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GUEST EDITORIAL

Regulatory harmonization: a view from India

For any drug to be marketed in a country, it must be passed by the local regulatory authorities. Different regulators have different criteria for passing a drug. Zerhouni and Hamburg in an editorial have urged greater global harmonization in the matter of drug regulations (*Sci. Transl. Med.*, 2016, **8**, 338ed6). At the time of writing their Editorial, Zerhouni was – and continues to be – head of R&D at the large pharma company Sanofi and a former head of the National Institutes of Health, USA and Hamburg was the immediate past Commissioner of the US Food and Drug Administration (USFDA). One can see that the editorial reflected Zerhouni's current – and perhaps Hamburg's former – problems. Given the authors' current or past affiliations, one can also assume that their comments were somewhat US-centric.

One can understand Zerhouni's pain. Every company's goal is to increase its revenue, and he is fairly central to Sanofi's efforts to do so. The editorial reports that an increasing part of a company's R&D budget is spent applying for regulatory clearances in various countries. It goes on to state that if there was a globally harmonized regulatory system, this expenditure might be significantly reduced and money thus saved could be spent on discovery. Perhaps. It might, however, be spent on marketing, as it has been estimated that more money can be spent promoting existing drugs than researching new ones (Gagnon, M.-A. and Lexchin, J., *PLoS Med.*, 2008, **5**, 29–33). It might also be spent on the enormous numbers of lobbyists that large companies maintain in Washington, USA. Alternately, it might be spent on an even larger salary for the CEO. In the case of Sanofi, the salary of the CEO is already so high that it was criticized by the French Government a couple of years ago (http://www.reuters.com/article/us-sanofi-pay-idUSKBN0LR0VU20150223). So the claim that 'money saved goes into R&D' – one that is made by industry every now and then – may not always be true.

'Global harmonization' and 'international best practices' are closely related positive-sounding terms that imply high standards. They are also supposedly in contrast to – for instance – the sometimes mishmash of regulations in India that can be difficult to navigate. I have no doubt that the Indian regulatory scenario could be improved. The question is whether harmonization is the way forward. Illustratively, and amongst other things, the authors point to the need for global harmonization on post-marketing monitoring of drugs. It has been reported that less than half the post-marketing trials required by the USFDA are initiated and for those that are completed, about 20% lead to new black-box warnings and 4% to product withdrawals (Umscheid, C. A., Margolis, D. J., and Grossman, C. E., *Postgrad Med.*, 2011, **123**, 194–204). Given these outcomes, it is clear that post-marketing trials need to be enforced with greater vigour. Since the US hardly has 'best practices' in this area, should not the domestic scene be cleaned up before going worldwide?

Let us return to the area of drug approvals. Even in the best regulated countries of the world, there seems to be subjectivity in the decisions and unseen influences on the outcomes. Some of the better-known cases that illustrate this are as follows: (1) In the US, regulators have been accused of being 'too cozy' with industry (http://pogoblog.typepad.com/pogo/2011/08/fdas-janet-woodcock-the-substance-behind-her-nonsubstantive-substantive-ties-to-industry.html). An extreme example of this was the FDA's approval of the drug Exondys for muscular dystrophy in 2016. Brought to market by Sarepta Therapeutics, Exondys costs US$ 300,000 for a year of treatment, even though many believe that it is a useless drug. A senior official of the FDA made a decision that was so controversial that a member of the committee resigned. The essence of the problem is captured by this anguished query: 'Is this going to be the new way to get a drug approved? Run a trial in a dozen people, generate unconvincing data, and then lobby Janet Woodcock?' (http://blogs.sciencemag.org/pipeline/archives/2016/09/20/sarepta-gets-an-approval-unfortunately).

In India, too, it has been recorded that files of multinationals have been cleared with atypical speed (Gulhati, C. M., *Indian J. Med. Ethics*, 2004, **I**, 4–5). The phrase used to describe such influence is 'regulatory capture by industry'. (2) Lobbyists have a strong role in law-making. A relevant example relates to 'data exclusivity', that is, the period of time for which generic drug companies are not allowed to use clinical trial data generated by the company developing the original molecule to support the formers'

applications to market a generic. Despite no economic evidence justifying the longer exclusivity for biologics compared to small molecules (Baker, B. K., *PLoS Med*., 2016, **13**(3), e1001970), industry lobbyists succeeded in obtaining 12 years of data exclusivity for biologics in the US (in contrast to the five years that holds for small molecules). This is so extreme that even the now-dead Trans Pacific Partnership (which was trying to harmonize certain trade and IP-related issues across 12 countries) cut it down to eight years. So should every country be 'harmonized' to 12-year exclusivity, which is what the US strongly argued for? (3) The first biosimilar was approved in Europe in 2006; so far 20 biosimilars have been approved there. The first approval in the US was as late as in 2015, and only three have been approved so far, one of which is from India (von Schaper, E., *Nature Biotechnol*., 2016, **34**, 454–455; http://www.business-standard.com/article/markets/biocon-surges-14-on-usfda-approval-for-biosimilar-of-cancer-drug-herceptin-117120400142_1.html). Which of the two was the 'correct' date, that should have been the global standard? (4) Decades ago, thalidomide was cleared in Europe but not in the US, with well-known consequences for many babies that died or were born with severe birth defects in Europe. With such clear examples of differences of opinion amongst the most advanced regulatory systems, and extra-legal influences on the process, is harmonization the biggest need of the hour?

Let us turn to another aspect of approving a drug. Drug developers and manufacturers seek certainty in the drug approval process. 'Approved' or 'not approved'? The former is of course better, but at least the latter is unambiguous. How about something in between: provisional approval for three years, subject to post-marketing studies whose results need to be filed by a certain date? The carrot combined with the stick. This has been done by Japan in the area of regenerative medicine and cell therapy, where therapies have been put through phase 1 and 2 clinical trials, but not phase 3 (Russel, A.; http://www.partnering-forcures.org/past-meetings/2013/agenda/view/4537). Such a proposal is likely to meet with fierce resistance by those seeking international harmonization, the chief argument being that one cannot recover the costs of R&D (past, present and future) unless one has (enormous) profits, and three years is too brief a period to do so. In contrast to the dominant discourse that it takes billions of dollars to cover the R&D costs of every drug and its associated failed drugs (http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-profile.pdf), it has been estimated that the actual costs are a small fraction of that, and that a company can recoup its investments within a year from the US market alone (http://www.thehindu.com/opinion/editorial/a-just-order/article4570090.ece). In fact, a former employee of a big pharma company remarked that no company would undertake any R&D effort if it could not recover the costs within a year or two (Anon., pers. commun.). Could India pioneer such an approval pathway? For that, the regulatory authorities would have to demonstrate an independence of spirit similar to that shown by India on the issue of patent rights, as exemplified by the following two cases: (a) in 2013, the Supreme Court decided that Gleevec was unpatentable in India, thereby reducing the price of the drug ten-fold (http://www.thehindu.com/opinion/lead/why-novartis-case-will-help-innovation/article4617473.ece), and (b) in 2012, the Government of India issued a compulsory licence to allow the Indian firm Natco Pharma to make cheaper Nexavar, with the price plummeting to 3% of the original.

In a recent reminder of the danger of harmonization, a vaccine for dengue brought out by Sanofi – and approved by the World Health Organization – has caused problems in the Philippines. Deployed on a large scale in that country, some patients who had had earlier dengue infections saw their symptoms worsening if they had been inoculated with the vaccine (http://www.rediff.com/business/report/how-india-narrowly-escaped-a-health-crisis/2017-1205.htm), leading to a crisis that rocked the nation late last year. It turns out that the Indian regulator has not cleared the vaccine so far, although several other countries have done so.

To return to Zerhouni's problem: Yes, money spent on multiple regulatory approvals is money that could be better spent elsewhere. Therefore, that is an issue for the company. But it is not necessarily an issue for the rest of humanity. What happens once a drug is approved? More often than not, it is priced so high that it is unaffordable to most. For those willing to struggle for price reductions, it is indeed a long battle. The Access to Medicine Foundation now tracks how individual Big Pharma companies are doing in terms of making their drugs (and soon, vaccines) affordable (Barron, D., *Irish Medical News*, 29 September 2015). Some companies are doing better than before, but by no means are most drugs affordable to most people. And although one is grateful for new drugs brought to market, it can be difficult to sympathize with the problems of multinationals in developing countries. At the very least it is irritating when foreign powers, multilateral organizations and so on, interfere in one's country's affairs. There is also great danger in it. The interference is most likely self-serving, and not in the interest of the country being advised.

Undoubtedly there is scope for some regulatory harmonization. However, in general, beware harmonization, even if it is proposed by such stalwarts as Hamburg and Zerhouni.

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