The Pharmaceutical Year That Was, 2018

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As usual, 2018 has been eventful. Some unfinished business has been dealt with, while other unfinished business has become even more unfinished!

Readers may remember the case of Dr. Martin Shrekli who featured in this review 2 years ago [1]. After founding Turing Pharmaceuticals, Shrekli acquired the US marketing rights for pyrimethamine, which is used to treat toxoplasmosis, especially in immunocompromised patients. Although well-past its patent expiration, Turing was the sole supplier of this small-volume product, and Shrekli abruptly increased its price from US\$13.50 to US\$750 per dose. Previously, Shrekli had led two failing hedge funds, and had founded another pharmaceutical company. Shrekli evidently siphoned funds out of his pharmaceutical companies so as to pay investors who had lost money with his hedge funds. Meanwhile, the Trump Presidential campaign was claiming that pharmaceutical company ‘price gouging’ was a widespread problem, with Turing as its greatest example (the extent of the problem was largely contradicted by a White House report in February [2]). In March, the Brooklyn court handed down its sentence for fraud: fines and restitution of US\$7.43 million, plus a jail term. Pending US Food and Drug Administration (FDA) blacklisting, it will be at least 7 years before Martin Shrekli can again visit the FDA in Rockville, Maryland [3].

Meanwhile, readers may remember the £90 million fine meted out last year by the UK Competition and Markets Authority (CMA): Pfizer had price-gouged with a humble centenarian, namely phenytoin [4]. Remarkably, on appeal, this fine was overturned in June. The Judicial Review ruled that the CMA did not “appropriately consider the right economic value of the capsules” and “did not make suitable comparisons with other drugs.” On 8 June, the CMA was “actively considering” whether to appeal further [5]. While,

a priori, the overnight, more than tenfold increase in the price of an ancient drug seems outrageous, the silver lining to the cloud is that there is at least one small part of the establishment that is willing to contemplate the fact that pharmaceutical products actually do have some true value.

The ClinicalTrials.gov database was put to good use this year in what must be the largest audit of registered clinical trials to date [6, 7]. Some 45,620 clinical trials were audited for funding (industry/National Institutes of Health/other), medical specialty, and design type (randomised/non-randomised, placebo-controlled/-uncontrolled, crossover/parallel-group, etc.). The dissemination (i.e. publication) rates for the three different classes of funding were also investigated. Both small molecules and biological products were included in the study. Perhaps unsurprisingly, randomised trials were more likely to be published than non-randomised trials. The report found oncology studies to be less likely than average to be published, but this is understandable for a therapeutic area where early-stage trials are commonly uncontrolled. Industry-funded studies tended to be unsurprisingly larger, had smaller proportions of uncontrolled, non-randomised and open-label designs, and had higher publication rates than academic- and not-for-profit-funded studies.

Cannabinoids were in the news during the early northern summer [8, 9]. Billy Caldwell, aged 12 years, has severe epilepsy (said, when untreated, to involve scores of seizures every day). In Canada, he had benefitted from treatment with ‘cannabis oil’, but when Mrs Caldwell brought her son to the UK their ‘cannabis oil’ was promptly confiscated by Her Majesty’s Border Force at London’s Heathrow airport. It quickly came to light that there had been a very similar confiscation from another boy entering from The Netherlands in February. In June, Mrs Caldwell waived patient anonymity by going public. Billy’s photograph appeared in the national media, and this personal clinical harm, caused by Government regulation, drew several days of negative newspaper coverage. The criticism intensified when someone in Government suggested that a general practitioner could file a clinical trial application with the UK national competent authority, the Medicines and Healthcare products Regulatory

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Agency (MHRA), to cover the use of the cannabis oil in this patient. Even so, swimming against the tide, many of the self-righteous and desperately concerned writers of letters to newspapers were conflating medical use with recreational use, and recreational use with physical addiction. But then, a remarkable thing happened. The Home Secretary (the Right Honourable Sajid Javid) decided that, as far as he was concerned, the evidence was sufficient for him to license the product in this “complex case”. Surprisingly, that licence did not come from the MHRA or the Department of Health (who also have a cabinet minister), i.e. from those who typically oversee such matters, even in single ‘complex cases’. Instead, this ‘cannabis oil’ was licensed for this named patient by the Home Office because it was their staff who had confiscated it in the first place. One wonders how much pharmacognosy was required for the Right Honourable Sajid Javid’s politics and economics degree from the University of Exeter, and how much training is given to H.M. Border Force officers in assessing pharmaceutical quality, efficacy and safety.

Just as committees of inquiry on cannabinoids were being announced by the Government’s Chief Medical Officer (Professor Dame Sally Davies), and the hue and cry over the Caldwell case was dying down, it was on 25 June that GW Pharma (London, UK and Carlsbad, CA, USA) announced that the US FDA had approved (pure) cannabidiol for the indications of Lennox–Gastaut and Dravet syndromes (which are two of the most severe forms of epilepsy, and probably similar to what Billy Caldwell suffers) [10]. Since then, some of the better-balanced journalists have been pointing out that tetrahydrocannabinol (THC) tablets are available in the UK as a Class B scheduled drug (therefore ranking with diamorphine, alias ‘heroin’), that smoking cannabis when medically prescribed is legal in several of the US states, and that cannabidiol lacks the psychotropic effects of THC. One hopes that Professor Dame Sally’s report will be evidence-based and clinically oriented, and not reinforce the existing haphazard, inconsistent and political processes that obstruct getting the right drug to the right patient.

European Regulation 436/2014 has still not been implemented. The European Medicines Agency’s (EMA’s) electronic portal is the hold-up, and a third postponement was announced during the northern summer.

There are a few things that nice people simply don’t discuss at posh dinner parties. In the UK, departure from the European Union (EU) has become one of them. About 2 years ago, the EMA, in its wisdom, and without knowing what the future arrangements might be,¹ decided to evacuate

its longstanding headquarters in a part of London known as the Isle of Dogs. It decided it was relocating to another EU country. After holding a ballot or two (presumably so as to get the right answer eventually), the choice of location came down to either Amsterdam or Milan; and, literally by drawing lots, Amsterdam then won. The Amsterdam bid had included a top-quality building for the EMA to move into in March 2019 (when the UK is expected to depart the EU). A recent inspection (early October 2018) shows that this ‘building’ in Amsterdam is actually a rather large, wet, muddy hole in the open air whose only structure is the stump of a central elevator shaft. Milan (and the Italian Government) are now taking the EMA to the European Court of Justice because the Dutch representations about the Amsterdam facilities might be described, at best, as prophetic, if not actually fraudulent. Meanwhile, the word on the street is that 30% of the EMA staff will not transfer to The Netherlands, and that by taking away all the British rapporteurships, there has been some 20–25% increase in workload for the rest of the competent national authorities.

“If your portal won’t work on the Isle of Dogs, you might go and try in the land of clogs.” (Anon.).

Happy New Year!

Compliance with Ethical Standards

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¹ It has been proposed that post-Brexit, the UK should remain with Europol, Euratom and the European Patent Office, and that the EMA, as another highly technical agency, might be a further candidate. The UK will automatically remain with the European Court of Human Rights because that Court is not created by an EU convention.

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