The Pharmaceutical Year That Was, 2015

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It has been an eventful year where political, economic and regulatory change have dominated any particular scientific advance. Leaders of Australia, Greece, and the UK have all been elected, some for a second time, and the US House Majority Leader has been unexpectedly replaced. Nonetheless, the political entertainment does not seem to have been quite as copious as usual this year; perhaps this is the lull before the storm of the 2016 primary, caucus, and general US elections.

At long last, this year saw the predicted pattern of economic recovery become established. As usual, the US is ahead of the UK, and well ahead of the rest of Europe. The economic problems in Greece at the beginning of the year still remain without disease-modifying treatment. In the middle of the year, the European Central Bank started printing money as a palliative measure: let's hope the horses had Parkinsonism and are still inside the stables of Brussels and Frankfurt. The next major hurdle will be when the Federal Reserve increases interest rates; its decision not to do so in mid-September 'may come back to bite 'em.'

The US FDA took an historic decision in March, when the agency found a way to approve a biosimilar without being ordered to do so by the federal courts [1]. This first approval was for filgrastim, which promotes white blood

cell maturation and release from the bone marrow. The innovator's product (Neupogen®; Amgen Inc., Thousand Oaks, CA, USA) had been approved in 1991 and was unchallenged in the market place for almost 24 years (much more than would usually be expected by patent, although the history of that is complicated in this case). In comparison with Europe, the reasons why the FDA has been so slow to recognize biosimilars are probably twofold. First, the social medicine pressures in Europe are much greater and governments are consequently more likely to want biosimilars and consequent price reduction as soon as possible. Second, the regulatory approach has differed. Europe has been quite comfortable issuing guidances that cover only single products, e.g. erythropoietin, filgrastim, etc. The FDA has been spending time trying to achieve an umbrella regulation with rules defining equivalence and interchangeability that would apply uniformly to all biological products. All this is pursuant to the Biologics Price Competition and Innovation Act of 2009. This Act has been little noticed by the public, press, and pundits in the US because it was overshadowed by the health insurance aspects of the Affordable Care Act (ACA) of 2010 [1]; the latter has become the totem of the general contempt with which the US President is treated by the Republican party. While they were at it, the FDA also tackled the issue of nonproprietary names for biosimilar products: the new filgrastim is officially known as filgrastim-sndz, to indicate that Sandoz Inc. (Princeton, NJ, USA) have developed Zarxio®. The plan is to extend this system of naming [1].

It will be interesting to see what the effect of biosimilars will be on product pricing. Generic small molecule products may fall to 10–20 % of the price of an unchallenged originator within 1 year of introduction. For biosimilars, production costs and scale-up constraints are much larger

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than for small molecules, and closer to those for the originator's product. This also brings a larger regulatory cost and slower approval process than for generic small molecules.

In Europe, the data transparency initiative took an unexpected turn early in the year when its European Medicines Agency (EMA) champion, Executive Director Dr. Guido Rasi, was dismissed [2]. Even after appeal, it was found that his appointment had been irregular, and not even the shortlist had been prepared properly. While the details remain more opaque than transparent (the reasons have been described as 'purely formal'), the irregularity must have been truly egregious to have exercised such an undemocratic organization. Meanwhile, the EMA settled its case with AbbVie mid-year [3]. From mid-2016, the EMA will distribute clinical study reports (CSRs) from any marketing authorization and a few other regulatory processes [4]. Companies are allowed to claim redactions in the case of commercially sensitive information, and it appears that companies will file parallel sets of redacted CSRs as a pdf file. These will be reviewed by the EMA and, if deemed suitable, will then be published with an added EMA watermark. Item patient data (and its anonymization) will form phase II of this enormous administrative exercise [4].

Meanwhile, the *British Medical Journal* (BMJ) has joined the transparency band wagon, promising to reanalyse and republish clinical trials whose conclusions it disagrees with. The BMJ calls this process "restoring invisible and abandoned trials ('RIAT')"¹ [5]. One would have thought that the EMA would have dealt with the invisible bit by giving away CSRs to whomever asks for them, starting from next year (see above) [3, 6]. The scientific principle that a statistical analysis plan should be written prospectively has been abandoned, and RIATs are designed retrospectively. Target number 1 was a placebo-controlled trial of paroxetine and imipramine in adolescents, which the BMJ's editor says she had had in mind right from the start of the RIAT project [5]. 'Restorative authors' are reanalysing patient-level data, undertaking an 'immense task'. A trained pharmaceutical physician might view this as a routine job. As for transparency, it is unclear whether these 'restorative authors' are entirely uninvolved with litigation against the manufacturer of paroxetine. In any case, this first RIAT confirmed the original CSR in that there was no evidence of efficacy. As for tolerability, in the paroxetine group ($n = 93$) the RIAT uncovered 70 severe adverse events, versus 25 in the placebo group ($n = 87$), exactly the same as the CSR [7]. Two more adverse events in the taper phase of the study were found by the RIAT (47 vs. 45 in the CSR), although the CSR and RIAT agree that 13 of these were severe. The biggest difference was that the RIAT claimed there were 11 'suicidal and self-injurious

patients' versus 7 in the CSR, while both reports agreed on one such case in the placebo group. Most curious of all is that, apart from this detailed (Good Clinical Practices-looking) analysis, the RIAT finds, in addition, 103 'psychiatric adverse events', versus none in the CSR. How this new class of adverse events has been retrospectively defined is unclear. The BMJ's editor, Dr. Fiona Godlee, chooses to conflate these findings with the 2012 GlaxoSmithKline (GSK) adverse event reporting failures, although this paroxetine CSR is 11 years older and there is no specific evidence offered that it was part of that case. Blame placed on the clinical scientists and investigators who produced the CSR seems unjustified. If the problem is the trial's published manuscript, then blame needs to be more focussed: the error is with the paper's authors and the editor of the journal of publication. Any perceived failure to retract a paper if, upon review, it truly is flawed, again resides with authors and editor. Meanwhile, paroxetine has never been licensed for this age group in either Europe or the US, therefore we must presume that the regulators reached the right conclusions, having been provided with all the data. If there has been off-label promotion of a product then there are also regulatory remedies for that, and no RIAT would have been needed to make that case. Ironically, GSK has been in the vanguard of data transparency, including a 1998 editorial on the subject by its then Chairman, in Dr. Godlee's own journal [8]. We are to expect more RIATs next year, and let us hope that the editorialising and journalist commentary in the BMJ becomes more objective, transparent, and relevant.

The financial markets have supported small biotech this year to a remarkable extent. One estimate is that there are now approximately 1600 investigational products in phase II or III clinical trials, distributed across the usual geographical areas (roughly: New England 350, Northern California 300, Southern California 250, UK 200, Switzerland 100, Germany 100, France 100, Italy 100, Israel 100, elsewhere 100) [9]. Meanwhile, initial public offerings (IPOs) are happening in the biotechnology industry. Alex Lash reported that five firms raised US\$220 million in the first 2 weeks of the year alone [10]. Bloomberg reported that whether IPOs or follow-ons, small biotech companies raised three times as much money in the first quarter of 2015 as during the entire previous year, and more than in any year in the past decade [10]—certainly the most optimistic year for biotechnology small-cap companies since the stock market crash.

From the EMA, *Good Pharmacovigilance Practices* is now almost completely in place. One or two of the later modules have not yet been published; however, the periodic revisions of earlier modules are also underway with opportunity for public comment. Module 8 is on postmarketing studies, and it is now the rule that the

Pharmacovigilance Risk Assessment Committee (PRAC) must review and approve all postmarketing pharmacovigilance protocols. Word on the street is that the PRAC is also now requesting Statistical Analysis Plans, even for merely observational studies. This would presumably suggest that protocols contain too little detail on the statistical planning of studies. Certain National Competent Authorities (NCAs) are now also exercising their rights to review such protocols if they are to be implemented in their country either in whole or in part. There seems to be a large potential for conflict between PRAC-approved studies and demands for additional bells and whistles (known as 'gilding' in Eurospeak) from NCAs.

Operation Pangea VIII took place this summer [11]. These operations are internationally coordinated assaults on drug counterfeiting and adulteration conducted within a short period of time. This year's operation included police raids on targeted premises in 115 countries, often with support from international private sector firms such as Legitscript, Google, and the credit card companies. Between 6 and 19 June there were two Internet domain closures, and some 50,000 illegal product seizures worldwide. One of those seizures alone, conducted by the Medicines and Healthcare products Regulatory Agency (MHRA) and Scotland Yard, was of 60,000 prescribing units of potentially dangerous pharmaceuticals, probably worth more than £1.5 million. The total seizures are thought to be at least 20 million prescribing units. A specific international warning against the use of dinitrophenol was also made during the operation [11].

An FDA initiative late in the year was the establishment of a Patient Engagement Advisory Committee (PEAC) [12]. There are currently no standards for assessing patient preference among competing devices; the initial task of this lay committee seems to be to advise senior FDA management on how these comparisons should be conducted.

Lastly, and with temerity, whither education in pharmaceutical medicine? It is clear that there are scientists, pharmacists, and others without degrees in medicine who are contributing to good pharmaceutical medicine throughout the world. This year, the Faculty of Pharmaceutical Medicine of the Royal College of Medicine, London, created an affiliation for such practitioners, who nonetheless remain excluded from the Diploma in Pharmaceutical Medicine. Avid recruitment to this underclass remains to be seen. The absence of an academic basis for the specialty in the US also retards the specialty. Efforts were made by the UK Faculty this year to reach out to the US. These vestigial efforts in London to resuscitate the specialty in the US unfortunately ignored many who could have provided advice based on experience. In particular, the work of the Academy of Physicians in Clinical Research (originally named the American Academy of Pharmaceutical Physicians) has been

ignored; that Academy did quite well for more than a decade and had achieved recognition of the specialty by the American Medical Association [13]. If this remains the goal of the faculty with its new President (installed in November 2015), then the fundamental need is for an educational standard ('board') in the US. Much of the groundwork has already been done.

So what might 2016 bring? There have been political rumblings on both sides of the Atlantic during the year concerning the prescribing of long-acting opioids. Doubtless, the manufacturers of these products are well aware of this, but spillover from the political arena into the wider world of pharmaceutical medicine seems possible for 2016. Another Operation Pangea can only be hoped for. A few more biosimilar approvals by the FDA during 2016 might also not be amiss; low molecular weight heparins should be a priority.

In Europe, the unexpected re-election of Prime Minister Tsipras in September suggests re-eruption of the Euro crisis before next year is out. In the US, the Federal Reserve's decision to raise interest rates has been on-again, off-again, while elections are also on the horizon. Yet, this year has seen evidence that the investment community can actually function amidst this political instability. Let's hope that continues; if so, then the overall situation can only be described as the 'new normal'.

Happy New Year!

Compliance with Ethical Standards

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