BY TAREN GROM

MOLECULE TO MARKET: A Drug-Development Timeline

The drug development process from lead generation to patent expiration is complex, fraught with risk, and extremely time and cost intensive.

DR. JENS OLIVER FUNK ■ *EMD Serono*

Organizations need to foster creativity and entrepreneurial spirit among their R&D staff members, facilitate random encounters and open sharing of hypotheses and data, and promote ideas off the beaten track."

According to the most recent report from the Tufts Center for the Study of Drug Development, it takes about 10 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing, and of these five, only one is approved. On average, it costs a company $1 billion to get one new medicine from the lab to the hands of consumers; in 2003, the cost was $897 million. And once the product reaches the market, myriad factors impact adoption and use — from proposed changes to patent life to a changing consumer world.

There are hundreds, if not thousands, of points of contact along the development continuum. For the purposes of this special issue, we have divided the process into three broad categories — drug discovery, early development, and full development — and then by seven areas of focus: target identification and validation, HIT finding, and lead optimization; early clinical safety and efficacy; Phase I trials; Phase II trials; Phase III trials; registration and launch; and postlaunch.

The R&D Model

Some industry leaders have been saying a new model for R&D is needed to bring new medicines to the market in a timely and cost-effective manner.

FAST FACT

CURRENTLY, IT COSTS, ON AVERAGE, MORE THAN $1 BILLION AND TAKES MORE THAN SEVEN YEARS FROM THE START OF CLINICAL TRIALS TO CONDUCT THE NECESSARY STUDIES AND WIN APPROVAL TO MARKET A NEW DRUG IN THE UNITED STATES.

Source: Tufts CSDD

MOLECULE TO MARKET:

- Discovery and preclinical testing take on average 6.5 years.
- Phase I studies take about 1.5 years.
- Phase II studies take about 2 years.
- Phase III studies takes about 3.5 years.
- Registration takes about 1.5 years.
- Average patent life is about 6.8 years

"One of the main areas we need to address is the current cost of developing new and innovative drugs," says Stephen Cutler, Ph.D., senior VP and chief operating officer at Kendle. "In 2009, the FDA approved about 20 NCEs while the biopharmaceutical industry spent roughly $80 billion on development. That's an average of $4 billion per NCE, which in reality is probably closer to $5 billion to $6 billion per NCE if we include all of research costs. Although there were another 60 product label extensions approved, the bottom line is drug development is simply too expensive. We need to be more creative and innovative to reduce costs without compromising the quality of development or safety for patients. Functional outsourcing, sampling-based and off-site monitoring approaches, and electronic health records all offer opportunities to reduce costs, and we need to embrace these options more aggressively if we are to make significant progress."

Many companies recognize that the need to develop novel drugs with higher efficacy and better safety requires a reassessment of the R&D model.

"Key organizational components for success include removal of artificial barriers, a fully integrated organization that allows forward and backward translational research, close collaboration between bench scientists and clinicians with leverage for an early clinical exploratory mindset, and a parallel biomarker R&D program to complement drug discovery," explains Jens Oliver Funk, M.D., senior VP and global head of TA oncology, EMD

PATRICIA BASSETT ■ *Unithink*

By providing tools that address the needs of multiple disciplines, it is possible to eliminate barriers and to facilitate close cooperation, leading to a faster and more effective drug development process."

DR. TROY MCCALL
■ *Cetero*

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According to Jean-Jacques Garaud, M.D., global head, pharmaceutical research and early development at Roche, to develop a new R&D model, it is important to address a critical flaw in current R&D models.

"By this I mean the attrition-based model, which most companies still subscribe to, but as it does not address the true nature and biology of disease," he explains. "Going forward, we need strong interactions between the areas of discovery and research, translational medicine, and experimental development. It is also important to maintain relatively small research and early development units that are independent and have autonomous decision-making processes. This enables a diversity of approaches and allows for a greater chance of success at bringing medically differentiated drugs to the market."

James DeSanti, founder and CEO of PharmaVigilant, doesn't think the overall direction of R&D will change — companies are still looking to bring new and innovative drugs to market.

"What will change is how they get there," he says. "It's no secret that skyrocketing costs and expanding timelines are major issues in clinical trials, and this has become more apparent in recent years. R&D can no longer ignore the big elephant in the room — inefficient, yet avoidable, expenses and delays. It's inevitable that R&D budgets will continue to come under the microscope, and adjustments will be made internally to compensate. As a result, there will be even more disparity among R&D units within the industry. This isn't necessarily a bad thing; it just provides more opportunity for creativity and innovation. This is where technology comes in."

Paul Boni, chief research officer at Grail Research, believes the opportunity for major change in the R&D process is for companies to more efficiently test and fail products.

"Despite our growing understanding of the biology of disease, drug development is still a numbers game, which means a lot of molecules need to be tested to find a successful one," Mr. Boni says. "Despite this, many companies are often reluctant to fail products that may not be promising. By asking the most difficult questions first and aggressively working to eliminate the weakest products, developers can rapidly identify the most promising molecules in the pipeline."

Mr. Boni adds that smaller pharmaceutical and biotechnology companies should consider using a virtual development model with greater frequency.

"As we all know, successful drug development requires highly specialized skills in a wide range of disciplines," he says. "If a company cannot justify the expense of bringing these competencies on board full time, partnering or hiring outside experts enables researchers to manage the development pipeline without the cost structure required to maintain those same skills in-house."

William Crown, Ph.D., president of i3 Innovus, says pharma companies need to shift from the traditional blockbuster approach to a marketing approach based upon managing a portfolio of products designed to meet the needs of smaller, more distinct clinical populations.

"It's all about identifying patients who will respond, and not trying to market to those who will not," he says. "The core concept is getting back to the science. The focus on tailored therapies is inherently more clinical and emphasizes getting the right patient on the right drug at the correct dosage."

Troy McCall, Ph.D., CEO of Cetero Research, says the current challenge is balancing when to dose healthy participants versus patients once a drug candidate emerges from preclinical research.

"The pharma industry needs to expedite viable drugs through the development process," he says. "Pharmaceutical companies also need to know earlier in the development pro-

DRUG COMPANIES STILL UNDER PRESSURE

Although drug developers are improving R&D efficiency, in part by terminating more unpromising drugs earlier in development, their continued success will depend on how well they partner with other firms at specific points on the development spectrum, according to the Tufts Center for the Study of Drug Development.

"Developers have made important progress in reducing R&D times, but because only three in 10 new drugs, on average, generate sufficient revenue to sustain R&D, pharmaceutical and biotech firms are under great and growing pressure to generate revenue to bring more products to market," says Tufts CSDD Director Kenneth Kaitin. "The simple fact is that product launches are not keeping pace with patent expirations."

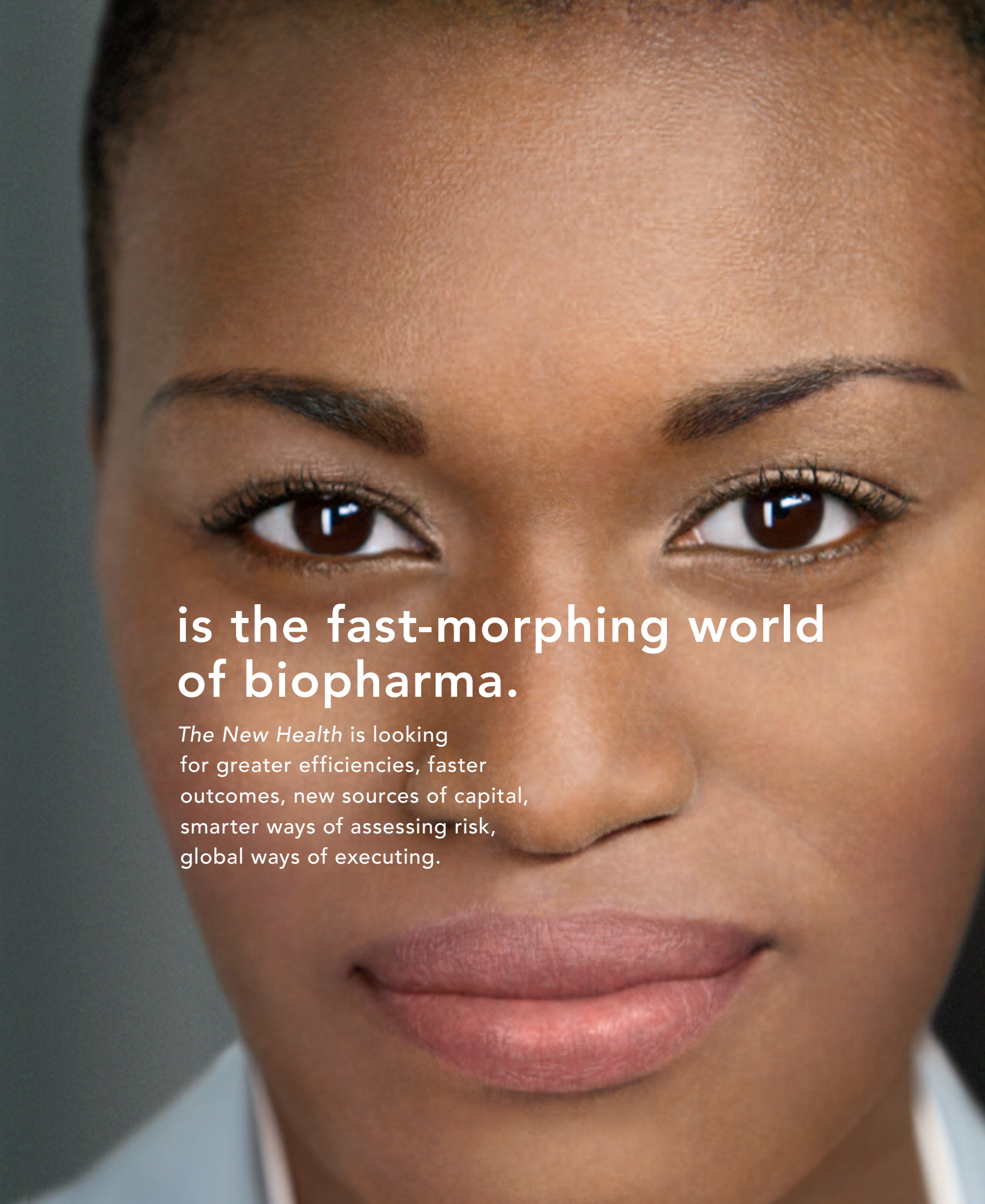
According to Tufts CSDD, worldwide sales for all drugs coming off patent from 2009 through 2012 will exceed $88 billion. Mr. Kaitin noted that while new technologies and improved protocol designs are helping to improve R&D efficiency, future success for many sponsors will depend on their ability to collaborate with other drug companies, and how well they engage and partner with outside service providers.

Among the near-term trends cited in the Tufts CSDD's Outlook 2010 report are the following:

- More firms will focus on improving clinical protocol design to help reduce trial costs and speed development cycles and to mitigate a trend toward increased protocol complexity.
- After the U.S. Congress concludes the current healthcare reform debate, a more activist FDA will focus on a regulatory pathway for follow-on biologics approvals, over-the-counter product and drug safety, foreign facility inspections, preventable deaths from chronic diseases, and vaccine manufacturing capacity.
- Clinical development times for novel protein products, which now average seven years are unlikely to decrease due to disease complexity, growth of study protocols that lengthen studies, and difficulty recruiting and retaining volunteers.
- Off-label prescribing of biopharmaceuticals in the United States will be subject to increased economic scrutiny, such as comparative effectiveness assessments, drug utilization reviews, and prior authorization.
- A tougher global operating environment that is forcing marginal research sites to exit clinical development will ultimately create a less fragmented global development landscape; higher-performing research investigators will be available to partner with sponsors.

Source: The Tufts Center for the Study of Drug Development. For more information, visit csdd.tufts.edu.

THE NEW HEALTH



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cess if the drug performs as intended in the target patient populations. CROs, along with sponsors, are developing new approaches to the study designs and the recruitment of patient populations."

For Kevin Hrusovsky, president and CEO of Caliper Life Sciences, the key to recharging the drug innovation cycle and accelerating small-molecule drug development is making each facet of the R&D process more clinically relevant.

"By strategically implementing new enabling technologies, the pharmaceutical industry can use time and capital more efficiently and increase the probability of achieving clinical, regulatory, and commercial success," he says.

To succeed in drug development, solutions that provide business insights into the development portfolio are key for consideration, says Michael Naimoli, U.S. life sciences industry solutions director at Microsoft Corp.

"It is difficult to manage what cannot be measured, so technologies that provide business process collaboration, business insights through dashboarding, and flexible computing environments in the form of cloud-based platforms are increasingly of interest to the industry," he says.

R&D Meets Commercial

While development in genomics, personalized medicine, and other areas are leading to medical advances with the potential to transform the diagnosis and treatment of disease, Scott Treiber, executive VP, clinical development solutions, at inVentiv Clinical Solutions, says companies are finding that it has become far more challenging to develop an idea and cultivate that idea into a marketable product.

"The downturn of the economy has led to fierce competition for limited funding, and policy changes and safety concerns have made the regulatory and approval process more complicated to navigate," he says. "As a result of the current economic environment, some specific challenges facing companies today include: higher cost of capital and barriers to entry/availability of capital; a more conservative and stringent FDA; increased risk aversion — setting unreasonable expectations; escalating costs for clinical trials and FDA compliance; patent reform legislation reducing the value of intellectual property; and greater competition from larger and foreign companies. There are also other, less-apparent roadblocks that companies encounter, including managing costs and overhead, finding sources of additional capital, and increasing awareness of the company and its products in a cost-effective manner."

Jeff Trotter, executive VP, Phase IV development, at PharmaNet, says commercial teams need to have some involvement as early as possible to ensure that measures most relevant to eventual stakeholders have been accommodated.

"While rarely are these measures seen as definitive from the perspective of the post-approval landscape, addressing them earlier generally provides a stronger, more market-responsive foundation that can better optimize the effort required to document these issues post-approval," he says.

To fully understand the market potential for a new drug, R&D and commercial organizations should begin working together at the earliest stages of preclinical research, prior to Phase I application, experts say.

"But often commercial organizations are not brought in until the later stages of a drug's clinical development process," says Nagaraja Srivatsan, VP and head of life sciences, North America, at Cognizant. "Ideally, commercial organizations should look at how the value of a new drug can be articulated early on, and make sure that the clinical trials are designed to highlight and show the value of the drug compared with its competition. Joint R&D and commercial governance forums to review strategic products/TAs at the operational leadership level should become a routine practice."

Robert Norris, founder and president of Complete Healthcare Communications, says if a company is entering a market that has a well-established leader, it may not want to tip its hand too early with the findings that it's bringing to the market because that gives the competitors time to respond or possibly even preempt what the company is doing.

"But if, a company is introducing a different class of drug, starting the marketing efforts in Phase II is probably the best approach," he says. "The sponsor can use that time to educate the practitioners on what the class is all about, which is not only beneficial from a clinical perspective, but from a marketing perspective as well. It creates a buzz about the compound."

Breaking Down Silos

In the last 10 years, there has been a slight shift within companies relating to earlier coop-

JAMES DESANTI ■ *PharmaVigilant*

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eration between R&D and commercial functions, but according to Patricia Bassett, VP sales EMEA at Unithink, there are still silos between the different functions within R&D.

"This is perpetuated by a lack of integrated systems within many organizations," she says. "This means that departments are neither motivated nor enabled to work seamlessly together. By providing tools that address the needs of multiple disciplines, it has now become possible to eliminate these barriers and to facilitate close cooperation, leading to a faster and more effective drug development process."

The challenge in R&D organizations is to retain individual functional characteristics, which have evolved to match specialized capabilities, regulatory requirements, development phase, etc., while moving the development organization to faster, safer, more comprehensive decision-making that ignores organizational and individual boundaries, says Patrick Chassaigne, director, late phase solutions, at Medidata Solutions.

"Computer applications have the potential to create the basis for underlying connections, allowing information flows, controls, joint processes, and new efficiencies that would power a new view of clinical information," he says. "This will not be achieved by the continued accumulation of traditional applications by traditional functions, but by the adoption of advanced systems and platforms that create data flows and process visibility through interoperability, cross-trial analysis, and metrics generation."

Global Trials

Increased globalization of drug development is being driven by several factors, including the ability to access diverse patient populations and the lower cost of conducting quality clinical research in emerging geographies.

"Another major driver is the increasing importance of new end markets in a number of geographies," says Mark Goldberg, M.D., chief operating officer of Parexel International. "In emerging markets, many countries, such as China and South Korea, are projected to be large end markets for biopharmaceutical products. Working in these countries, and numerous others, cost and time efficiencies can be brought to the development process through global development strategies. Larger, more complex global development programs have created more opportunities for sponsors and service providers to partner to bring more innovation to study design and execution."

John Andrews, Ph.D., director of regulatory affairs, Americas, at Chiltern, says emerging and changing markets will challenge drug development within the next five years.

"As new markets emerge, the importance of coordinated submission, review, and approval of marketing applications will be required in order to make the worldwide process more efficient and cost-effective, both for the industry and for the national regulatory agencies and competent authorities," he says. "Global drug development, as opposed to country or regional, will be increasingly critical and country-specific; otherwise, regional approvals will be less effective."

Dr. Andrews says currently the differences between countries in terms of safety and efficacy can be a challenge for global approval.

"Consistent application of standards for preclinical pharmacotoxicology studies followed by the early clinical determination of pharmacodynamic, pharmacokinetic, and exposure variables will be required for smooth progress through Phase I, II, and III clinical trials and, ultimately, marketing approval," he says. "Consistent expectations for early information, including acceptance of and agreement on dose selection criteria, relevant pharmacodynamic parameters, and, finally, clinical endpoints for marketing approval, specific to each indication, will permit true global drug development." ✦

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MOLECULE TO MARKET: PLAN FOR SUCCESS

Today, only one in 25,000 products will complete the journey from preclinical development to product approval. Those companies that prevail must overcome a vast range of uncertainties and challenges, and successfully navigate a process that is complex and full of interdependencies. While there is no perfect formula for taking a compound from the lab to a commercially successful product, there are a few critical success factors that can help guide the process and form the basis for an aligned, cohesive organization that can commercialize products in an integrated, coordinated way. While these principles are very basic, focusing on them throughout the clinical development and commercialization process can have dramatic effects on company performance.

Decisions about allocating resources — both financial and staff time — are fundamental to long-term success, particularly in early product development, where some projects will be identified as drivers of the company's future growth and others will be left behind. It is essential that these decisions are based on both probability of technical success and expected commercial success.

Historically, commercial teams have had limited involvement in the clinical development process, but today some companies are recognizing the value of bringing commercial perspective into the process as early as preclinical development. Commercial input often begins with market research, an essential tool for connecting clinical development to market needs. Early-stage assessments derived from this research typically include a basic evaluation of market size and competitive landscape, along with a pre-efficacy forecast and preliminary resource requirements. Coupled with a target product profile, these can be valuable tools for driving investments toward products with the greatest commercial potential.

During Phase II, commercial input can help ensure that clinical trial design leverages unmet need in the market, thus forming a preliminary platform for differentiation. Results from these early trials can be invaluable for market conditioning and engaging key opinion leaders and the medical community.

Collaboration among clinical, regulatory, and commercial functions is most critical, and often most challenging, during Phase III trial design when the label is being formed. Data generated must not only provide a basis for differentiation, but claims that clearly communicate that differentiation. Trade-offs may be necessary between a trial design that would yield a highly marketable label and one that will deliver speed to market and ease of approval, but making these decisions with input from all functions will help ensure the most favorable result.

Source: Clare Colletti, VP and Managing Director of Global Commercialization, inVentiv Advance Insights, the strategic planning and consultative arm of inVentiv Health. For more information, visit inventivhealth.com.