The Pharmaceutical Year That Was, 2013

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Last year ended with Europe wallowing in its Euro-crisis, the United States (US) Congress wrangling over its budget (eventually unresolved, leading to a legislative ‘sequestration’), the promise of a Pharmacovigilance Risk Assessment Committee (PRAC) within the European Medicines Agency (EMA), a European initiative towards publication of clinical trials data, and an unremarkable number of truly new product approvals on both sides of the Atlantic [1]. Much of that carried on this year, while the economic situation continues to stagger and stutter.

As mentioned last year, 2013 has seen the PRAC getting into its stride at the EMA [2]. The PRAC advises the Committee for Medicinal Products for Human Use (CHMP), the Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh), the EMA secretariat and the European Commission on all aspects of pharmacovigilance and risk management. The PRAC is comprised of: a Chairperson, a member (or alternate) from every member state, six members ex officio and technically qualified from the European Commission (EC), and another two EC members (with alternates) for public calls of interest for healthcare professionals and patients. They all have 3 year terms, renewed easily the first time, and after competition thereafter. The PRAC aims to review all Product Licence Applications (PLAs) from the point of view of proposed pharmacovigilance and risk management

activities. These are all Module 1 components of the electronic Clinical Trials Dossier (eCTD), and thus are restricted to the European marketplaces. In addition, the PRAC will be reviewing Periodic Safety Update Reports (PSURs; these now require formal risk-benefit assessments), Post-Assessment Safety Studies (PASS), as well as doing general signal detection and making ‘for cause’ pharmacovigilance inspection decisions. For licensed products, these responsibilities differ little between centralised process and other approvals. Lastly, the PRAC is empowered to take urgent action on its own initiative in cases of serious threats to the public health. Flexing its muscles, in January 2013 PRAC recommended the withdrawal of three products from the entire EU, and most recently (September 2013) is recommending against short-acting beta-agonists in pregnancy [3]. A slang has developed in the United Kingdom: purity, efficacy and safety come first, and then the National Institute for Health and Care Excellence (NICE) has become known as a ‘fourth hurdle’. The PRAC might yet become known as the fifth hurdle.

A new distraction this year is that the US Food and Drug Administration (FDA) doesn’t quite know whether it can regulate ‘electronic cigarettes’ [4]. In ordinary parlance, these breath-actuated inhalational devices deliver vaporized nicotine, and are shaped like a cigarette. The amusing angle of this regulatory uncertainty is that the FDA is, however, now attempting to regulate tobacco itself. The Family Smoking Prevention and Tobacco Control Act (2009) gave the FDA the authority to regulate products containing tobacco. A regulatory pathway for tobacco products has been contrived, based upon the notion of “substantial equivalence”. On this basis, there have been two new product approvals and at least four rejections [5]. The two approvals so far (“Newport Non-menthol Gold Box 100s” and “Newport Non-menthol Gold Box”) had

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different characteristics than forerunner products but were reckoned not to raise “different questions of public health” [5]. In comparison to the usual criteria for the approval of new drugs, this colander of political framework and quasi-scientific logic can only support arbitrary decision-making. Perhaps some politician, somewhere in the US, will recognize this for the sham regulation, bureaucratic bonanza, and waste of public money that it is.

At the time of writing (early October), a major scandal is unfolding in China. A large European pharmaceutical company has basically been accused of corruption (i.e., bribery). It appears that similar charges will also be brought against other pharmaceutical companies [6]. The issue, as promulgated, appears to be whether funding for physicians to attend conferences is legal, and whether such payments (involving some travel agents) was excessive, possibly resulting in personal gain by those who might prescribe the Company’s drugs. Currently, the only information is the interpretations in the newspapers, where, unsurprisingly, a sense of proportion seems to be lacking. No real harm to patients has been alleged (such as dispensing counterfeit or adulterated drugs, serious adverse events, or failing to report the same; all of which have occurred in previous scandals). Moreover, whatever did happen seems to be well outside of the Companies’ own operating procedures, possibly suggesting that there were some rogue employees. Some of those employees are now under house arrest and massive fines for their employer(s) are in prospect. Secondary prosecutions are also threatened in *prima facie* uninvolved countries (such as the US and UK) under their own anti-corruption laws. If pharmaceutical companies are to be the new ‘soft targets’ or ‘cash cows’ for governments, based upon uncontested legal challenge, then those governments will quickly learn that the resources that are available for expropriation are far smaller than have been reaped from the banks and the oil companies in recent years. There must also be pharmaceutical company executives thinking that if the operation cannot be controlled in foreign countries, then perhaps it should not be attempted there at all.

The capability of regulatory authorities to withhold product approvals, rather than allow conditional approvals (a much-vaunted, progressive approach to modern drug regulation), seems to continue. This year has seen no better an example than the rejection of sugammadex by the FDA. This is an highly specialised product used for the reversal of neuromuscular blockade in the operating room. The FDA cancelled the advisory committee meeting, and refused New Drug Application (NDA) approval, because it needed more time to assess a completed hypersensitivity study [7]. There can be no more highly monitored clinical situation than the operating room. Surely there could be no better clinical scenario for a highly restricted conditional approval?

The 2012 list of drug and biologic approvals at the FDA appeared in early 2013 [8]. There are 103 products on the list. Many are generics, alternative formulations of previously approved drugs, or combinations of previously approved drugs. Arguably, about 24–26 products are truly innovative, which does not represent much change from 2011. Generalizing these data across the whole FDA is wrong because of the differences in divisional workloads and working practices [9]. The various regulatory routes, and multiple-stage processes (e.g., centralised approval followed by national licences) prevents a direct comparison with drug approvals in Europe for the calendar year.

Another current concern is the publication of clinical trials data [10, 11]. During 2013, the EMA has made good progress in this direction [12]. The registration of clinical trials has become compulsory on both sides of the Atlantic [in spite of the US regulations preventing publication of the existence of an Investigational New Drug (IND), except to a participating patient] [13]. The European regulators are intent on taking this further, to include publishing the clinical trials data themselves. In broad terms, the potential benefits are: (1) preventing redundant conduct of replicate negative studies, (2) making all data on approved products available to prescribers, and (3) providing substantial databases for third party meta-analysis. The counter arguments are: (1) while one may debate who actually owns the data, it is clear that the EMA doesn’t, and has no right to give it away, (2) this is a large potential gift to parties in jurisdictions that simply don’t respect international copyright and patent laws, (3) particularly in the case of rare diseases, a potential threat to patient confidentiality, and (4) plaintiffs’ lawyers, by taking snapshots or ‘soundbites’ (i.e., small amounts of data taken out of the larger context), will be able to contrive yet more lawsuits that lack a scientific basis. The last is, admittedly, not a new activity [14]. Overall, the need seems to be more urgent for licensed products than for Investigational Medicinal Products (IMPs) because the large majority of the latter will never be prescribed. The proposals will clearly (and appropriately) not lift the restriction on product sponsors from making statements that are outside approved labelling. However, the large risk is that third parties can freely partake of the hard-won data and then publish whatever they like about any small fraction of it. These third parties might not have the best of scientific motives, such as competitors’ marketing departments, activists, and journalists. Lastly, this seems to be an issue that politicians and bureaucrats can least well deal with: it requires proportionate action, balancing the interests of all concerned stakeholders, and not least, respecting the interests of the patient. While one can empathise with the potential benefits, if the result is a chilling effect on clinical research, then we shall all have lost, again including patients.

A useful service of the US FDA is to publish drug shortage details and supplier contact information [15]. The current list (October 2013) includes 114 products; while a large number are small volume injectables, these include such unique products as aminocaproic acid, desmopressin, and epinephrine (adrenaline). Occasionally, the reasons for these shortages are given (e.g., shortage of a natural product starting material). However, in most cases, there is no specific reason given, and economic unattractiveness must be suspected. Acute medicine, anaesthesia, intensive care, and other specialised services beware.

So what might 2014 bring? On the regulatory front, the EMA has issued for comment three new draft guidances on biosimilars [16]. Things seem to be going fairly well in Europe as far as biosimilars are concerned, and the draft guidances do not seem to contain many radical changes. But one wonders what undercurrents have driven the re-opening of consideration of the basics of biosimilars in Europe. The aphorism “if it is not broken, then don’t try to mend it” comes to mind. Doubtless, the US FDA will be observing closely, and maybe this is their learning opportunity. At least the process should be transparent, so watch this space.

The entire history and philosophy of therapeutics is based upon ‘first, do no harm’ (Sydenham, c. 1675, possibly following Hippocrates c. 400 BCE). The capability of mammals (including human beings) to re-establish functional homeostasis under the stress of disease is amazing. The issue always boils down to: Can one’s prescription really do better than homeostasis in this particular patient?

Intelligent pharmacovigilance and risk management practices (‘pharmacovigilance’) inform good prescribing decisions, directly or indirectly. Good pharmacovigilance can help identify the appropriate populations where drugs are needed, as well as preventing those same drugs from doing harm. One must ask the question whether regulatory authorities are as interested in the former as in the latter (beyond, perhaps, their interest in orphan drugs, which also needs modernization in the US) [17]. For example, has any important iatrogenic hazard ever been discovered by the small industry of expedited serious adverse event reporting? Regulatory authorities should be applying their substantial expertise towards reducing the number of unnecessary licence refusals (albeit with appropriate restrictions), and leveraging advances in pharmacovigilance methodology is one way to do it. Let us hope that in 2014 the PRAC can lead us all in that better direction for both investigational drugs, marketed products, and above all, for patients.

The European countries that were in financial jeopardy a year ago are still in peril. The Euro-crisis went into abeyance during the few months leading up to the general elections in Germany (it was summer, so doubtless all the European players were on their long European vacations).

But re-eruption must now be likely. In contrast, there are clear signs of recovery in the US, with modest economic growth. There are also signs that the US investment community is reawakening. One hopes that small biotech companies will find it easier to obtain funding in 2014 than during the last 5 years.

Happy New Year!

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