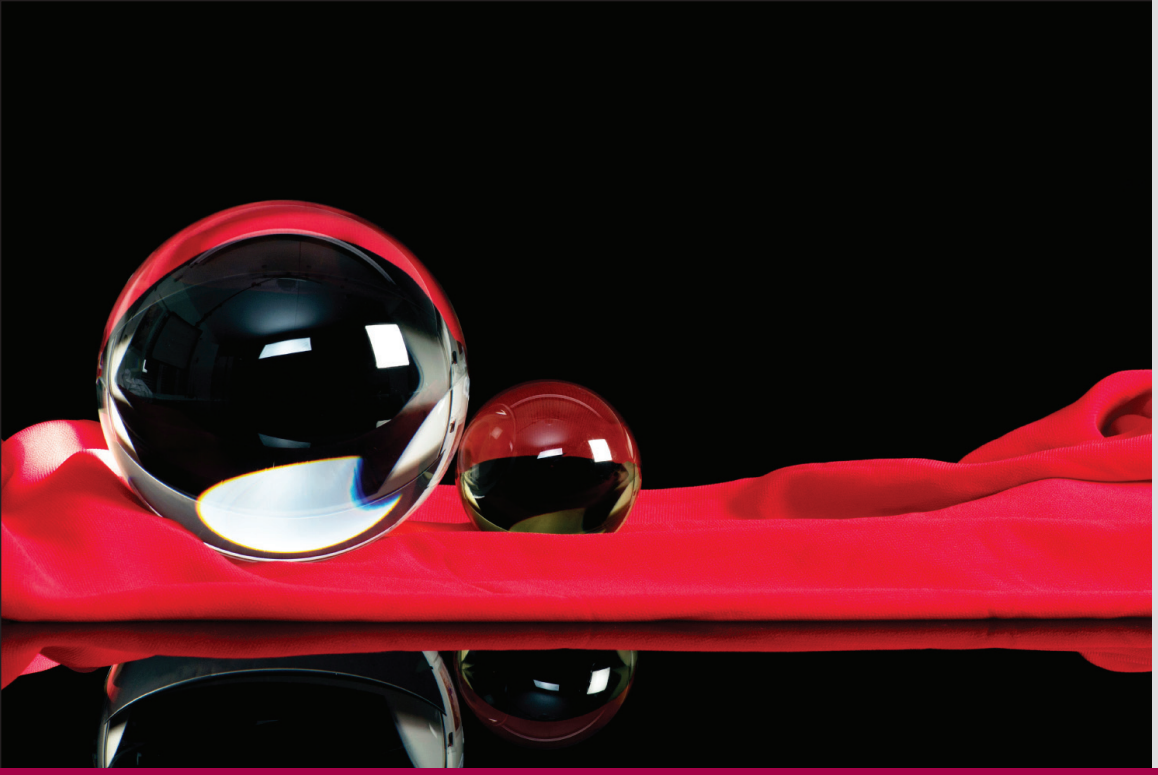

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REGULATORY FOCUS

Looking to the Future in Regulatory Affairs

By Oliver Cox and Siegfried Schmitt, PhD

Predicting the future is, of course, like gazing into a crystal ball; therefore, the reader is warned that the following is based in part on indicators from industry and the regulators, but mostly on personal considerations and expectations, and discussions with peers in the regulatory community.

There are many strands to consider when looking to the future in regulatory affairs. The first strand is the regulations and how these are likely to be impacted by a globalized regulatory healthcare authority and interpretation by various stakeholders. The second strand is the world's response to public healthcare challenges in an increasingly interconnected environment. With limited investment incentives, these public healthcare challenges may take a back seat to other research and development (R&D) priorities across the pharmaceutical industry. And lastly, as the pharmaceutical market searches for that next blockbuster and as R&D pushes scientific frontiers, the regulations will have to change to keep pace—not only with more-complex therapies but also with the drive to develop individualized medicines.

Global Standardization

Currently, global regulatory submissions (dossiers) and strategic development plans must be tailored to accommodate a range of specific local requirements for data and regulatory obligations in their target markets. A typical example of these differences would be the data requirements for nonclinical evidence for a biosimilar product approval in India compared with those in the EU. In India, extensive *in vivo* work is required in the absence of a relevant species,[1] whereas in the EU, the Committee for Medicinal Products for Human Use (CHMP) queries the need for any studies in nonrelevant species.[2] Although healthcare regulations are prone to political interference, global harmonization is continuing through

several channels and bodies, such as the International Conference on Harmonisation (ICH).[3]

The R&D woes of the pharmaceutical industry are well known[4] and include increased costs, fewer innovations and a looming patent cliff. Industry's task is made more difficult by the global variations in existing regulations. Regulators are reconsidering their roles as guardians of drug safety, quality and efficacy and supporters of the drug supply. Adequate drug supply is dependent upon the viability of the healthcare industry, which, in turn, will be helped by sustained global initiatives to harmonize regulations for medicinal products, thereby reducing the burden of costly local regulations and data requirements.

Many regulatory professionals are familiar with ICH and its interactions with both regulators and industry. International standards are commonplace not just in the pharmaceutical sector but in a range of industries. The international guidances produced by ICH provide a useful resource for aligning the regulatory requirements for drug products. ICH's 20th anniversary publication references an African proverb: "If you want to go fast, go alone. If you want to go far, go together."[5] In an increasingly globalized and networked pharmaceutical industry, the message in this proverb rings truer than ever. Going forward, the ICH mission may need to be widened to embrace increasingly sophisticated regulations in emerging economies. For ICH's 30th anniversary publication, the tagline "Harmonization for consistency, efficiency and excellence" may well be apt. But even if regulations become better harmonized, regulatory departments still will have to deal with a plethora of agencies around the world.

Super Regulatory Agency

In an apolitical world, we could perhaps aspire to one global regulatory agency or "super regulator." Regulatory expertise could be centralized and shared globally. This model already works to some extent in Europe through the European Medicines Agency (EMA), so why should it not work on a global scale? Following are some advantages of consolidation.

The first is budgetary. Regulatory agencies have not been spared from the effects of the global economic downturn. Even at some of the best-funded agencies, resources are stretched. Many find it difficult to meet their own targets for processing regulatory submissions and responding to industry in a timely manner. A single "super regulator" would be funded and free from the local budget constraints and fluctuations.

Furthermore, agencies find it increasingly difficult to keep pace with the volume and the technical content of novel submissions. With shared global resources, such bottlenecks could be removed. Also, unnecessary duplication of effort could be avoided. Currently, when a sponsor submits an application in various jurisdictions, the core dossier content must be reviewed and interpreted by each regulatory agency. A global agency could pool regulatory talent and expertise. A global dossier review would be handled consistently and efficiently by one set of assessors based on one set of data requirements established according to scientific best practice and defined and implemented by this single regulatory entity.

The ultimate benefactor would be the patient—more drugs of more consistent quality at lower cost, faster and available everywhere.

Priority Medicines

In 2004, the World Health Organization (WHO) was commissioned by the Netherlands' Ministry of Health to produce a report on the topic of "Priority Medicines for Europe and the World."[6] The report, updated in 2013, acknowledged that without certain incentives, pharmaceutical companies cannot be expected to prioritize or even address specific areas where treatments are lacking, inadequate or in danger of becoming ineffective (e.g., antimicrobial resistance).

We live in an increasingly overcrowded and interconnected world where public health challenges easily spread across borders and need to be addressed in a concerted manner. Initiatives are required to bring together the health authorities of the global community to address prioritization of research into public health issues and to tackle chronic industry underinvestment in medications to address these challenges. Encouraging the pharmaceutical industry to address some or all of these healthcare gaps, as identified by

WHO, will require global policy and regulatory initiatives. Given the long timelines to identify and develop new and novel treatments, this challenge should be acted upon sooner rather than later.

The widely differing approaches to establishing reimbursement for drugs pose an additional hurdle to the development of priority medicines. Regulatory professionals will have to interact with payers in addition to dealing with healthcare authorities, as it is ultimately the payers who decide whether an approved medicine will be profitable.

Pharmaceutical Frontiers

As medical technology advances and knowledge gleaned from patient data resolution and analysis increases exponentially, regulations should be increasingly flexible to keep pace.

Individualizing drug selection and drug dose to the patient is one example of a technological advance that challenges the current regulations. These personalized medicines offer new and more accurately targeted treatment opportunities to benefit patients and potentially reduce medical errors and adverse reactions. Personalized medicines already are on the market; in the EU, at least 23 products for which predictive biomarkers are measured before patient exposure have been approved by the European Commission.[7]

As analysis of a patient's data becomes faster and more accurate, physicians will be able to prescribe medicines tailored not just to small sub-populations but also to specific individuals. However, personalized medicines pose unique challenges to both prescribers and regulators. Key issues for regulation of personalized medicines include adjusting clinical trial design, providing regulator-led guidance and scientific advice and the form this advice and guidance may take. Other issues include labeling, the need to re-think approaches to pre- and postmarketing phases of development and how the reimbursement system might operate.[8]

Apart from personalized medicines, a range of other new product types including advanced therapy medicinal products, antibody drug conjugates (with engineered sites for conjugation) and BITES (Bi-specific T-cell Engager) and DARTS (Dual-Affinity Re-Targeting)[9] are pushing the limits of regulatory expertise within pharmaceutical organizations and agencies.

Conclusion

Although there is a need for more fully harmonized regulations and greater interoperability between regulatory and healthcare agencies, and a current effort to achieve these goals, there likely always will be differences in the regulations and in their interpretation. We are still a long way away from a single, multinational (if not global) regulatory agency that would allow the filing of a single global dossier. On the other hand, there are trends toward a common approach as exemplified by the Common Technical Document (CTD). For now, regulatory departments must continue to deal with a wide variety of regulations and regulatory bodies.

One thing that is changing in the regulatory arena is the amount of liaison and interaction with other interested parties, such as healthcare providers and, ultimately, payers for the purpose of reimbursement. Thus the regulatory professional becomes more of an enabler, go-between and mediator, which is a step away from the traditional role as custodian of submissions and authorizations.

The other key change that we foresee involves becoming familiar with new and challenging technologies, such as personalized medicines. There are only a few regulations and guidances available, requiring regulatory professionals to draw on their expertise to come up with inventive and innovative solutions for gaining both marketing approval and eligibility for reimbursement.

For all these reasons, the future of the regulatory profession is one full of opportunities, challenges and variety.

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