BY DENISE MYSHKO

» R&D REGULATORY

A MORE CONSERVATIVE REGULATORY LANDSCAPE

The FDA is raising the bar on new drug approvals, especially where safety is a concern.

In the last few years, the FDA has come under strong criticism for the rate of adverse events, high-profile drug recalls, and contamination of both food and drug products. Agency officials have made steps to address drug safety and provide a more open and transparent regulatory environment. For the pharmaceutical industry, this is likely to mean increased oversight.

The FDA has certainly been more conservative in recent years in its approach to benefit and risk, says Richard Lev, chief compliance officer of Publicis Touchpoint Solutions.

"The FDA also has set a very high bar for new drug approvals," he says. "This is due in part to the public perception of drug safety as well as congressional pressure over costs."

Experts say a more conservative approach can be seen with some of the agency's recent decisions. Recent high-profile advisory committee decisions against approval of investigational weight-loss drugs Qnexa and Lorcaserin demonstrate the agency is beginning to err on the side of caution, says Ken Kramer, Ph.D., senior VP, medical director, at Alpha & Omega Worldwide, a part of The Core Nation.

"It also does not help that we are hearing allegations of companies hiding data and not reporting serious safety signals," he says. "Events like these, if true, can only harden the hearts and minds of the FDA. My educated guess is that we should prepare for more denials where approvals once roamed."

Dr. Kramer says the recent tribulations of Avandia have caused some pain in the industry, but they also provide an opportunity to learn.

"Our industry, and this includes the FDA, must understand that transparency goes a long way in producing good will even in the toughest times," he says. "Medicine is a science, but it will never be an exact science, so perfection cannot be expected. What the public can expect is that those trusted with their health and well-being will try their level best to be straight with them."

Mr. Lev says today the FDA has some additional regulatory options, such as risk management programs (REMS) and the ability to require Phase IV studies that, in theory at least, allow it to make more nuanced decisions.

"For example, the recent safety concerns with Avandia led to a strict risk management plan rather than withdrawal of the drug," he says. "The impact of this more conservative FDA approach is that the cost of new drug approvals remains extremely high, which could hamper innovation if this trend continues."

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FRAMEWORK FOR POSTMARKETING STUDIES

The Institute of Medicine recommends a conceptual framework to help the FDA evaluate the ethical issues involved in determining whether companies should start or continue clinical trials on approved drugs and in ensuring that these studies are ethically conducted. A more detailed analysis of these issues and their implications and effects will be included in the committee's final report, which will be completed in the spring of 2011.

FDA has recently gained enhanced authority to require drug companies to undertake studies of their products after they are put on the market, which presents the agency with additional challenges.

The FDA should:

- Ensure that any randomized, controlled trial to evaluate the efficacy and safety of an approved drug that is suspected of causing serious adverse events is conducted only when the existing evidence and any evidence from new observational studies would be insufficient to enable the agency to make responsible policy decisions.
- Determine that questions about a drug's possible risks or risk-benefit balance rise to the level of requiring a policy decision, such as whether to revise the product's label.
- Make sure that trials are appropriately designed to resolve uncertainties about efficacy and safety and to minimize risks to participants. Risks should be judged acceptable by appropriate oversight bodies, and participants and studies should be continuously monitored to assure that the risks continue to be acceptable.
- Develop a process of informed consent that continues over the course of the trials, and participants should be promptly advised of substantial changes in clinical practice or professional standards and new research findings that could affect their willingness to accept the risks associated with a trial.
- Apply principles and practices of regulatory science to ensure that its policy decisions reflect the best available scientific evidence and analytic techniques and that they are made in a transparent way to ensure public accountability.

Source: Institute of Medicine.
For more information, visit iom.edu.

Richard Lev
Publicis Touchpoint Solutions
"The impact of a more conservative FDA approach is that the cost of new drug approvals remains extremely high, which could hamper innovation if this trend continues."

Jay Bolling
Roska Healthcare
"There's an opportunity for pharma companies to create a positive reputation in the future by adopting a more patient-centric approach and bringing greater value to their patients."

The evolving industry and regulatory environment has become more complex with the decrease in R&D, heightened customer needs and expectations, and increased focus on the value proposition of products and comparative effectiveness research, says Stephen Webb, president, North America, at Registrat-MAPI.

"I expect there will be a continued trend focusing on product safety, risk evaluation, and mitigation strategies, CER, and early product lifecycle planning," he says. "Regulatory agencies are probably now, more than any time in the past, open to collaboration with manufacturers to perform more effective early lifecycle planning, clinical development, and risk assessment that will provide better real-world evaluation and evidence-based science."

All safety issues cannot be identified in an NDA, particularly if they are rarely seen, emphasizing the need for postmarketing surveillance and REMS, where these safety issues will be caught, says Anne Tomalin, president of i3CanReg.

"We can expect more demand for REMS, detailed investigation of class-safety issues, and more rigorous and faster safety decisions when predetermined signals are reached," she says. "We will also see more cooperation among regulatory agencies and sharing of safety data and safety decisions."

Rob Vollkommer, principal of CSC Healthcare Group, says companies need to continuously demonstrate comparative effectiveness and safety throughout a product's lifecycle in real-world conditions.

"That's a big challenge for most biopharmaceutical companies because their research processes and capabilities have been optimized to perform the pre-approval clinical trials and data analysis that is required to obtain initial regulatory approvals," he says. "As a result, there is a widespread need for these companies to adapt their research and drug development processes to make better and more proactive use of healthcare data (i.e., electronic medical records, claims, labs, etc.) that is being used to inform key decisions by all stakeholders."

He says vast repositories of healthcare and research data are being amassed by others, including academic medical centers, health systems, payers, regulators, and associations more aggressively than ever.

"These repositories will be increasingly used to better understand unmet medical needs, conduct comparative effectiveness research, monitor product safety and identify patients for clinical trials," he says. "There are several initiatives under way to link healthcare stakeholders together into research networks to expand the reach and productivity of research and surveillance."

Ms. Tomalin says the agency should con-

Rob Vollkommer

CSC Healthcare Group

"Biopharmaceutical companies, now more than ever before, need to continuously demonstrate comparative effectiveness and safety throughout a product's entire lifecycle in real-world conditions."

Jay Norman

Quintiles

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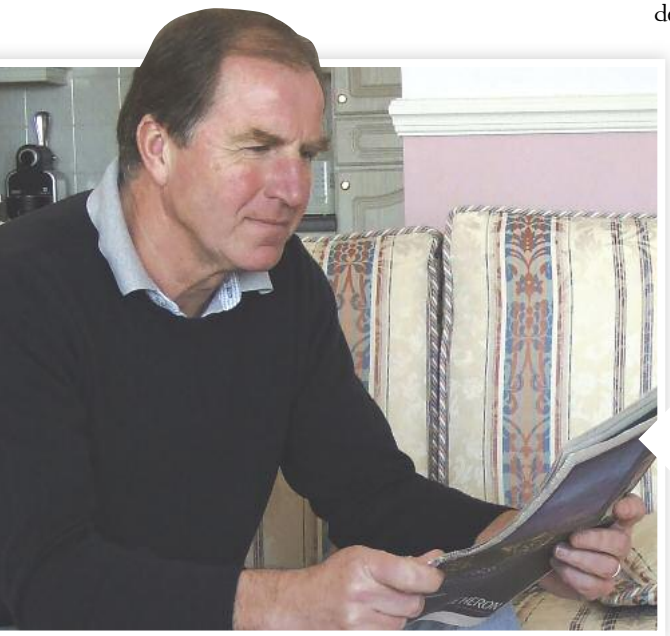
tinue to emphasize the need for REMS, the epidemiological investigation of class safety issues, and the international cooperation of regulatory agencies, particularly EMA and Japan. The agency should also consider the possibility of setting up a division separate from CDER or CBER to focus entirely on drug safety issues.

"Drug development will become more of a continuum with clinical studies focused on safety being conducted postapproval," she says. "Pharma companies need to invest in epidemiological expertise and develop ways to cooperate among themselves in investigating class issues. With transparency in the way pharma companies handle safety issues and deeper patient education on pharmaceutical safety issues and drug development, it should be possible to minimize the impact of these safety issues on the industry's reputation."



BEST PRACTICES FOR SAFETY ADVANCES

Rather than relying on regulatory direction, pharma has the opportunity to be proactive in response to increased pressures from the public and other stakeholders to improve corporate responsibility and demonstrate greater transparency in the handling of safety issues, says Jay Norman, president of the consulting group at Quintiles.

"The industry will need to be more proactive in reducing the complexity involved with developing and marketing a new drug," he says. "Although drug development methods have advanced to include more sophisticated science techniques, risk identification, and safety monitoring methodologies have fallen behind. There are significant opportunities to transform both the drug development process and risk identification and monitoring sciences, but they must all be conducted in tandem."

The industry should continue to partner with the FDA to understand the requirements for assessing the risk/benefit profile of new drug therapies and work toward an acceptable path toward approval, says Melody Brown, VP of regulatory affairs at Millennium: The Takeda Oncology Company.

"Pharma companies should continue to design studies to be able to appropriately assess the risk of new drugs as well as the benefit they provide to patients," she says

The industry must also reduce complexity and accelerate outcomes in order to succeed in the new health landscape, Mr. Norman says.

"This means greater collaboration in public-private partnerships and real multi-directional transparency at the corporate and regulatory levels," he says. "Industry must be active and aggressive in evolving the science base instead of waiting for regulators to declare how outcomes should be measured and decided. The passive approach will do nothing to improve industry's reputation or product development and marketing."

Sponsors have begun to realize that the vendor community possesses particular skill sets and often has much more breadth and depth in niche areas than sponsors themselves, says John Blakeley, executive VP of ERT.

"There is a real potential to reduce costs and increase safety with this approach," he says. "In the specific case of cardiac safety, there are some high-profile instances where drugs have been pulled from the market because of safety concerns. Had the sponsors of those drugs worked more closely with an outsourced vendor that specialized in those particular safety areas, there would have been a greater likelihood that those issues would have either been discovered or the development would have been steered in a different direction to create a drug that would not have had the same potential issues."

The FDA is likely to require greater

Stephen Webb

Registrat-MAPI

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postapproval oversight and surveillance through mechanisms such as Phase IV studies and REMS programs, and may consider limiting a product's indication to a tighter subset of patients — if applicable, says Jay Bolling, CEO and president of Roska Healthcare.

"Patient CRM programs will take on greater importance to help educate and inform patients of potential safety issues, motivate them to talk with their HCPs if they experience any AEs, and ensure they take their medications properly," he says.

Mr. Bolling says the industry should integrate patient education and CRM programs into brand labeling.

"They should promote patient education and CRM programs to physicians as an integral part of the prescription and encourage pharmacies to dispense these materials," he says.

Mr. Webb says the increased scrutiny on the FDA and industry will require companies to do a better job in product lifecycle planning and clinical development programs to conduct better safety, efficacy, and quality analyses that are more generalizable to the targeted population.

"This will also most likely include more direct-to-patient collection, analyses, and interpretation of patient reported outcome (PRO) data," he says. "Pharmaceutical, biotech, and medical-device companies are going to have to start planning for the postapproval period earlier in the product lifecycle. This includes early lifecycle planning, risk assessment, adaptive trial designs, and comparative effectiveness research." ✦

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Sound Bites From The Field

JOHN ARROWSMITH, PH.D., is Scientific Director, Thomson Reuters, which delivers critical information to leading decision makers in the financial, legal, tax and accounting, healthcare, science, and media markets. For more information, visit lifesciencesconsulting.thomsonreuters.com.

"The increase in drugs not meeting new regulatory endpoints is noticeable. In some cases the endpoints actually changed between the Phase II PoC and submission. The most common examples are seen in oncology, where the change from progression-free survival to improving overall survival has caused several Phase III submission withdrawals. It clearly signals the need for companies to seek scientific advice before Phase II and to maintain an ongoing dialogue with regulators throughout Phase III."

GIL BASHE is Executive VP, Makovsky + Company, an independent global public relations, investor relations, and branding consultancy, focused in financial services, professional services, healthcare, technology, branding, and investor relations. For more information, visit makovsky.com.

"FDA fragmentation is hampering drug approvals, and the balance between policy and science is confusing companies. For example, the pain medication abuse epidemic warrants clearer guidance to companies developing abuse deterrent opioid products. Too often advisory panels have no real-world clinical, reimbursement, and policy experience in the sectors they evaluate. The FDA will have to overhaul its approval process and modernize methods, steps it has already started to take."

NANCY BEESLEY is Executive VP, HC&B Healthcare Communications, a full-service healthcare marketing agency that services pharmaceutical, medical device, biotechnology, hospital, payer, and provider clients. For more information, visit hcbhealth.com.

"There will likely be longer times to approvals, which can mean a higher-end cost of drugs. The FDA will have no choice but to make an arduous process even longer. It can also mean that smaller companies can't bring drugs or devices to market as well as bigger conglomerates because they can't afford the long runway. So some of the smaller biotech and pharma makers won't make it or they will be acquired by larger ones. It just means more big pharma companies. Honest, open communication with a real sense of common purpose is needed between regulators and sponsors. It's amazing what can be accomplished when we realize that we are aligned to deliver the safest, best-possible products to patients."

JAMES J. DESANTI is CEO, PharmaVigilant, a SaaS company, which provides broad technologies to streamline the clinical trial process for biopharmaceutical companies. For more information, visit pharmavigilant.com.

"Trials are becoming more global in scale and thus are more difficult to keep tabs on in terms of collecting, managing, and analyzing the critical trial data. As such, the FDA and other regulatory agencies around the world, such as the EMA, are going to start looking at the trial data and regulatory submissions with a much more critical eye and expecting sponsors to provide better access and transparency to both the data and the regulatory documents.

Sponsors will most likely be asked to provide regulatory documents and trial data on demand. This will be difficult for those sponsors still running paper-based trials because their infrastructure is antiquated as a result. North American sponsors, particularly those running global trials in emerging regions, are getting hit with a lot of infractions because they're not able to supply the regulatory agencies with the data and documentation on demand."

RICHARD GLIKLICH, M.D., is President and CEO, Outcome Sciences Inc., a provider of patient registries, technologies for evaluating real-world outcomes, and quality reporting services for healthcare providers. For more information, visit outcome.com.

"The FDA is already reacting with increased scrutiny of the safety data in new drug applications by requesting additional studies, implementing REMS programs, etc. and by changing the avenues by which it can monitor drug safety, such as the Sentinel Initiative, post-marketing commitments, etc. These efforts will grow in number and sophistication. Pharma companies need to also respond with increasingly robust postapproval data collection programs and increasing sophistication with respect to how they will deal with potential signal from the efforts of others in analyzing available data, including FDA's Sentinel program. Industry brings tremendous methodological strengths, therapeutic knowledge, and resources that can only benefit all parties in devising a better safety net."

HARRIS KAPLAN is CEO, Healogix, a provider of marketing research and consulting for the pharma and biotech industries. For more information, visit healogix.com.

"Regulators are limited by their mission. The FDA's primary focus is efficacy and safety, and the agency therefore wants to know if a drug is effective and if there are any adverse effects. Unless the drug is first-in-class or a compelling breakthrough, expect the agency to require larger pivotal trials and more head-to-head data. We will see an increase in the number of drugs delayed or approved subject to a REMS program. This trend will also impede new product adoption. Unless a new product is a breakthrough, physicians are likely to be much more conservative and slower to adopt than in the past."

TIM MOHN is Industry Principal, Sparta Systems Inc., a provider of enterprise quality and compliance management solutions. For more information, visit spartasystems.com.

"The FDA's primary concern is the impact of pharma products to human health, which should be the industry's concern as well. Regardless of how much data is captured by companies, the most important thing is for the industry to completely, accurately, and transparently share this information to regulatory bodies for appropriate oversight."

SYED MOINUDDIN is Account Director, MedThink Communications, a healthcare agency that provides full-service offerings with a focus on scientific and promotional communications. For more information, visit medthink.com.

"The industry should move away from me-too products and focus on new drug classes that truly

meet an unmet need or advance current treatment options. Companies should spend more resources and time on strategic and scenario planning to better understand what should be developed and what should not."

SHEILA ROCCHIO is VP, Marketing, PHT Corp., a provider of ePRO solutions used in clinical trials around. For more information, visit phtcorp.com.

"Industry and regulators can work together to focus more on patient experiences and improved HRQOL vs. just efficacy and adverse event incidence. The agency should partner with industry to help companies detect harmful side effects earlier and provide options that include collecting more PRO data across trials and doing more safety monitoring throughout the trial using ePRO systems."

JOHN ROSS is Chief Operating Officer, SDI, which is a healthcare analytics organization that provides innovation services that help the healthcare industry solve a wide range of business challenges. For more information, visit sdihealth.com.

"Major hurdles, including cost, time, and ethical issues, make it difficult to measure comparative effectiveness of treatment plans. Regulators and biopharmaceutical companies will take advantage of available tools to track outcomes. Secondary data sets, such as longitudinal patient-level data, allow us to study patient treatment paths and experiences over time to determine whether they resulted in positive or negative outcomes. Studying practitioner and patient behavior as it unfolds in the current healthcare setting — the way healthcare is really practiced — leads to more relevant interventions, education, and recommendations."

STEPHEN M. SIMES is Vice Chairman, President, and CEO, BioSante Pharmaceuticals, a specialty pharmaceutical company focused on developing products for female sexual health and oncology. For more information, visit biosantepharma.com.

"The FDA should help the public, including Congress, to understand what an FDA approval means. There is general lack of understanding of the phrase safe and effective. There must be more public discussion of the positive outcomes of FDA approved products, as well as a commitment by the industry to bring better products to market. The major issue is that in the cynical environment in which we live, any program will be considered self-serving."