Regulatory Writing

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Bad Pharma and the regulators

The recent publication of the book *Bad Pharma* by Ben Goldacre[1] has caused quite a stir in the medical writing community (and indeed throughout the pharmaceutical industry). Before I read the book, I had thought that it would mainly target the marketing side of the pharmaceutical industry and that the criticism of the regulatory side would be relatively light. Well, I was wrong. Ben Goldacre dedicates a whole chapter to the regulatory agencies and they receive regular mentions throughout the book. He essentially suggests that the regulators give the drug companies a relatively easy ride, indeed that they are toothless and easily influenced by the all-powerful drug companies who do pretty much as they please. This point of view does not, however, fit well with my impressions from working with regulatory affairs departments. In my experience, companies are very conscious of what the regulators think and, in general, if a regulator says 'jump' the company jumps.

Toothless regulators or compliant companies?

As evidence of the toothless nature of the regulators, Ben Goldacre explains that drugs have very rarely been taken off the market by the regulators, whether for safety reasons or due to lack of efficacy in long-term studies following marketing authorisation. And this is no doubt true. However, one problem with using this fact as evidence of soft regulators is that many drugs are voluntarily withdrawn by the company. If you turn Ben's logic on its head, this could even be taken as an indicator that companies *are* afraid of the regulators. An illustrative example is natalizumab, a treatment for multiple sclerosis and by all accounts a very effective one. The company decided to withdraw the drug because three patients on natalizumab developed progressive multifocal leucoencephalopathy (PML), a rare but serious and often fatal condition caused by an opportunistic infection of the nervous system. Before the drug was reintroduced, the company negotiated a comprehensive risk management plan with the authorities. Neurologists and patients are now made aware of the importance of being vigilant for early signs of PML. As a result of starting treatment for PML earlier and a better understanding of which treatments are most effective, the death rate associated with the condition is declining. The labelling was also changed so that it was only indicated in patients with more aggressive disease (and those who would most stand to benefit from the treatment). The strenuous efforts to stratify risk as more data became available mean that patients can now make informed decisions about the benefits (a very effective treatment compared with other available options) and the very real but now much more quantifiable risks.

Ben Goldacre also criticises the fact that many of the studies required by the health agencies as a condition for granting marketing authorisation (especially when the approval is based on surrogate endpoints) are not actually performed, or that the data are not handed over to the health authorities. Although the lack of compliance might, at first glance, seem high (one in three according to figures quoted in the book), once again it does not tell the whole story. Often these additional studies, or follow-up measures or post-authorisation commitments as they are also known, are fairly long (for example, studies of overall survival in a fairly indolent cancer) and so difficult to perform. For example, other effective treatments may become available over time and investigators are no longer willing to enrol patients into the study and give them what they consider an inferior treatment.

Off-label use

Often, follow-up measures will refer to a specific indication. When the study associated with the follow-up measure is negative, the indication will often be withdrawn. Ben Goldacre argues that because many of these withdrawals refer to specific indications only, the drug is still available (as it is approved for another indication) and susceptible to off-label use (thanks in part to the powers of marketing). The European Medicines Agency (EMA) is not entirely blind to the possibility of off-label use, as illustrated by a 'questions as answers document' which discusses off-label use of celecoxib in patients with familial adenomatous polyposis.[2] My impression of talking to doctors in Spain is that they are often aware of the labelling and are uneasy about off-label use.

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The increasing regulatory burden

So I would not call the regulators entirely toothless. In fact, there seems to be the generalised impression among drug companies that there is an ever-greater regulatory burden. I do not have any metrics to back this impression up, but there are some examples of recent legislation that seemingly increase the regulatory burden. For example, in Europe, it is now a requirement for an approved Paediatric Investigation Plan (PIP) to be in place before marketing authorisation can be granted. Such a plan commits the applicant to perform the agreed studies in children, although it could be debated as to whether the effort might not be better employed in other developmental activities. However, regardless of the usefulness of the PIP legislation, the fact is that it is rigorously enforced, as reflected when the decision by the EMA to oblige a company to consider paediatric indications other than those included in the adult programme was challenged in the European Court of Justice as a 'misuse of power'.[3] The court upheld the EMA's original decision.

Are things improving?

Although a reading of the above text might lead to the conclusion that I am an apologist for the pharmaceutical industry, I can assure you that this is not the case. I think that the pharmaceutical industry is and has been involved in some rather dubious practices (for example, I have attended medical congresses and seen first-hand the lavish outlay on promotional material and slick satellite symposia). And Ben Goldacre does have some very interesting points to make. On the regulatory side, yes, there have been some failures. His suggestion that, to avoid a natural reluctance to admit mistakes, there should be a proper separation between the body responsible for approving a drug and the one responsible for monitoring a drug once approved (with powers to withdraw a drug) is an interesting one.

In his concluding remarks, Ben contends that the measures that have been taken are largely cosmetic and that the abuses by the pharmaceutical industry continue. He mentions the lack of compliance with the Food and Drug Administration requirement that companies are now required to publish the results of a completed study within a year on the clinicaltrials.gov database, citing a 'recent' study.[4] However, the study considered trials that were completed in 2009. As the results part of the database was only launched in late 2008, it might be reasonable to think that things have changed since then as companies implement their result-disclosure mechanisms. Incidentally, the same study suggests that industry-sponsored trials are more likely to report results within the 1-year timeframe compared with non-industry trials.

In the case of transparency or lack of it (a central theme throughout the book), the EMA does now have its central clinical trials database up and running. It is not perfect, for sure, but it is better than nothing at all. On its website, the EMA does publish European public assessment reports and withdrawal assessment reports, which give some insight into the thinking of the regulators when they authorise or refuse to authorise a drug. This is not perfect transparency, obviously, and it does not address issues such as the release of old clinical study reports and other documentation by the regulators, but it is a start. I remember reading about the case for evolution put forward in *The Blind Watchmaker*, by Richard Dawkins. The creationists ridiculed the idea that something as complex and apparently perfect as an eye might result from chance mutations driven by natural selection. The point that Dawkins makes is that even an imperfectly functioning eye is better than no eye at all and so can serve as a stepping stone to a perfect one. In the case of the drive for transparency, surely a small step in the right direction is better than no step at all? It is important, though, that there is a constant push towards improvement. In this sense, *Bad Pharma*, for all its hubris, may serve its purpose by bringing some of the very real issues facing the pharmaceutical industry into the public eye. And Ben Goldacre is right that public scrutiny is extremely important.

References

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Note from Editor: A review of *Bad Pharma* also appears on page 50 of this issue.