

Commentary

The Globetrotting Regulator

Peter J. Pitts

is a former FDA Associate Commissioner, is President of the Center for Medicine in the Public Interest.

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I AM PUTTING IN a lot of miles on behalf of international regulatory fraternity.

Like Johnny Cash said, “I’ve been everywhere” — or at least it seems that way. Recently I’ve visited with government health officials in China (both PRC and ROC), the Philippines, Malaysia, Egypt, Algeria, Saudi Arabia, Jordan, the United Arab Emirates, Kuwait, Russia, Brazil, Colombia, South Africa, Indonesia, Kenya, and many other points in-between. And the only thing that’s grown more than my frequent flyer miles is my respect and admiration for those over-worked and under-appreciated civil servants toiling on the front lines of medicines regulation.

It’s a global fraternity of dedicated (and generally under-paid) healthcare and health policy professionals devoted to ensuring timely access to innovative medicines and quality generics drugs.

But, just as in similar Western agencies (USFDA, EMA, Health Canada, etc.), “doing the right thing” is often a battle of evolving regulatory science, tight resources, competing priorities ... and politics.

There are many languages, priorities, pressures, and impediments (social, political, cultural) to consider, but one thing everyone agrees on is that quality counts. But what does “quality” mean — and does it mean the same thing from nation to nation, product to product, and for both innovator and generic medicines? The good news is there’s general agreement that lower levels of quality for lower cost items aren’t acceptable. But the bad news is that there are gaps and asymmetries in how “quality” is both defined (through the licensing process) and maintained (via pharmacovigilance practices).

Can there be a floor and a ceiling for global drug safety and quality? Even as we embrace differential pricing, should we allow some countries to have lower standards than others “based on local situations?” Can one

man’s ceiling be another man’s floor? Can a substandard medicine ever be considered “safe and effective?”

Aristotle said, “Quality is not an act, it is a habit.” Habits are learned and improve with iterative learning and experience. And nowhere is that more evidently manifested than through the many and variable methodologies for generic medicines licensing and pharmacovigilance practices. From paper-only certification of bioequivalence testing and questionable API and excipient sourcing, the safety, effectiveness, and quality of some products are, to be generous, questionable.

Is this the fault of regulators; of unscrupulous purveyors of knowingly substandard products; of short-sighted, overly aggressive pricing and reimbursement authorities? It depends. While there are many different and important avenues of investigation, the most urgent are the asymmetries of how quality is defined, measured, and maintained. That which gets measured, gets done.

National 21st century pharmacovigilance practices must take into consideration the realities of funding, staff levels, training programs, and existing regulatory authority. Increasing regulatory budgets is problematic. Should licensing agencies consider user fees for post-market bioequivalence testing of critical dose and narrow therapeutic index drugs? That’s a contentious proposition—but agency funding is an often over-looked 800-pound gorilla in the room and deserves to be seriously discussed and openly debated.

Another uneven issue is that of transparency. While regulatory standards are undeniably an issue of domestic sovereignty, shouldn’t there be transparency as to how any given nation defines quality? “Approved” means one thing in the context of the MHRA, the USFDA, and Health Canada (to choose only a few “gold standard” examples), but how can we measure the regulatory competencies of other national systems? Is that the responsibility of the historically opaque WHO? What about regional arbiters? Should there be “reference regulatory systems” as there are reference nations for pricing decisions? And how would this impact the concept of regulatory reciprocity?

And then there’s the danger of regulatory imperialism. Expecting other nations with less experience and

Correspondence:

Peter Pitts, Center for Medicine in the Public Interest, US.
Email: ppitts@cmpi.org

resources to “harmonize” with the USFDA or the EMA isn’t the right approach. Rather we should seek regulatory convergence, because that gives us a pathway to improvement – with the first step being the identification of specific process asymmetries that can be addressed and corrected. Just as every nation has its own unique culture and cuisine, so too must it design its own regulatory philosophy and structure. It’s not about replicating the USFDA or the EMA – it’s about converging towards best practices.

Two of the most important health advances of the past 200 years are public sanitation and a clean water supply. Those achievements helped to control as many public health scourges as medical interventions helped eradicate. In our globalized healthcare environment of SARS, Avian Flu, and Ebola, it’s important to remember that a rising tide floats all boats.

Working together to raise the regulatory performance of all nations will help all nations create sound foundations to address a multitude of regulatory dilemmas such as the manufacturing of biosimilars, the control of API and excipient quality, pharmacovigilance and, yes, even counterfeiting.

Whether it’s in Cairo, or Amman, Riyadh, Brasilia, Kuala Lumpur, Dubai, Beijing, Bogota, Pretoria, Nairobi, or White Oak – a regulator’s work is never done. Global regulatory fraternity is essential to success. It’s about building capacity through collaboration.

Difficult? Surely. But, as Winston Churchill reminds us, “A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.”

And at the top of the list is quality.

Without quality, safety and effectiveness are non-starters. Without quality, healthcare spending is not just wasteful – but harmful. Without quality it’s all about price without any consideration for value. Without quality, regulation is a sham.

Consider the Middle East and North Africa. In April 2015 I spent three fascinating days in Sharm El Sheikh, Egypt at the Second Arab Conference on Food & Drugs.

Delegates from the Levant to Morocco had a lot to say and share. The fundamental take-away was that the Arab world is serious about coordinating their efforts in healthcare in general and in regulatory affairs specifically. “Convergence” and “harmonization” were the two key words of the event.

(The Middle East/North Africa Region – MENA – consists of 22 nations – but just 2% of global pharmaceutical sales.)

I was honored to present a plenary address on “Advancing Medicines Quality via New Strategies in Bioequivalence Regulations, Pharmacovigilance Practices, and the Identification and Management of Substandard

Pharmaceutical Events,” as well as chair the event’s panel on pharmacovigilance, sharing the panel with governmental thought leaders such as Dr. Amina Tebba (Morocco), Dr. Amr Saad (Egypt), Dr. Emad Munsour (Qatar), and leading global policy experts Dr. Hisham Aljadhey (King Saud University), and Michael Deats (WHO). I also participated on a panel discussing the urgency of IP, as well as another on biosimilars – specifically the vexing debate over nomenclature, physician notification, and therapeutic substitution.

With healthcare policy (as with life in general) – wherever you go, there you are.

Much of the conversation centered on controlling costs – specifically pharmaceutical costs – without the appropriate balance of time spent on the pennywise/pound foolish consequences of many of these policies. The IP panel tried to add balance to that debate by strongly presenting facts and figures on the value of innovation.

Dr. Rasha Ziada (Egyptian Ministry of Health) made the important point that if a pricing authority doesn’t take outcomes into consideration, it will lead to overall price distortions. Amen. And Dr. Ola Ghaleb (Ministry of Health, United Arab Emirates), spoke about the UAE’s strategy of performance-based risk-sharing arrangements – but also how politics can derail any decision-making process. Her honesty was refreshing. Net/Net – Outcomes is now capitalized and bolded in the international lexicon of healthcare policy.

While many of the presenters discussed the value of sharing pharmacoeconomic data across borders, there was not a counterbalancing discussion of the value of sharing clinical data for approvals and outcomes-based decision-making processes. But there was certainly an effort (both on many of the panels as well as during the breaks and after hours) to stress the urgency of this agenda. The good news is that many speakers (sometimes in passing and other times passionately) made the point that it mustn’t just be about “getting the lowest price,” but also appropriately pricing the most clinically effective treatments. Bravo.

Delegates agreed the conference was useful – but that action is required. In short – talk is cheap. My feeling (speaking privately with senior government officials from many of these nations) is that there is serious momentum for change (and even reinvention). But only time will tell.

As Deming said, “Change is not required. Survival is not mandatory.”

At the closing plenary session came “The Sharm El Sheikh Declaration” that called for:

- Strengthening drug post-marketing regulation through the establishment and

activation of pharmacovigilance centers, while working on workforce qualifying and training.

- Urging Arab countries to invest in training inspectors of pharmaceutical factories to raise the quality of the inspection process and ensuring the application of current good manufacturing practice (cGMP).
- Urging Arab countries to authorize bioequivalence studies and ensuring that they conform to the technical requirements of Good Clinical Practice (GCP) through regular inspection visits.
- Urging international drugs regulatory authorities in the Arab world to activate drug post-marketing monitoring programs through establishing pharmacovigilance centers and equip them with trained pharmacists and doctors.

(Pleased and proud to say that many of these recommendations came from the conference panel I chaired on pharmacovigilance.)

In May 2015 my regulatory travels took me to Asia. In Jakarta I met with senior hospitalists to discuss the impact of Indonesia's new legislation (designed to provide universal access to healthcare) and its impact on both the quality of medicines available and a physicians right to choose both therapy and brand. Senior healthcare leaders are concerned that, by insisting the lowest priced product be used, suboptimal outcomes will increase for those patients unable to access private healthcare. They recognize that a system that provides broader access to low quality care is not a victory. Bioequivalent does not equal identical. Biosimilar does not equal identical. Quality should not be negotiable. The stakes are high.

Next up was the Javanese capital of Yogyakarta for a symposium on pharmacovigilance held by Ahmad Dahlan University. A senior Ministry of Health official shared the fact that, for a nation of 250+ million, there are but 10 people focused on pharmacovigilance. Talk about

the Java Jive! She spoke of the need to develop better risk-based assessment protocols and more aggressive information sharing with other nations in the region (adverse events, bioequivalence test results, API and excipient quality inspections, etc.). Quality is a team effort.

Meetings in Hanoi and Ho Chi Minh City focused on quality with a more specific focus on the need for more regular bioequivalence testing using patients under treatment (as opposed to healthy volunteers) in order to better understand the uptick in Substandard Pharmaceutical Events (SPEs). SPEs occur when a product does not perform as expected—perhaps because of API or excipient issues. SPEs can arise because of an issue related to therapeutic interchangeability. In Vietnam they are beginning to understand and appreciate that Small is the new Big. The need to focus on individual patient outcomes and on long-term care rather than short-term cost.

The last stop on my Asian tour was Taipei, where I had the opportunity to speak to a colloquium of oncologists. Their fear and frustration was similarly directed towards a government healthcare program that mandates the use of lowest cost products. Nowhere does this cause greater angst and anger than with healthcare professionals treating patients with cancer. The unintended therapeutic consequences caused by short-term, price-driven government policies on quality and clinical outcomes cannot be underestimated. Those on the front lines (physicians and pharmacists) understand this – as do patients. Recognizing there is a problem is the first step towards solving it.

What have I learned? Many things, but most importantly that medicines regulation – regardless of language or location – isn't just a job, it's a personal public health mission.

And so home again, home again, jiggy jig to an American healthcare system debating many of the same issues – bioequivalence, biosimilarity, interchangeability, physician notification, substandard pharmaceutical events, patient/physician/pharmacist education, the price/value equation, short-term savings vs. long-term patient outcomes.

It's a small world after all.