair 2006). In a Phase 3 study of a treatment for overactive bladder in which the primary efficacy endpoint included a count of the patients' daily number of micturitions, use of eDiaries reduced error variance by 33.5%. The sponsor, Sepracor, translated the 33% drop in error variance into a 50% decrease in the number of patients who would have been needed to detect the drug's effects.

A further element in the cost equation is the trial's complexity and number of endpoints. Subsys' Phase 3 trial handled multiple endpoints in time and symptomatic variables, though it measured only one symptom: pain. Jakafi's pivotal study was even more complex with its multiple endpoints and symptom measurement. But again, ePRO appears not only more efficient, but more rewarding than paper reports.

In complex studies, eDiaries have some advantages over paper diaries, including the ablity to make "smart" queries that route patients to different question sets depending on their answers. Another option with eDiaries is to include cognitive tests, such as having the patient track something around on the screen. Such actions are integrated into patients' everyday experience, again encouraging compliance and reducing overall costs.

"There has also been considerable progress in integrating eDiaries with all of the trial data, including biological data." Dr. Arthur Stone, Stony Brook University

timed intervals tied to corresponding endpoints. Unlike the Jakafi trial, the Subsys trial used the ePRO tool specifically for the collection of its primary efficacy data.

"We were looking to prove early efficacy," says Neha Parikh, senior director, clinical operations, at Insys. "The most valuable thing to us in a clinical trial is the data and then being able to use the data we collect. We needed a reliable and validated tool to measure patient response at specific time points. We considered paper diaries, but electronic collection of patient-reported outcomes fit our needs, and the FDA was moving in the same direction."

The primary endpoint for Subsys was the summed pain-intensity difference at 30 minutes after dosing, with secondary endpoints of 5, 10, 15, 45, and 60 minutes. Patients rated their pain intensity on a visual analog scale of 0 to 100. In addition to changes in pain intensity after dosing, patients rated their level of pain relief at time points of 5, 10, 15, 30, 45, and 60 minutes and their global satisfaction with the study's medication at 30 and 60 minutes postdose. Both pain relief and global satisfaction were measured on five-point categorical scales.

The eDiary instrument had the added effect of regulating and recording treatment compliance. Patients initiated each dose when they had breakthrough pain and were then prompted by the eDiary to do their entries at the given time points. Their records were correlated with the measured-dose sublingual spray.

"Patients were trained, once they were feeling a breakthrough pain episode, to enter their pain intensity into the diary and then dose with the medication. Five minutes later, it would prompt them for their pain intensity again, then at ten minutes, and so on, for sixty minutes," says Parikh. Every patient in the study went through an open-label period where they were titrated to an effective dose. Once they achieved their successful dose of the study's medication, patients entered the double-blind period of the study. Patients utilized the eDiary in both periods of the study.

Parikh says Insys began designing the study in 2007, in a "collaborative approach" with its supplier. Starting with the time-based endpoints, she says it was then a matter of drawing on the supplier's experience with similar trials to match the eDiary configuration for the data-collection needs. "We worked hand-in-hand with the development team to design the eDiary for the study."

ePRO EXPANSION

Although eDiaries most often come into use in Phase 3 trials, the instruments are also employed in earlier phases of clinical development and prior to that, starting with patient selection as well. A typical trial might use eDiaries during the baseline area of the trial, prior to the administration of placebo or drug or multiple drugs, and then at other points later in the trial to help define efficacy outcomes.

"There has also been considerable progress in integrating eDiaries with all of the trial data, including biological data," says Stone.

GLOBAL PRO

Beyond measures by the FDA to encourage patient-reported outcomes (PRO) measures in clinical trials, the agency's own criteria for PRO data and an electronic patient data consortium in Europe are pushing investigators and sponsors toward greater use of patient eDiaries, or ePRO, in clinical development. The FDA's PRO Guidance sets the standards for patient data including appropriate security of ePRO data. The Critical Path Institute (C-Path), in cooperation with the FDA and the medical products industry, has formed the Patient-Reported Outcome (PRO) Consortium "for the purpose of developing, evaluating, and qualifying PRO instruments with the FDA for use in clinical trials designed to evaluate the safety and efficacy of medical products." Meanwhile, Europe's Clinical Data Interchange Standards Consortium (CDISC, www.cdisc.org) has created SHARE, a global, accessible electronic library to enable "precise and standardized data element definitions that can be used in applications and studies to improve biomedical research and its link with healthcare, based on the principles behind computable semantic interoperability, i.e. the ability for computer systems to be able to exchange information while retaining the meaning of this information." SHARE subscribes to a common information model, the Biomedical Research Integrated Domain Group (BRIDG) and is a key catalyst in encouraging integration of all patient-data types, from the clinical to the practice setting. Among the aims of the CDISC, SHARE, and other initiatives is the general adoption of eDiary technology to collect PRO data in clinical research.

"As eDiary data is collected, it can be integrated into a database that also contains data from other aspects of the trial, including all kinds of biological data, which can be sent back to clinicians and researchers."

The same qualities even out the expense calculations of ePRO versus paper PRO, says Stone. "eDiary data can be integrated and analyzed very quickly because, in particular applications, the data is sent to central servers, often immediately. And one of the big advantages of using eDiaries is that you don't have the extra step of translating from paper diaries into an electronic form which is very expensive, in addition to other problems with paper, such as incorrectly completed questionnaires."

Besides applying ePRO at more stages of clinical development, researchers are finding new applications unique to the technology. Some portable eDiary units are fitted with monitors for cardiac function or glucose level, for example, and may someday make DNA or other biomarker scans. Connectivity might be via the internet, Bluetooth, smartphone, or Wi-Fi options.

Most eDiaries are dedicated units — specially configured smartphones powered with custom software. Other systems use laptops or computer chips in custom-built units. But the vision of eDiaries with "apps" for monitoring patients' bodies begs the question of whether ePRO will become just an extension of smartphones, which already offer features such as heart-rate monitoring. Stone doubts such a future.

> The use of so-called eDiaries or ePRO instruments requires especially careful design and engineering, integration with trial protocols and endpoints, and security measures.

"A lot of folks think that creating an eDiary is a straightforward scheme. But years of research and practice have suggested that this is not just a simple technology issue. There is a host of human factors. It's a matter of understanding how people use the device, where they foul up with the device, and so on. Over the years, suppliers have made a tremendous effort at making these devices compatible with people's lifestyles. That's what yields high compliance."

ePRO ADVANTAGES

Both Stone and Parikh echo other researchers in their observation that patients find ePRO anything but a burden. They say patients generally have a positive experience using eDiaries, preferring them over other modes of data collection — an intangible but logically important benefit of the "direct-to-data" PRO approach, translating to its demonstrated high rates of patient compliance.

Parikh also stresses the superior effects of ePRO in obtaining critical data that flows more efficiently through the regulatory process: "The electronic database allowed for a hassle-free transfer of data to the FDA."

Perhaps the icing on the cake for Parikh and the Subsys investigators is the ability to access and integrate PRO data in real time. Direct-to-data in that sense means untold savings in time, data cleanup, and validation on a daily basis during the trial. Perhaps that explains why, nearly every time a drug is approved based on ePRO, its sponsor gives a large share of the credit to the electronic solution.

Pharmaceutical Supply Chain: The Next Green Frontier

By Gary Hutchinson

The life sciences industry has been relatively slow to put the principles of environmental citizenship into action. In examining the progression of environmental stewardship within our industry, it's evident the greatest momentum has come from the manufacturing side. This is not surprising, since manufacturing offers the most control over infrastructure, significant economies of scale, and immediate improvement opportunities. Companies intent on reducing water consumption and improving waste stream management have seen small changes to manufacturing processes yield big results.

GOLDEN OPPORTUNITIES IN COLD CHAIN SUSTAINABILITY

Despite steady progress on the manufacturing side, cold chain sustainability efforts are still in their infancy. In lieu of real advancements, we've witnessed a reliance on overdesigned thermal packaging for temperature-sensitive products. The reasons are twofold. First, there are widespread misperceptions and misunderstandings about shipping environments and thermal control requirements of the transported products. And second, strong process controls are not always in place to indicate if temperature excursions may have potentially affected the quality of temperature-sensitive products.

Overdesigned packaging is inconsistent with a comprehensive cold chain sustainability effort. It's expensive to manufacture, the additional weight adds to the shipping costs, and when its job is done, the material often returns to the environment as waste.

Biopharmaceutical manufacturers interested in improving their cold chain sustainability should consider an integrated cold chain management system. This approach includes appropriate packaging, deferred shipping when possible, and proper temperature monitoring and controls, all of which can lower the overall carbon footprint and improve multichannel environmental efforts. Innovative packaging companies are starting to identify ways they can reduce their environmental footprint and support these manufacturers as they strive to achieve sustainability goals.

ASSESSING MANY SHADES OF GREEN

A growing number of businesses (mine included) conduct environmental sustainability assessments to help companies evaluate their existing practices and design plans for improvement. Most use ISO 14000, a core set of standards used by organizations for designing and implementing an effective environmental management system. A complementary set of standards, ReCiPe 2008, provides 18 mathematical models to convert an inventory analysis into an impact assessment and is considered the most comprehensive and rigorous open-source technique to date.

The assessments themselves and how they are used are evolving, becoming more meaningful to downstream decision makers who place a premium on environmental stewardship and how products and services can help them realize sustainability goals. Here is one example of how that works. Temptime Corporation recently commissioned a full product life cycle impact analysis of its cumulative heat-and-freeze monitoring devices, which are mainly used for vaccines and biologics. While most impact assessments use only carbon footprint as a metric for environmental impact, this assessment was more comprehensive and went well beyond the boundaries of carbon footprint/CO2 generation. It measured inputs and outputs relative to human health, ecosystems, resources, water depletion, climate change, and cumulative energy demand.

The assessment included comprehensive sustainability profiles for two of the company's major products and comparative analyses with other marketed monitoring technologies. The combination makes a powerful case to a growing audience of decision makers now placing a premium on environmentally sustainable business practices, services, and products. And the assessment highlights an area of opportunity for companies employing greener cold chain technologies in their business operations.

Minimizing the environmental impact of the cold chain begins with a deeper understanding of the shipping environment and appropriate packaging, applying an international standard to assess environmental impact to understand areas of opportunity and developing a plan to drive incremental improvement.

About the Author

Gary Hutchinson is president of Modality Solutions, LLC, which provides engineering/controlled environment logistics for biotechnology and other high-risk, highly regulated products.

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PROFILE INFORMATION

Nice Insight survey respondents comprise people who work at the following types of companies:

- Biotech 27%
- Emerging Biotech 8%
- Specialty Pharma 16%
- Big Pharma 29%
- Emerging, Niche & Start-Up 20%

niceinsight

OUTSOURCING TRENDS

Attributes of Outsourcing Partners Ranked in Order of Importance

QUALITY

When selecting partners, survey respondents ranked Quality as their number one priority.

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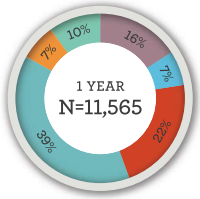
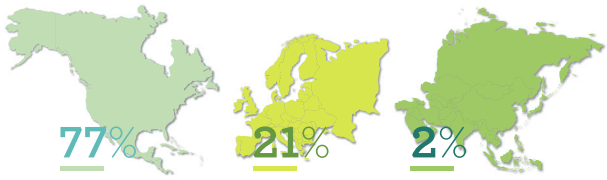
Within Pharmaceuticals and Biotechnology, survey respondents work in the following departments:

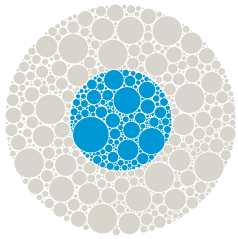


- Manufacturing 16%
- Regulatory 7%
- Operations 22%
- R&D 39%
- Purchasing/Procurement 7%
- Quality (QA/QC) 10%

Respondents' Business Location By Region



MARKETING COMMUNICATION UPDATES

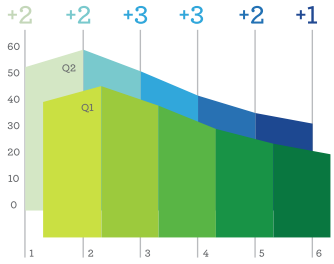


109 different companies had marcom changes

- 36% Marcom changes
- 64% No marcom changes

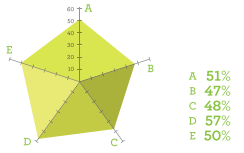
Phase Of Development When Outsourcing Partners Are Engaged
% engaging partners

		Q1 vs Q2	
1	Discovery	49%	51%
2	Pre-Clinical	53%	55%
3	Phase I	47%	50%
4	Phase II	39%	42%
5	Phase III	33%	35%
6	Phase IV / Post Launch	30%	31%



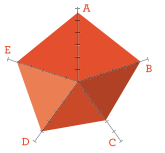
Q2 Breakdown By Sponsor
A: Big Pharma B: Specialty Pharma
C: Emerging Pharma D: Biotech
E: Emerging Biotech

Overall DISCOVERY 51%



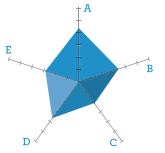
A 51%
B 47%
C 48%
D 57%
E 50%

Overall PHASE I 50%



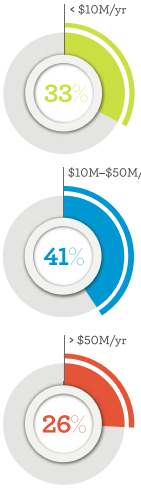
A 57%
B 52%
C 39%
D 50%
E 51%

Overall PHASE III 35%



A 44%
B 34%
C 21%
D 37%
E 29%

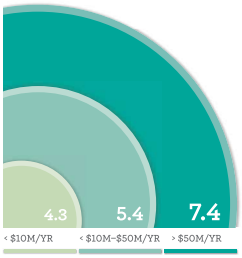
Annual Outsourcing Budgets



Average Number of Services Outsourced by Expenditure

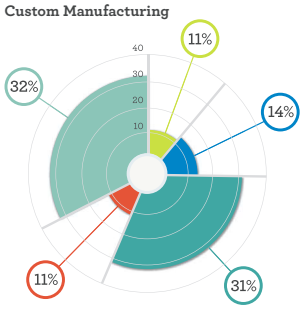
5.3 Q2 Overall

As outsourcing budget size increases, so do the number of different services outsourced.



SERVICE OUTSOURCING TRENDS

Custom Manufacturing



23% of survey respondents reported their company would outsource Custom Manufacturing services in 2012

- Big Pharma 11%
- Specialty Pharma 14%
- Emerging, Niche & Start-Up 31%
- Biotech 11%
- Emerging Biotech 32%

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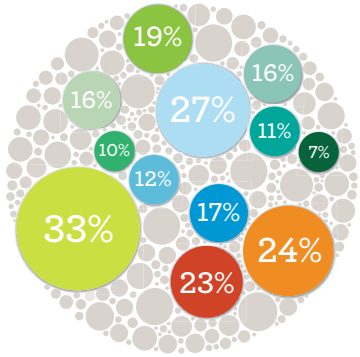
% of Respondents Who Plan to Attend the Following Industry Events



- AAPS 33%
- Bio International 27%
- Bio Europe 24%
- Contract Pharma 23%
- BPI 19%
- ChemOutsourcing 17%
- DCAT 16%
- DIA 16%
- CRS 12%
- CPhI Europe 11%
- Informex 10%
- Interphex 7%

Q2 Outsourcing Trends

19% of survey respondents reported their company will outsource Packaging Projects in 2012.

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Why It's Time To Reassess Your U.S. Patent Strategies

By Jeffery Duncan

Disputes over patent rights have long been commonplace in the life sciences sector, where research and intellectual property are the key drivers of revenue. But with the America Invents Act (AIA) signed into law by President Obama on September 16, 2011, life sciences companies now need to reassess and adapt their U.S. patent strategies. The rules are dramatically changing, particularly with regard to the AIA's provisions concerning novelty and prior art.

Most significantly, the AIA's new Section 102 represents a radical departure from the United States' unique first-to-invent patent system in adopting a first-inventor-to-file approach similar to that found elsewhere in the world. Rather than granting patent rights to the first proven creator of an invention, the AIA grants patent rights to the first inventor to file a valid patent application. Companies will no longer need to expend considerable time and resources to support first-to-invent claims but will need to focus on creating the most efficient patent application process.

This change is effected by the amended Section 102 under the AIA, which explains the new definition of prior art. Section 102(a) defines the two categories of prior art — prior disclosures and prior-filed patent applications; Section 102(b) provides exceptions to the two categories defined in (a); Section 102(c) provides the status of "common ownership" for the products of joint research agreements; and Section 102(d) defines when a patent or published application is effective as prior art.

Since the new provisions of Section 102 do not take effect for applications filed before March 16, 2013, companies have time to file applications under the current scheme before the AIA takes effect. Nevertheless, forward-looking organizations should begin now to prepare for the new system.

WHAT TO KNOW ABOUT THE PREFILING DISCLOSURE

Three major changes emerge in the new Section 102(a)(1), which defines prior art as anything that was "patented, described in a printed publication, or in public use, on sale, or otherwise available to the public" before the current applicant submitted a patent filing. Again, the *prior* in prior disclosure refers to a public disclosure prior to the effective filing date of the application, not to the date of invention — thus, the first-to-file system.

In a second major change from current law, the new Section 102(a)(1) adds "or otherwise available to the public" as a catch-all description. Naturally, no one knows exactly what that means right now. The intent was to leave the AIA sufficiently flexible to cover future information-dissemination technologies.

In a third major change, the geography of certain types of prior art has been significantly broadened. Under the current law, although items published or patented anywhere in the world counted as prior art, activities, such as those that would place the invention "on-sale" or "in public use" counted as prior art only if they occurred in the U.S. Under the AIA, any disclosure of the invention occurring anywhere in the world will be considered prior art unless it qualifies as an exception.

EXCEPTIONS TO PREFILING DISCLOSURE

The new Section 102(b)(1) allows two exceptions to the first category of prior art. First, a disclosure made within one year before a patent application is filed will not be prior art if "the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor." This one-year "personal grace period" means that, if the inventor waits more than a year after a public disclosure before filing the patent application, his own disclosure will be prior art against him.

Most critical, this exception does not apply to disclosures by anyone who did not gain the information from the applicant, regardless of whether the invention occurred before the public disclosure. To be clear, there will be no more "swearing behind" third-party references by showing an earlier invention date.

For the second exception, if the inventor(s) or someone who obtained the invention from the inventor(s) makes a public disclosure within a year of filing and an unrelated party makes a subsequent disclosure, the disclosure by the unrelated party will not be considered prior art. The key consideration is that the first public disclosure must have occurred one year or less before the effective filing date. Since the disclosure by the inventor is required to be public, a discreet "on sale" activity by the inventor might not qualify to invoke this exception.

PRIOR PATENT APPLICATIONS

The second category of prior art is defined by Section 102(a)(2), namely, prior-filed patent applications. A published or issued patent application constitutes prior art if it was effectively filed before the effective filing date of a second application and names another inventor. Even if both applications name one or more of the same inventors, the prior application is prior art to the second application unless the first and the second applications name exactly all of the same inventors.

EXCEPTIONS TO PRIOR PATENT APPLICATIONS

This category of prior-filed applications has three exceptions. In the first, or "derivation" exception, a prior application will not constitute prior art against a second application if the relevant subject matter disclosed in the first application was obtained from the inventor(s) or someone who obtained the subject matter from the inventor. If the two applications claim the same subject matter, the conflict will be resolved in a newly created "derivation proceeding," the details of which are beyond the scope of this article.

Under the second exception, if the prior application was filed after a public disclosure by the inventor(s) of the second application, the prior application will not constitute prior art as long as the inventor effectively filed the second application within a year of making the public disclosure. If the second patent applicant made a public disclosure more than a year before the first application, that disclosure would by itself constitute prior art to both applications.

Third, if the prior and subsequent applications were owned by or subject to an obligation of ownership to the same person, then the prior application is not prior art. Thus, if a co-worker files an application before the second effective filing date for the claimed invention, the subject matter disclosed in the prior application will not be prior art against the second application as long as both applications are owned, or subject to an obligation to assign, by the time the second application is filed. However, if the prior application was published or issued before the effective filing date of the second application, the published or issued application would still be prior art.

With the America Invents Act (AIA) signed into law by President Obama on September 16, 2011, life sciences companies now need to reassess and adapt their U.S. patent strategies.

Again, the critical date in these exceptions is the effective patent filing date of the claimed invention, not the date on which the invention was conceived. Unless the patent applicant can show (1) prior public disclosure by the inventors, (2) derivation from the inventors, or (3) common ownership, novelty will be based solely on the date on which the application is filed.

In view of these major changes, companies should incorporate the following four actions into their patenting strategy. First, because no one can know whether proving prior invention will be important in the future and because that first-to-invent prior-

ity disappears on March 16, 2013, companies should do all they can to file their patent applications before that date. Due haste is especially important for companies in the life sciences sector, where it is common for competing companies to be working on similar research projects and racing to bring them to market.

Second, life sciences companies should anticipate the fast-paced filing process under the AIA. Forward-looking companies are working now to streamline their invention disclosure and application filing processes, since a delay as short as one day could cost a patent under the AIA. Companies should prepare a foolproof tracking and recording system for all prefiling disclosures by the inventor and anyone in contact with the inventor, as these disclosures may affect the patentability and revenue potential of the invention. All details should be reliably preserved and accessible for possible use during patent prosecution or litigation years later.

Third, because common ownership of a prior-filed application will keep it from being prior art against a subsequent one, it is more important than ever for companies to create legal agreements requiring all employees and contractors to assign rights to all inventions. If a company works with another entity to jointly research and develop products, as is increasingly common in the life sciences, it is critical to memorialize that cooperation in a joint research agreement. Under the new Section 102(c) of the AIA, if a written joint research agreement is prepared at least by the time a second application is filed, a prior application will be treated as co-owned, and not prior art to the second.

The America Invents Act spells big changes in U.S. patent law. Those life science companies that depend on protecting their research and their intellectual property for the success of their business, should study it and adapt their patenting strategies accordingly — or risk losing valuable patent rights.

About the Author

Jeffery Duncan is a former shareholder on and chair of the Biotechnology & Pharmaceuticals Practice Group at Brinks Hofer Gilson & Lione, one of the largest IP law firms in the United States. He is now vice president, intellectual property, at Elevance Renewable Sciences Inc., and a patent law instructor at The John Marshall Law School in Chicago.

The Slow Progression Of Pharma Regulatory Harmonization

By Cliff Mintz, Ph.D., contributing editor

The regulatory environment for the approval and marketing authorization of pharmaceutical products has grown increasingly complex in recent years. The various worldwide regulatory agencies that oversee these products must ensure they are safe, efficacious, and manufactured according to prescribed quality standards. However, the regulations guiding the approval of pharmaceutical products in various regions of the world have evolved independently of one another. Consequently, there is an enormous amount of diversity in the regulations, laws, and procedures for registering new pharmaceutical products.

These differences, coupled with increasing globalization of the pharmaceutical industry and new opportunities in rapidly emerging markets in Asia, Latin America, the Middle East, and Africa, have renewed the call from pharmaceutical companies to standardize or "harmonize" the regulations and requirements for marketing authorization of pharmaceutical products throughout the world. "The world has gotten smaller, and the need for new medicines is growing," said Mukesh Kumar, Ph.D., senior director of regulatory affairs and quality assurance for Amarex Clinical Research. "It makes sense to develop a set of common standards across developed and developing markets," he added.

Proponents of harmonization contend that it helps to: 1) control research and development costs and minimize the use of animal testing without compromising safety and effectiveness, 2) prevent duplication of human clinical trials, 3) reduce drug development times and ensure economical use of resources, and 4) streamline the regulatory assessment process for new drug applications, thereby creating a transparent regulatory process that does not delay or hinder drug development and improves global access to new medicines.

Kevin Moore, Ph.D., senior scientific liaison for the United States Pharmacopoeia (USP), offered that "Harmonization primarily seeks to improve the quality of medicines and to preserve resources by reducing the amount of redundant testing required as manufacturers are increasingly multinational." On the other hand, Tim Sandle, Ph.D., head of microbiology at United Kingdom-based, Bio Products Laboratory (BPL), suggested that the ultimate goals of harmonization vary among individual stakeholders. He said, "Politicians and businesspersons will see economic advantages, whereas scientists (like me) and regulators will see harmonization as a means by which quality, safety, and efficacy can be built into tests and processes to create international regulatory standards." Nevertheless, there is general agreement that harmonization will benefit all stakeholders ranging from drug manufacturers to regulators and, most importantly, to patients who will ultimately use the drugs.

While much progress has been made toward harmonizing pharmaceutical regulations over the past 20 years, most of it has taken place in developed markets that include the United States, Europe, and Japan. However, over the last five years or so, regulators from emerging markets have begun to recognize the benefits of harmonization and have taken a more active role in its implementation. Amarex's Kumar agrees that much progress has been made, but there is still a lot to be accomplished in harmonizing pharmaceutical regulations, especially in emerging markets.

HARMONIZATION IN DEVELOPED MARKETS

The International Conference on Harmonization of Technical Requirements for Human Use (ICH) is the organization that is largely responsible for most of the harmonization that has taken place in developed markets. ICH members include the FDA; the Pharmaceutical Research Manufacturers of America (PhRMA);

the Japanese Ministry of Health, Labor, and Welfare (JMHLW); the Japan Pharmaceutical Manufacturers Association (JPMA); the European Medicines Agency (EMA), and the European Federation of Pharmaceutical Industry Associations (EFPIA). Other organizations, including WHO, USP's Pharmacopoeial Discussion Group (PDG), the Pan American Network on Drug Regulatory Harmonization (PANDRH), and the International Pharmaceutical Excipient Council (IPEC), have also contributed to the success of the harmonization effort in developed nations.

Over the past two decades, ICH has issued more than 50 guidelines for technical requirements associated with all aspects of drug development (nonclinical, clinical, and quality), an electronic dictionary of medical terms, and — its most noticeable contribution — the common technical document (CTD), a harmonized electronic submission platform for marketing authorization, recognized by most regulatory agencies around the world. There is universal consensus among drug manufacturers and regulators that the CTD has helped to expedite the drug review and approval process and has also made the exchange of information among drug regulatory authorities much quicker and easier.

Touting the successes of the CTD and other ICH initiatives, Betty Kuhnert, Ph.D., executive director of training services at PharmaNet Development Group, observed, "Gone are the days when you had to load hundreds of volumes of paper documents on a truck for a submission to a given country." Also gone are most of the clinical studies done for one specific country. Instead, global clinical trials and bridging studies allow extrapolation of foreign clinical data to new regions. However, it is important to note that the ICH's guidelines are recommendations and not compulsory. In other words, while ICH guidelines exist, there is no penalty for not adhering to them. Nevertheless, some regulatory agencies (e.g. EMA), have formally adopted several ICH guidelines, while others have been officially integrated into EU legislation.

THE EVOLUTION OF THE REGULATORY HARMONIZATION INSTITUTE

ICH's successes in the U.S., European, and Japanese markets triggered an international interest in pharmaceutical harmonization that culminated in several regional harmonization initiatives (RHIs) in non-ICH countries. These include the Association of Southeast Asian Nations (ASEAN), Asia-Pacific Economic Cooperation (APEC), the Gulf Cooperation Council (GCC), the Southern African Development Community (SADC), and the Pan American Health Organization (PAHO).

Over the years, ICH and these RHIs have worked closely with one another (via ICH's Global Cooperation Group) and, more recently, in 2007 formed a joint working group with the goals of 1) reducing country and regional differences in technical requirements that impact the availability and cost of new medicines, 2) promoting the international movement of pharmaceuticals that are safe, effective, and of high quality, and 3) promoting the conduct of human clinical trials and data collection that meet international standards.

Yet, despite these efforts, in 2012, several industry trade organizations and pharmaceutical companies, including BIO, the Generic Pharmaceutical Association (GPhA), Astra Zeneca, and Bausch and Lomb, formed the not-for-profit Regulatory Harmonization Institute (RHI). Dean Erhardt, principal of D2 Pharma Consulting, LLC and RHI's President, said that the institute was created because global harmonization efforts to date have failed to include significant and meaningful input from nonregulators, do not provide an appropriate balance between regulators and business, and do not adequately represent the interests of emerging nations.

RHI, a membership only organization, intends to better represent the regulatory interests of emerging nations through educational and training initiatives that include whitepapers, seminars, workshops, and other activities. Interestingly, however, RHI's membership-only requirements suggest that its education outreach activities will be fee-based. Therefore, the institute's ability to have a broad impact on global and regional harmonization efforts (especially in emerging nations) may be somewhat limited.

THE CHALLENGES OF HARMONIZATION

While drug manufacturers and regulators agree in principle that harmonization makes sense, "It is very difficult to implement across different markets based on historical, political, and economic issues," said Amarex's Kumar. Likewise, USP's Moore suggested that full regulatory harmonization will be extremely difficult or impossible because most countries have differing regulatory and/or legal requirements that are rooted in historical practices and precedent. Finally, RHI's Erhardt added that while harmonization offers obvious benefits to the pharmaceutical industry, drug makers have largely been excluded from the conversation. "Unless there is more industry involvement, the success of harmonization initiatives, particularly those in emerging markets, will likely be extremely limited," he said.

The ongoing globalization of the pharmaceutical industry highlights the need for a new strategic approach to harmonize technical and regulatory standards for drug approvals and marketing authorization. Harmonization (both global and regional) will undoubtedly help to minimize duplication, better control development time and costs, and, most importantly, create a more transparent regulatory system that will ultimately allow greater patient access to medicines.

The successes of ICH and other organizations committed to harmonization suggest that it is possible both regionally and globally. However, to sustain the harmonization movement's momentum more industry involvement will be necessary. Because regulatory harmonization is beneficial to both pharmaceutical companies and consumers, it is likely that more industry representatives will join regulators and government officials at future harmonization talks.

International Incentives: Are They All They're Cracked Up To Be?

By Gail Dutton, contributing editor

After helping to clone Dolly the sheep in 1996, Alan Colman, Ph.D., was approached with recruitment offers by institutes from around the world. He refused them all until 2002, when a $6 million grant lured him to Singapore. Six years later, he returned to the United Kingdom, accepting a post at King's College London. Publicly, he said his return would pave the way for UK/Singapore collaborations.

Last year, former U.S. National Cancer Institute researchers Neal Copeland and Nancy Jenkins also left Singapore after its research priorities abruptly shifted to emphasize commercialization. They accepted positions in Texas.

The access to funding that attracted Colman, Copeland, and Jenkins also attracts companies. Economic development agencies approach companies with incentives that include a wide range of grants, tax incentives, logistics help, and other enticements, including streamlined bureaucracy. According to EDB (Economic Development Board) Singapore, for example, "It takes 15 minutes to register a business online, 3 weeks to receive approval for clinical trials, and 24 to 36 months for a manufacturing facility to be operational."

Brendan O'Callaghan, VP of biologics, therapeutic proteins, and contract manufacturing operations for Merck, insists, "The significant growth for pharma won't be in developed world markets but in emerging markets. Therefore, although economics is a key driver, economics alone doesn't provide all answers." Access to markets with growth potential is another important factor, followed by the availability of local talent and local government support. Further, the convenience of the location in terms of access to air travel and major cities also comes into play.

Using those criteria, Novartis identified China, Russia, and Brazil as high-growth emerging markets. Novartis spokesman Eric Althoff says the company is investing $1 billion to build the largest pharmaceutical R&D institute in China. "It is studying epigenetics, stem cells, hepatitis, and infection-based cancers endemic in the region."

In Russia, Novartis is building a new manufacturing plant in St. Petersburg to produce innovative pharmaceuticals and generics. "Russia is an attractive climate for investment because of its long history of scientific development and technology, its growing pool of local business and scientific talent, tremendous natural resources, and its quickly-recovering economy," Althoff says. Compared to other Russian locations, St. Petersburg offers a convenient location, attractive cost structures, and a supportive local government, as well as access to leading universities and talent.

Novartis also is establishing operations in Brazil, signing a letter of intent with the Brazilian Ministry of Health, outlining nine initiatives addressing local production, technology transfers, National Health System disease priorities, and R&D.

GOVERNMENT SUPPORT

With regions throughout the world committed to attracting life sciences companies, organizations are working closely with governments not only to gain financial incentives and access to top talent, but also to share priorities and improve local disease awareness and management, while improving business standards.

In China, for example, Novartis has a joint research laboratory with Fudan University to study cancer genetics and cell biology and to develop innovative disease models. This and similar academic partnerships provide hands-on experience for emerging Chinese talent and help develop scientific expertise in the region.

In another partnership example, multinationals are committing resources to combat neglected diseases. Novartis is working with the government of Brazil and with the World Health Organization to help eradicate leprosy. Working together, Novartis and the Singapore EDB established the Novartis Institute for Tropical Disease in 2003 to discover novel therapies and preventive treatments for dengue fever, tuberculosis, and malaria.

INDUSTRIALIZED NATIONS' STRATEGIES

Incentives and partnerships aren't limited to emerging nations, of course. Industrialized nations also are actively working to attract life sciences businesses. "In the 1970s Europe was growing, and Ireland offered a very well-established education system, an English-speaking population, and an easily accessible time zone," O'Callaghan says. The Irish also were comfortable working within regulated environments.

"Now, 40 years later, the pharmaceutical industry has a huge installed base, the infrastructure is established, and academic research continues to seed the talent pool," O'Callaghan adds. Some of Ireland's initial benefits have been diminished by EU harmonization regulations, which tend to equalize the relative benefits of any particular EU member when compared to another.

To retain companies, Western nations are capitalizing on their life sciences experience, established regulatory environments, and installed base. For example, Ireland is working with unions to moderate wage inflation and with utilities to contain energy costs as part of a national effort to build a more competitive industrial framework.

In the United States, Congress reauthorized the Prescription Drug User Fee Act (PDUFA) and in 2011, the Small Business Innovation Research (SBIR) program. The FDA, for its part, is attempting to reform itself to foster innovation.

TAXES CAN MAKE THE DIFFERENCE

"A well-regulated environment and the ability to grow a business are more important than the tax rate," says Dave Shanahan, global head of life sciences for IDA Ireland. Taxes do play a role, however, as CFOs point out each January at the JP Morgan Healthcare Conference. In terms of taxes, Shanahan says, "Ireland has a corporate tax rate of 12.5% and an effective tax rate of 11.7%." That's comparable to Switzerland's and Portugal's. But French multinationals, he notes, often pay no taxes despite a 33% tax rate.

Singapore has a 17% corporate tax rate and offers enticing incentives, including streamlined bureaucracy, as it builds its life sciences industry.

China's corporate tax rate is 25% but, under the Enterprise Income Tax rule, businesses classified as "Chinese tax residents" receive a 100% tax incentive for certain technology transfers. Foreign businesses may receive a 5% tax exemption for technology transfer. The details of obtaining those tax credits, however, are ambiguous, so may not be leveraged.

OTHER CONCERNS

Specific risks attached to working internationally vary by country but include changing research priorities such as those that frustrated researchers in Singapore, an evolving and sometimes erratic regulatory system in China, a limited infrastructure in Brazil, and corruption that is still an issue in many regions.

Organizations also must contend with widely varying business practices and attitudes toward innovation and work itself. China, for example, has imposed two temporary bans on stem cell research, which directly affects NeuralStem's work. Richard Garr, president and CEO of NeuralStem, says he expected a fluid environment and unpredictable delays. "You never know when things will happen." Garr maintains Chinese bureaucracy still moves faster than it does in the United States or the EU. ChinaBio, however, notes China's SFDA (State Food and Drug Administration) takes one to two years to process NDA (new drug application) submissions. A recent study in the *New England Journal of Medicine* reports that the median total review time for NDAs was 322 days at the FDA, 366 days at the EMA (European Medicines Agency), and 393 days at Health Canada.

Risk/reward calculations may differ internationally, also. "The Chinese government is promoting innovation very aggressively," Garr says, so it fast-tracks innovative therapies for incurable diseases. In the United States, the FDA is expected to expand the fast-track option later this year.

Intellectual property protection remains a key concern for innovative companies. Laws may not be uniformly enforced or understood, so, Garr says, "It's hard to know what protection you actually have. As a business, look at where it makes sense to have IP in emerging markets."

NeuralStem established a manufacturing facility in 2011 in China's Suzhou BioBay to develop GMP-equivalents for cell-based research for Chinese clinical trials. "We decided the technology, science, and medical expertise are available in China now to deliver our product, a spinal injection that treats chronic motor disorders caused by stroke. In the United States, stroke affects a total of 1 million people, but in China 2.5 million new stroke patients are added each year. "We're in China because this is an enormous public health problem and at the BioBay because of its facilities and proximity to Beijing. There are no incentives," Garr says. Perhaps not, but there is a climate conducive to innovation. Regardless of where companies invest, the right business climate and significant market potential generally trump governmental incentives.

The Impact Of DMPK Clinical Failures

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), out of 10,000 compounds that begin the drug discovery process, a mere 250 make it to the preclinical stage, only five will enter the clinic, and just one will land on the shelves of pharmacists. It is a process that takes up to 15 years or more and costs more than $1 billion.

These exorbitant attrition rates, often associated with pharmacokinetic issues (PK), are blowing holes in drug development pipelines. That's tragic for patients and for drug developers. Given that attrition rates as high as 40% have been attributed to PK issues, drug developers need to carefully evaluate the quality of the Drug Metabolism and Pharmacokinetic (DMPK) studies conducted on their behalf. Not doing so can cause a company to potentially spend millions of dollars unnecessarily, if an unqualified candidate is moved along the drug development pathway or if a qualified candidate is "killed" too early in the process.

Fortunately, companies can avoid these unnecessary costs by integrating DMPK studies early in the drug development process and by incorporating new technologies. These steps allow more accurate allometric scaling to man and better prediction of therapeutic index, factors that can cause attrition to significantly decrease.

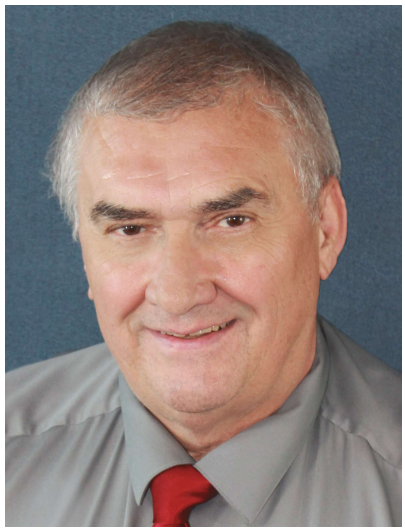
Biopharma and biotech companies are finding that paying early attention to the quality of the DMPK program with which they are pacing their studies is a good investment. In fact, doing so can reduce clinical failure rates to as little as 10%. Whether the research is done within their own companies or with CROs, a top quality DMPK program is supported by the scientific expertise necessary to assure successful IND (investigational new drug) submission and clinical success.

Bringing a safe and effective compound through the pipeline successfully requires specific expertise in many areas of the IND-enablement process, but it is particularly essential to consider four categories into which all DMPK data falls. Ensuring expert knowledge in each of these areas allows drug developers to significantly improve their chances of bringing the best drugs to market. Your DMPK team should address these four categories by considering the following questions:

1. What are the physiochemical properties of the drug molecule?
2. What are the kinetics of movement of the drug (metabolite) through tissues and fluids (concentration-time data)?
3. What are the dynamics of interaction of the drug with proteins, nucleic acids, etc., that influence PK (drug-drug interaction, etc.)?
4. How has the body changed the drug; what is the metabolism of the drug qualitatively and quantitatively?

Some of these studies are simple, off-of-the-shelf, box-checking protocols, and it likely does not matter where you place these studies. Other areas, such as quickly identifying MIST (Metabolites in Safety Testing) liability issues, production of reactive metabolites, full metabolite structure ID, and covalent binding of metabolites, require special expertise that is essential to maximize the financial gains of lowering attrition rates.

Successful drug developers know that applying high DMPK standards early in the development process by considering these four dimensions will allow them to better identify the most promising compounds as well as those that will fail early-on. By identifying these candidates early in the process, unnecessary development costs are avoided, and failure in the clinic is minimized. A comprehensive, timely, and multidimensional approach to DMPK research helps to identify failure, so the chances of successfully bringing a safe and effective compound to market are maximized.



John James Vrbanac, Jr.

John James "Jim" Vrbanac, Jr., Ph.D., is director of absorption, distribution, metabolism, and excretion (ADME) and senior study director at MPI Research. He is responsible for overseeing the ADME department by providing leadership for business development, scientific advancements, and high-quality performance of the ADME team, as well as managing the overall planning and conduct of nonclinical investigations.

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Preparing For A Successful FDA Inspection

Routine inspections by the U.S. FDA are as important for non-U.S. pharmaceutical manufacturers as they are for U.S.-based companies. This is especially true for Swiss companies, which export a great share of their products to the United States. As a whole, Switzerland exports approximately 10 times more drugs and APIs than it consumes. For non-U.S. companies, which must undergo regular inspections by their native countries' regulatory agencies, the FDA inspections provide extra validation that their products meet the highest effectiveness and safety standards and open the door to the U.S. market. An FDA inspection may seem intimidating, but it is a vital part of our business.

ALWAYS BE PREPARED

Lead time before FDA inspections is typically very short, leaving little to no opportunity for preparations. Therefore, always being ready is essential to a successful inspection. A company should give consideration to the following priorities as it prepares for an inspection:

- Be in control, from development to purchasing, producing, and shipping.
- Have retrievable documents showing what you do, what you did in the past, and what you will do in the future. Document all processes and ensure that documents are accurate and readily available.
- Communicate with your staff, suppliers, customers, and the authorities in charge, and document all communication.
- In advance of the inspection date, assign qualified staff to work with the FDA inspectors and provide employees with the tools they need to get the job done.
- Train all staff to interface with the FDA investigators.
- Assess your quality risks in the broadest conceivable sense and from every possible angle, and take steps to mitigate the risks.
- Be ready to learn from your experience and from the FDA inspectors, who have broad expertise.
- Most importantly, never lose track of your main goal: protecting patients' health and safety.

WHAT FDA INSPECTORS ARE LOOKING FOR

During the past 10 to 15 years, we have noticed a shift in how inspectors evaluate a company's performance. They are increasingly moving away from checking specific details (e.g. calibration dates of balances, reanalysis dates of reference samples, or logbook entries on the cleaning of storage areas) and instead are focusing primarily on evaluating decision-making processes.

This shift underscores how important it is to ensure that all employees, regardless of their level within the company, embrace the commitment to patient health and safety. This commitment has now become the main quality differentiator among companies, and it goes well beyond checking the right boxes on a form.

Such commitment is particularly important for subcontractors that deal with a product mix of commercial APIs on the one hand, and development APIs in Phases 2 to 3 on the other hand, and that work with customers ranging from start-ups to the largest global players. The decision-making process has to be adapted to the respective development partnerships, asking project leaders to demonstrate not only scientific expertise but also a great amount of flexibility.

Peter Müller

Peter Müller, Ph.D., is senior scientific advisor, delegate of the Dishman board of directors, and member of CARBOGEN AMCIS AG's management team.

Regardless of differences in company size, the key principles remain the same for all types of customers and all levels of personnel: open and timely communication and science-driven, structured decision making. These are what inspectors are routinely checking for.

WHAT TO DO ON INSPECTION DAY

While doing homework is most important, there are things to keep in mind on inspection day:

- Be hospitable. Consider that the inspectors are guests needing a conveniently located hotel, directions to your facility, the approximate distance and time it takes to travel there, special meal requests, etc.
- Dedicate a team to manage the inspection on the day of the audit.
- Instruct your staff to do their best to understand what the inspectors are looking for and encourage them to assist FDA inspectors.
- Set up space for inspectors and assist with rapid copying, stamping, and delivering documents at the inspectors' requests.

The most important thing a company can do to successfully pass an FDA inspection is to commit to quality every day, not just on inspection day.

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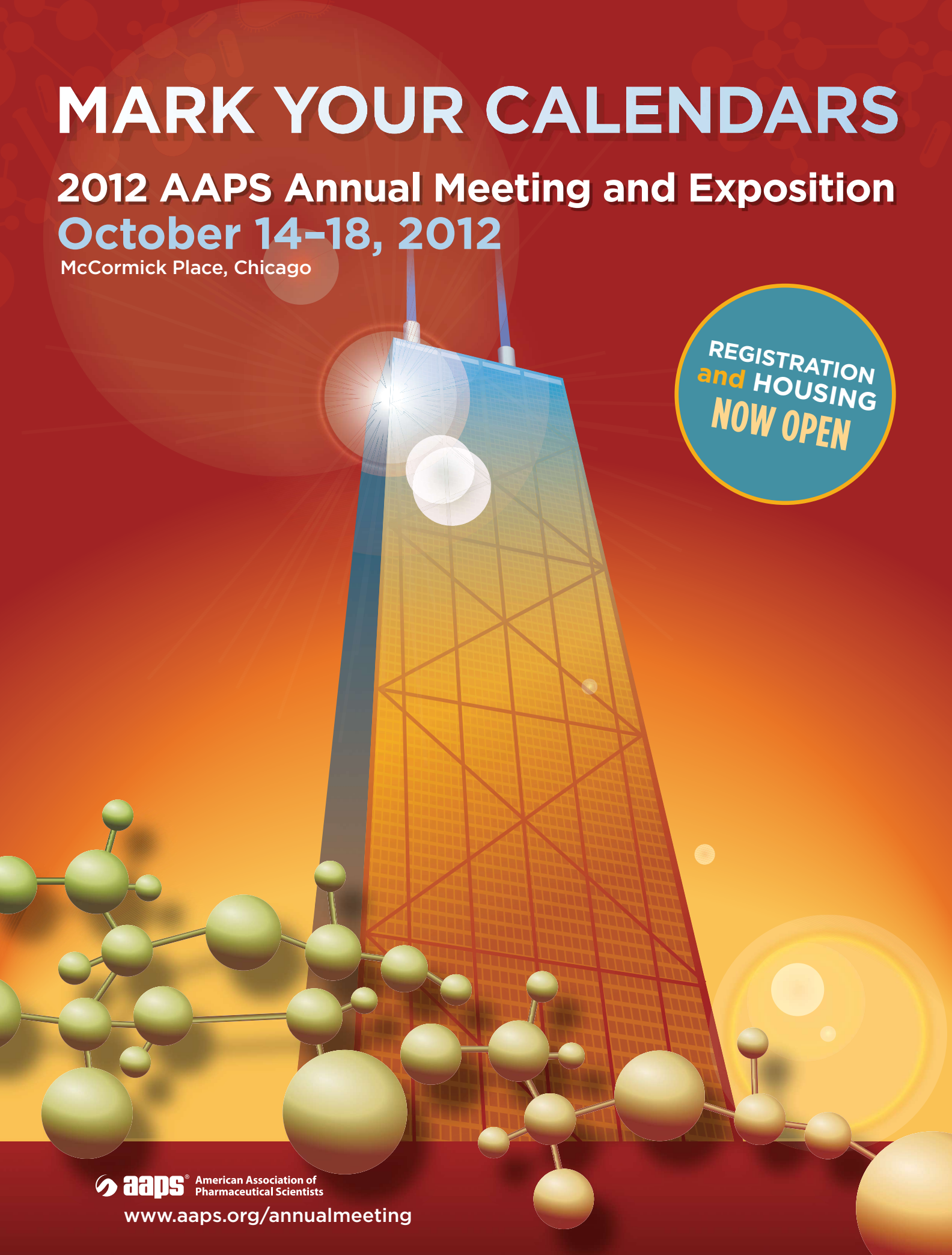

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Raising Life Sciences Capital: An Alternative Way

There are various strategies public life sciences companies use to raise equity capital. Common approaches are conventional financing vehicles such as marketed follow-on offerings, registered directs, and private investments in public equities (PIPEs). These methods require selling shares in large quantities at a fixed price at one specific time.

However, a financial strategy that has become more popular for these companies over the past few years is an at-the-market (ATM) financing vehicle. An ATM offering involves selling newly issued shares to the existing market at market prices via a broker-dealer over an extended period of time. It allows a company to maintain control of its capital raising activity while minimizing cost and share dilution.

THE RISKS OF TRADITIONAL FINANCING STRATEGIES

The various traditional approaches to raising capital have proven to be beneficial and allow companies to raise a significant amount of capital in a short period of time. However, a life science company depending solely on traditional financing strategies to raise capital may encounter risks associated with these financial strategies.

The risks that can affect traditional financing strategies can be both external and internal. A prime example of an external risk would be a volatile market. This can cause a company to do financing during a time its stock price is not at a valuable price point. Internally, a company can plan for events such as an upcoming partnership or a data announcement that does not turn out the way they were expected. These risks could lead to delays in financing or result in a financing not as successful as planned.

Traditional financing for a life sciences company can become costly and could total about 35% of the raised capital. Traditional finance offerings typically are announced at an average discount to the prior closing price of about 7.5% and underwriters' fees run roughly 5%. Another cost that is encountered is warrants, the value of which can average 24% of a transaction or higher. Companies that are running out of capital will confront costs above these numbers.

These issues have resulted in life sciences management teams looking into alternative financing strategies, such as ATMs.

ADDING AN ATM OFFERING TO THE FINANCIAL TOOLBOX

ATM offerings allow public companies to avoid the risks and costs that are often associated with more traditional financings. This is because ATMs raise capital for the issuer in a manner very different than a conventional offering. With an ATM, a company sells shares, through a broker-dealer acting as an agent, incrementally over a period of time into the existing trading market in amounts and at prices determined by the issuer. Unlike conventional follow-on offerings, ATMs enable the issuer to maintain control of its capital-raising activities. A company can choose when to sell shares, including times when the market is volatile, because ATMs give companies the flexibility to sell shares only on days that are advantageous for the company.

ATMs do not preclude companies from also using other types of financing vehicles. Rather, an ATM can work in conjunction with other financing vehicles in a company's financial toolbox. A company can employ both traditional financing strategies and ATM offerings. Doing both adds another layer of flexibility for a company. It can first utilize an ATM to raise capital very cost effectively and then if additional capital is needed, it can use conventional methods that are usually much more expensive. A forward-thinking company can also take advantage of an ATM and raise the needed capital over an extended period of time rather than hoping that market conditions will allow a conventional offering when the need for capital arises.

Another benefit of including an ATM in a company's financial toolbox is the relatively low cost of engaging an ATM. As we mentioned above, a conventional offering can cost about 35 percent of the capital raised in a transaction if warrant costs are added to the price discount after the deal is announced and fees are paid to the underwriters. The main cost associated with an ATM is the underwriting fee, averaging 3.8 percent, which is generally a straight percentage of the capital raised. There are no warrants or commitment fees that are part of the transaction.

Todd Wyche

Todd Wyche is a founder and managing director of Brinson Patrick. Mr. Wyche's leadership has been integral in the growing use of at-the-market offerings by issuers in the life sciences industry.

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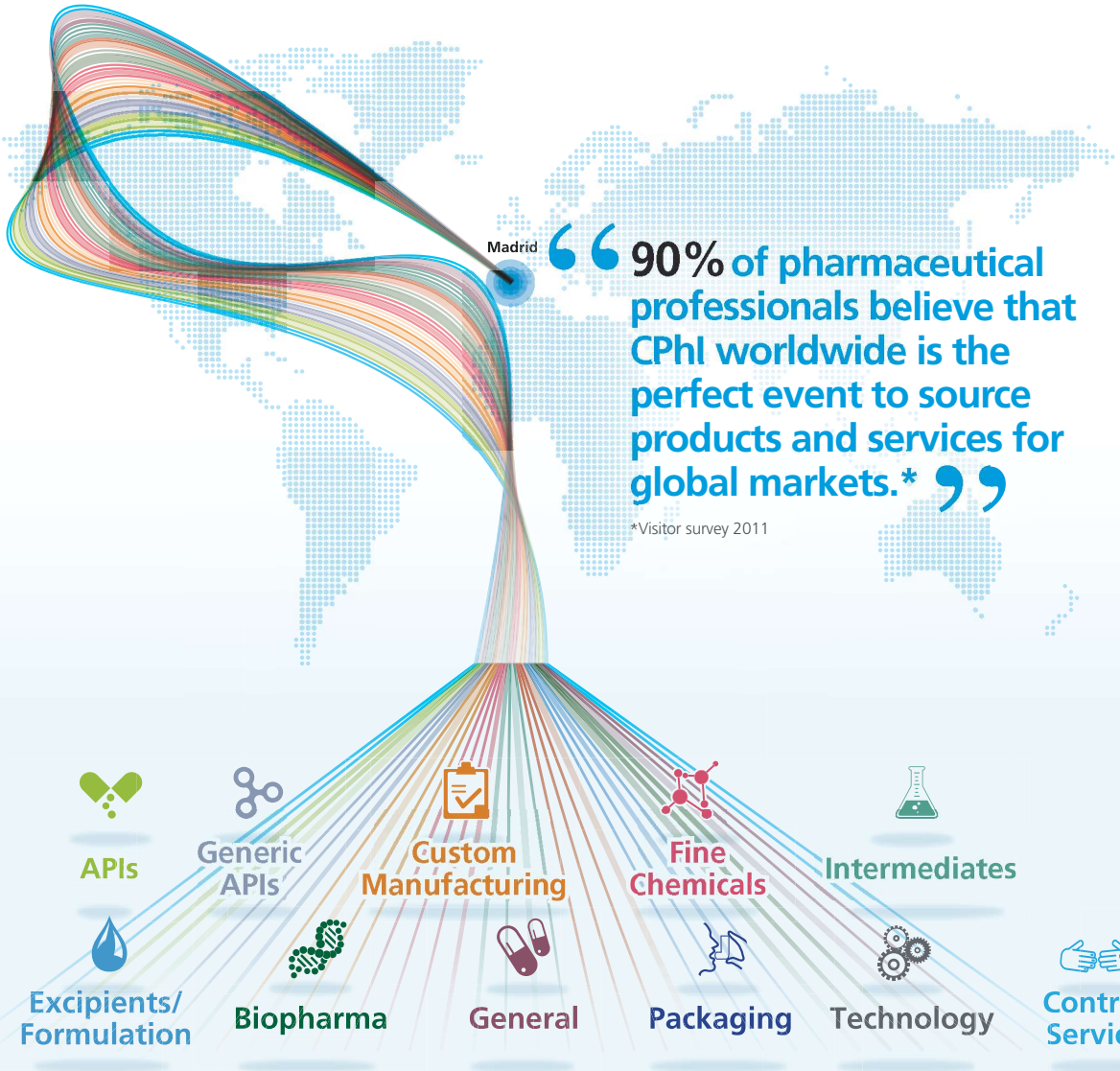

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Creating New Realities From Vision

The Key To Success For Any Leader

By Ron Karr

As senior executives, one of the responsibilities you are charged with can be best described by the quote from Wayne Gretsky, "I go to where the puck is going to be, not where it is." Any forward-thinking company that wants to stay at the head of the pack needs to imbed this philosophy as the backbone for making all decisions. But what skills are required for an executive to lead by this philosophy, and what are the common traps one is likely to encounter? The first and most important skill is the ability to visualize the end result.

WHAT DOES IT TAKE TO VISUALIZE?

It all starts with an idea. You know the ideas we get unexpectedly. Like when you walk down the street in a blighted neighborhood and see a building that someday you believe will be valued real estate. But then your next thought is "Nah, that will never happen," and you walk away. Twenty years later you happen to drive by that location, and you kick yourself for not acting on your intuition. And then you are completely ticked off when you see your competition doing what you thought about initially but never acted on.

To use vision properly to help create new ideas and improve productivity and market differentiation, you need to start with a clean slate. Forget about what you know the world to be. Simply start writing down your thoughts on where your company and/or department must go. Do not entertain thoughts as to why this cannot happen based on today's reality. Hold your vision in your conscious mind. As you hold this vision in your conscious thoughts, ideas start to happen, actions become apparent, and you are on the road to creating a new reality.

The key behaviors you must exhibit are the need to trust your instincts, believe in your vision, and to be okay with the fact you don't have the answers initially. Many people stop because they don't have the answers. Leadership is about creating a vision first for solving problems and then going about finding the answers and implementation.

This is exactly what we did with a multinational chemical manufacturer engaged in a critical competitive situation. They had created a technological advance in the market only to see its position erode to competition. When they hired me to help reposition them with their largest customer who was only giving them 25% of their business, we started with a clean sheet of paper and captured their vision. The end result was an industry first where the client was awarded a 10-year negotiated agreement (no bid) valued at $200 million. This was for what was once perceived as a commodity product and now is viewed as essential for their customer's success.

It all starts with vision. What is your vision today? Are you capturing it? Don't worry about not having the answers. They will come if you are committed to it and hold it in your conscious thoughts at all times. This is what successful leaders do.

Ron Karr is CEO of Karr Associates, Inc., a firm that specializes in business transformation. His advisory services and highly rated keynotes and workshops have generated well over half a billion dollars in incremental revenues for his clients. Ron is the author of the best-selling book ***Lead, Sell or Get Out of the Way*** and will be the 2013-2014 president of the National Speakers Association.

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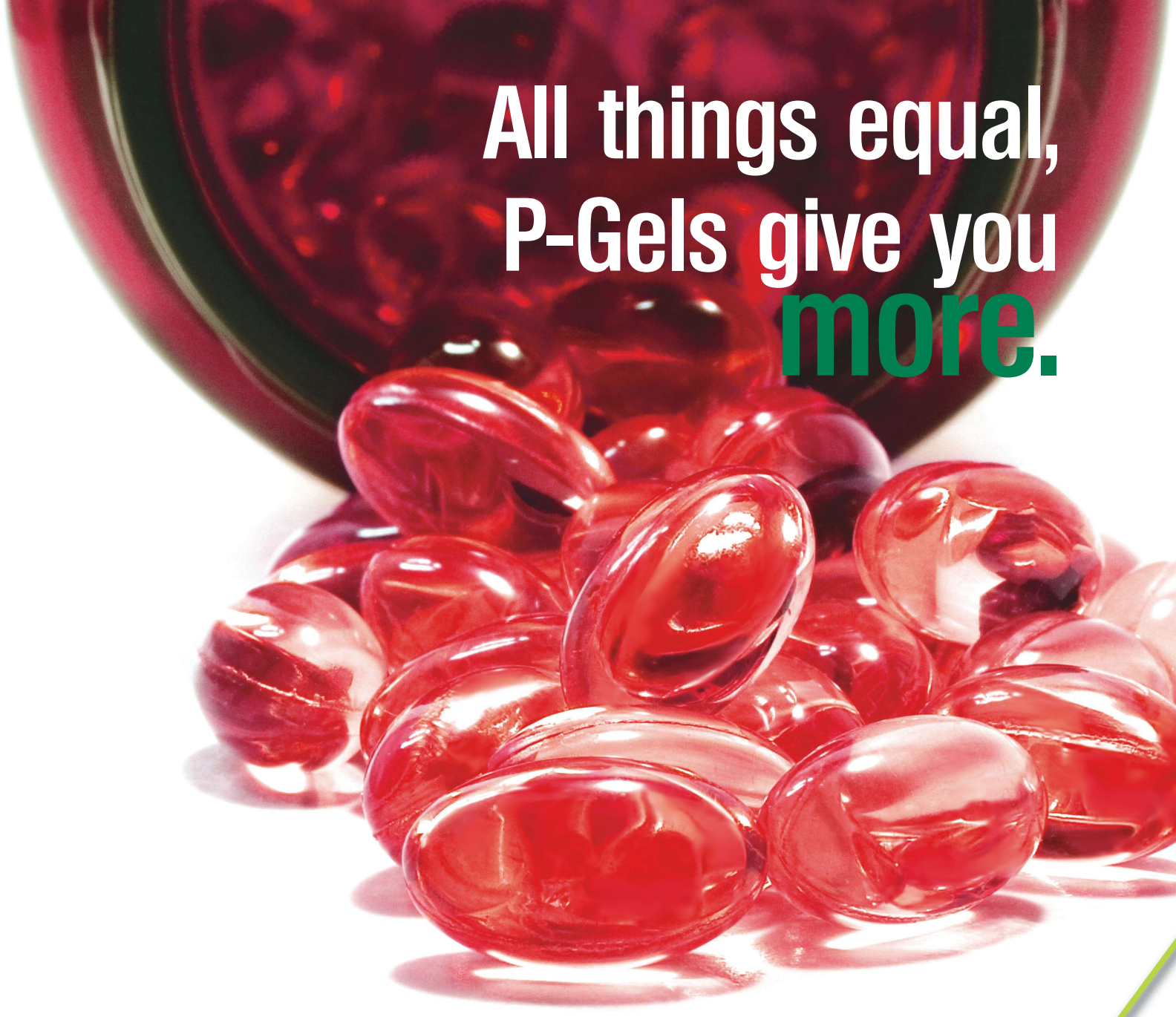

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