Megatrends in Clinical Safety and Pharmacovigilance

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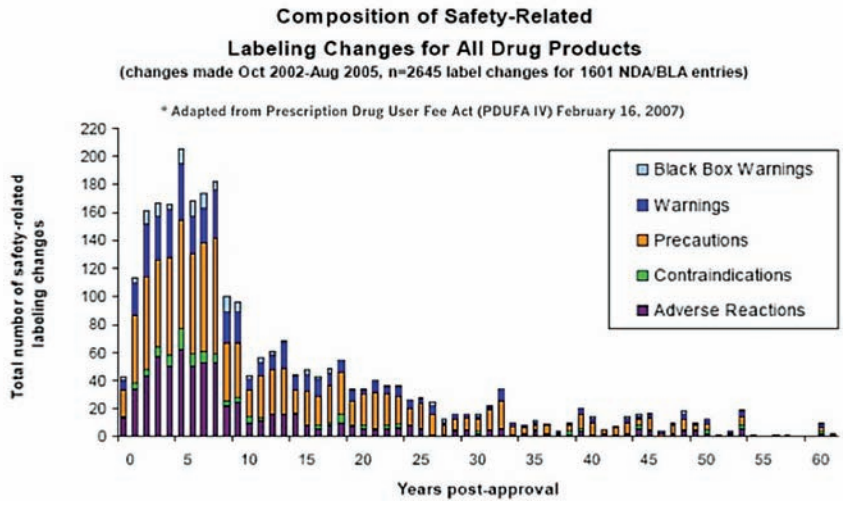
If ever there was a "golden age" of stability in the world of clinical drug safety and pharmacovigilance (PV), that age is now ending! Drug safety is now becoming much more risk averse, globalized and proactive. The parties involved have reached the realization that the collection of safety data is only the beginning: signal analysis, risk evaluation and risk minimization to better protect the public health are now understood to be the real goals of drug safety and PV.

It has become clear that the idea that when a drug is approved for marketing it is deemed to be "safe and effective" is far too simplistic; a drug's safety profile is barely known at the time of launch. Safety data is captured during the entire life span of the drug. FDA reviewed safety labeling changes done from 2002-2005 and found that new warnings (including black boxes), precautions, contraindications and adverse reactions were added as long as 60 years after first approval! See the chart below. The lesson here is that eternal vigilance is the foundation of drug safety and risk minimization.



Much work has been started in the last decade to expand the usefulness of PV. Several "megatrends" are now underway and are briefly summarized below:

WE REALLY NEED LOTS OF DATA!

The spontaneous reporting system of adverse events (AEs) was, and to a large degree, still is the mainstay of collecting safety data on marketed drugs. However this system, relying on the voluntary reporting of AEs by health care professionals and the public works slowly and haphazardly, especially for older drugs. Many efforts now in the US (FDA's Mini-Sentinel, the Observational Medical Outcomes Partnership (OMOP) and others), in Europe (the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), Vigibase and others), and elsewhere are creating and linking large (hundreds of millions of lives) databases that will allow prospective and retrospective signal development and evaluation. This will change the way drug safety is done though, as with all software, version 1.0 will not be too useful but 10 or 15 years down the road, version 3.5 will likely be the game changer.

BUT WE HAVE TOO MUCH DATA!

The downside of having enormous amounts of data is that we do not know what data is reliable, preliminary or wrong. In the spirit of openness and full disclosure, early signals are being posted on websites in the US, EU and elsewhere often with disclaimers saying that it is not known if this signal will ultimately turn out to be real or a false alarm. This puts patients and practitioners in a bind (e.g. do statins really cause memory problems in the elderly?). It is hard to know what is real and actionable amid the mass of data and noise.

WE ARE HARMONIZING BUT EVERYONE IS HARMONIZING DIFFERENTLY.

Following the work of the International Conference on Harmonisation (ICH), which began in 1989, many of the regulatory requirements in drug safety (both for the clinical trial and post – marketing settings) were harmonized. These agreements are now starting to unravel. Led by efforts in the EU, the accepted standards for expedited reporting ("15 day reports") and Periodic Safety Update Reports (PSURs) are now changing significantly. The EU version of the PSUR is now changing into a Periodic Benefit/ Risk Evaluation Report which will no longer be a pure safety document but a effectiveness/ efficacy/risk evaluation analysis. Although there is much logic in this approach, which is saying that "one size does not fit all", the new requirements will produce additional work for companies and regulators.

DRUG SAFETY (LIKE EVERYTHING ELSE) IS GLOBALIZING.

ICH comprised the regulators and industry associations of the US, EU and Japan with several other countries observing but not fully participating. Thanks to the spread of the internet, social media, smart phones, easy air travel, webinars, the English language and the outreach of the Uppsala Monitoring Centre, drug safety is now being done in many more countries around the world. In general, it is good to have many sets of eyes looking at data especially when there are billions or trillions of datapoints. However, there is now enormous duplication of effort on the part of the companies and the regulators. Whether this will lead to better pharmacovigilance, earlier discovery of drug toxicity and the rapid minimization of risk remains to be seen.

THE WORLD IS BECOMING RISK AVERSE.

The public and the health agencies are becoming far more risk averse following multiple drug withdrawals (Baycol, Vioxx etc.), accidental or intentional contamination of animal and human food (melamine, heparin and chondroitin) and the rise in drug counterfeiting and theft. As the world globalizes, as supply chains stretch thousands of miles, as more and more drugs are being exported and imported and as drugs are now becoming commodities (the decision to buy

is made purely on the basis of price), there is a feeling that we are losing control. Health agencies are acting in a more protective and conservative manner, taking more and more of the benefit/risk judgments away from the patient and practitioner. Many techniques are now being developed and studied in the PV world to pick up toxicity earlier and with fewer patients exposed. Maybe this will work and maybe it won't.

REGULATORY ENFORCEMENT IS BECOMING STRONGER.

Health agencies are visibly becoming tougher and more vocal in regard to industry (and academia) adhering to all regulatory and best practice requirements. We are seeing more warning letters, more health authority PV inspections, and use by the FDA of the Park Doctrine which states that a responsible corporate official can be held liable for a misdemeanor and possible subsequent felony without proof that the corporate official acted with intent or even negligence, and even if such corporate official did not have any actual knowledge of, or participation in, the specific offense - http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176738.htm. In France, current crises over the safety of the diabetes drug Mediator and a silicon breast implant are leading to changes in the handling of drug safety in France and elsewhere in Europe. India and China are also revamping their drug safety systems.

SOCIAL MEDIA AND OTHER MODERN FORMS OF COMMUNICATION WILL CHANGE DRUG SAFETY BUT WE DON'T YET KNOW HOW.

Many more individuals and groups are now paying attention to medications and drug safety. The easing of access to data (FDA, Health Canada, the EMA, the MHRA (UK) and others have their safety data available on line) and the creation of multiple interest groups using social media have created a new and lightening fast dynamic in drug safety. FDA, Health Canada, AFSSAPS (France) and other health agencies now have Facebook pages and FDA and others are also tweeting.

A safety problem or issue (whether correct or not, whether fully understood and investigated or not) can go viral in minutes. Crisis management is now the routine in drug safety.

Nobody doubts the good intentions of these efforts which are increasing costs and using more resources both in government and industry. Whether they will improve drug safety and public health remains to be seen.

What can one do? Stay informed, keep up with new requirements and best practices, network with global colleagues in the drug safety world and, if you have the time and energy, get involved in the changes being made in drug safety. ●