

Improving transparency of the Therapeutic Goods Administration

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The review panel would like to hear from the general public, health professionals, industry and media on the transparency of the TGA (TGA). I believe that it is important also to collect the views of other stakeholders as well.

Health information providers. Many health professionals and consumers may not rely directly on the TGA to get information on medicines but get information from secondary information providers such as journals or textbooks including the Australian Medicines Handbook. Health information secondary providers are heavy users of all information posted by the TGA as they rely on this information to inform their publications. As a former editor the Australian Medicines Handbook I can appreciate the improvement in the TGA transparency from the time (not long ago!) when they refused to provide us with the product information of new approved medicines (we were asked to refer to “drug information centers”!) to the posting of the AUSPARs. The introduction of the AUSPARs is indeed a major step forward and TGA staff must be congratulated for the efforts they place into their production. For example, the publication of the AUSPARs allows us to understand why denosumab is approved in Europe for the treatment of bone loss in prostate cancer patients receiving hormone ablation and why this indication has been rejected by the TGA in Australia (AUSPAR January 2011).

Researchers. Researchers are also very interested in information held by the TGA, Currently, they can be very frustrated as they have no access to clinical data on new drugs (in contrast with the FDA, see below).

Citizens. Citizens are not only interested in the TGA transparency in order to access information. They rely on the TGA for the marketing of safe and effective medicines and would like to know whether the TGA is performing as it should to ensure protection of the public health. The total dependence of the TGA on drug industry for its funding carries an enormous risk of compromising the public health role of the TGA in order to fulfill the requirements of its main client, the drug industry, such as the early approval of new medicines. The two main consequences of industry funding are the risk of bias in the evaluation of benefits and risks associated with the use of medicines and the limits imposed on TGA activities because of the lack of government funding. This is not to say that the TGA staff and experts are not very skilled and conscientious people. However, recent scandals in France, and in the US FDA, have shown that the risk of compromising core regulatory functions is real as medicine agencies are under intense pressure of drug companies. Under these circumstances, it is of utmost importance that the TGA is totally transparent so that its activities can be controlled and it remains accountable to the public they serve.

As a health information provider, researcher and Australian citizen, I would like to present my views on why and how the transparency of the TGA should be improved.

Reasons for improved transparency

Health professionals, patients and the public have a fundamental right to the complete body of scientific evidence available on the health effects of medicines. Without access to this information all medicine use is by definition misinformed. This is particularly true for new medicines when there is limited information published in medical journals. While the TGA has improved the release of information on new medicines in publishing the AUSPARs, there are still many areas where transparency should, and could, be improved.

In my own experience as a health professional and a medicines information expert, I am often obliged to rely on documents released by other medicine agencies to make reliable assessments of the value of new medicines. For example, while undertaking systematic reviews for the Australian National Breast and Ovarian Cancer Centre on three new medicines for advanced breast cancer lapatinib (Tykerb), bevacizumab (Avastin), and a new albumin-bound formulation of paclitaxel (Abraxane), I compared the results published in medical journals with those included in the FDA medical reviews and/or with briefing documents available on the FDA website. This showed that analyses reported in journals were of lower quality and were given a favorable interpretation by minimizing toxicity and ignoring methodological shortcomings compared to FDA medical and statistical reviews (Vitry 2010). Giving public access to complete drug data held by regulatory agencies is also important because of the publication bias. For example, an independent review in 2008 of antidepressant trials registered with the US FDA found that the trials that produced negative results were less likely to be published, and that may have led to an overestimation of the health benefits provided by antidepressants (Turner, Matthews et al. 2008). Many trials submitted to the FDA were recently found to be unpublished 5 years after new drug approvals (Rising, Bacchetti et al. 2008). Accordingly, the information that is easily available in the published medical literature is incomplete and potentially biased.

Transparency also allows external experts to double-check the validity of the authority's conclusions. This can be illustrated by the example of the antidiabetic drug muraglitazar, which was recommended for approval by an FDA advisory committee in 2005. At the same time, an independent research team published findings from its analysis of the therapeutic value of muraglitazar (Nissen, Wolski et al. 2005). The researchers conducted their analysis using documents from Phase II and III clinical trials of the drug that had been released under public disclosure laws. They found that the drug was associated with an excess incidence of serious adverse cardiovascular events and concluded that the agent should not be approved. Muraglitazar development was stopped in 2006.

Transparency: towards international benchmarks

In all countries, calls have been made to increase the transparency of regulatory authorities. Internationally, Medicines Transparency Alliance (MeTA) is a pilot multi-stakeholder alliance including the World Health Organization and the UK Department for International Development working to improve access and affordability of medicines for the poorer countries by supporting openness and disclosure of information to improve decision-making and efficiency (see <http://www.medicinestransparency.org/>). In 2009, the World Health Organization produced a manual of indicators "Measuring Transparency in the Public Pharmaceutical Sector" (see

<http://www.who.int/medicines/areas/policy/goodgovernance/AssessmentInstrumentMeastranspENG.PDF>)

A European Union directive – Directive 2004/27/EC, amending Directive 2001/83/EC – was issued in 2004 that included new rules on transparency (2004). Under the revised directive, European drug regulatory authorities were required to make available in the public domain records of their meetings and decisions taken on marketing authorisations together with their assessment reports and underlying reasons for their judgments. In November 2010, The European Medicines Agency (EMA) published its new policy to give wider access to documents related to medicines for human and veterinary use (European Medicines Agency 2010). It has also released an “Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use” (European Medicines Agency 2010).

Prior to the existence of the revised European directive, there was limited information available on negative decisions on medicines made by the EMA, such as in cases where it had rejected applications for marketing. In the ten years prior to 2005, of the 395 products assessed by the EMA, only seven negative opinions were issued and as many as 84 dossiers were withdrawn by the manufacturer (Garattini 2005). Pharmaceutical companies tended to withdraw their marketing applications if they expected to get a negative opinion from the EMA’s scientific advisory body, the Committee for Medicinal Products for Human Use (CHMP). In doing so, they avoided damage to their image, since neither the withdrawn application nor the CHMP’s negative opinion were revealed to those outside the regulatory environment. In the face of widespread off-label prescribing, it is therefore important to ensure that the public has access to information about unapproved uses. In its roadmap to 2015, the EMA has also announced that it would seem appropriate to explore, in collaboration with the pharmaceutical industry, what incentives could be offered to make the information on failed medicine-development process available as it would generate useful information and scientific knowledge in terms of avoidance of repetitive and redundant animal or clinical studies, avoidance of the use of inappropriate parameters etc (European Medicines Agency 2011).

This is not to say that these agencies have set the highest benchmark desirable. The FDA is not required to post all key information related to the approval of a New Drug Application. Documents may be heavily redacted to prevent illegal disclosures of “confidentially commercial information”. The FDA does not disclose information when an approval is withdrawn by a sponsor or whether the agency has placed a hold on clinical studies, or why it does not approve a marketing application (Asamoah and Sharfstein). This situation may change as, in June 2009, Food and Drug Administration (FDA) Commissioner Dr. Margaret Hamburg launched FDA’s Transparency Initiative

<http://www.fda.gov/AboutFDA/Transparency/TransparencytoRegulatedIndustry/PhaseIIITransparencyReport/FDATransparencyInitiative/default.htm>) to help fulfill President Obama’s commitment to openness in government and the U.S. Department of Health and Human Services (HHS) goal of making transparency a priority. The EMA has also to make improvements. In 2009, the French publication Prescrire and the Medicines in Europe Forum analysed 81 requests for information from the EMA between 2005 and 2008 (2009) and found that the EMA was still reluctant to divulge information and slow to respond.

An area of great importance for both consumers and health professionals is information on medicines safety. Currently, there is limited information on medicines safety available on the TGA website, mainly Medicines Safety Update and irregular safety advisories. The TGA should examine how to allow better access to the national adverse drug reaction via a direct access similar to that in Canada (Canadian Adverse Drug Reaction Monitoring Program Online Query and Data Extracts) or data files from the Adverse Event Reporting System like in the USA. The TGA should consider maintaining a database of safety changes in the Product Information with easy access by product name. The TGA should provide minutes of advisory meetings on pharmacovigilance issues as in the United Kingdom or New Zealand and consider the provision of periodic safety update reports (PSUR) that companies have to provide regularly to regulatory authorities.

I am also very supportive of the CHOICE recommendations on the lack of transparency of the ARTG on the public availability of all complaints about the promotion of therapeutic goods referred to the TGA by Complaint Resolution Committee (CRP), the Complaint Resolution Committee (CRC) of the Complementary Health Care Council, or those handled directly by ARTG.

Recommendations

The TGA should compare its level of transparency with other similar countries and aim to comply at least with international benchmarks set up by other regulatory authorities in Europe and the United States.

The TGA should make available the agendas and minutes of all TGA government committees, in particular the Advisory Committee on the Safety of Medicines (ACSOM), the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on Non-prescription Medicines (ACNM), the Advisory Committee on Non-prescription Medicines (ACNM), the Australian Influenza Vaccine Committee (AIVC), the National Drugs and Poisons Schedule Committee (NDPSC), the Advisory Committee on Medicines Scheduling (ACMS), the Advisory Committee on Chemicals Scheduling (ACCS), the National Coordinating Committee on Therapeutic Goods (NCCTG), and the Therapeutic Goods Committee (TGC).

The TGA should make available TGA committees' full reviews of the assessment of new medicines as well as full reports of safety assessments.

The TGA should make available information when an approval is withdrawn by a sponsor and the reasons why.

The TGA should establish and publicize their policy concerning the availability of all documents they hold relating to their evaluation and post-marketing surveillance of therapeutic goods.

The TGA should examine how to allow better access to the national adverse drug reaction database.

The TGA should consider maintaining a database of safety changes in the Product Information with easy access by product name.

The TGA should provide minutes of advisory meetings on pharmacovigilance issues.

The TGA should provide access to the periodic safety update reports (PSUR) that companies have to provide regularly to regulatory authorities.

Transparency and conflicts of interest

Recent scandals have highlighted that the issues of conflicts of interest are not confined to health professionals and academics in their relation with drug companies but are also very relevant to institutions. Transparency of medicine agencies should ensure that they remain accountable to the public that they serve. Last year, the refusal of the World Health Organization (WHO) to release publicly the conflicts of interests of the members of its advisory committee on vaccines was condemned in an inquiry of the European Parliament (Flynn 2010). This has tarnished the WHO's reputation and diminished its credibility among the public and health professionals (Cohen and Carter). The current public health fiasco caused in France by Mediator^o (benfluorex) has revealed grave deficiencies in the regulation of a drugs market that is under intense pressure from the pharmaceutical industry (see

<http://english.prescrire.org/en/81/168/46752/0/NewsDetails.aspx>). The report on benfluorex-Mediator^o from France's Inspection Générale des Affaires Sociales, the public welfare inspectorate details the unacceptable behaviour of the drug company Servier, as well as the numerous dysfunctions, equally unacceptable, on the part of drug regulatory bodies" (see report at <http://www.igas.gouv.fr/spip.php?article162>). These behaviours exposed patients to totally unjustified risks and resulted in a large number of victims including between 500 and 2000 deaths. The report states that "There is also, despite the progress made in this area since 1993, the weight of conflicts of interest on the part of experts who contribute to the work of AFSSAPS (the French Health Products Safety Agency). There are ties of financial interest and other ties that ought to be declared to the Agency, which is not always the case, according to statements by the current chairman of the marketing authorisations committee himself. (...) More globally, AFSSAPS, which is a public health agency, currently finds itself structurally and culturally in a situation of conflict of interest: Not because of its financing, which is something approaching an unofficial tax, but by a sort of institutionalised cooperation with the pharmaceutical industry that leads to a co-production of expertise and of the decisions that stem from it."

In Australia, concerns have been raised about the ties with the drug industry of advisers on the Australian flu vaccine policy. More recently, potential conflicts of interest between the experts providing advice to government and links with the pharmaceutical industry, were noted in a detailed investigation commissioned by the WA Minister for Health.

(<http://www.mediastatements.wa.gov.au/Pages/default.aspx?ItemId=133873>).

A recent review of policies and procedures in three European drug regulation agencies, the Irish Medicines Board, the United Kingdom Medicines and Healthcare products Regulatory Agency, and the European Medicines Agency, showed that, while official statements about conflict of interest laws and codes of practice suggested that conflicts of interest are prohibited, in practice,

the approaches to conflicts of interest support the ideas that conflicts of interest cannot and need not be eliminated as the risk of bias can be managed (Lexchin and O'Donovan).

The European directive 2004/27/EC requires that member states ensure that members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry that could affect their impartiality. Any such financial interest must be declared on a yearly basis. In October 2010, the European Medicines Agency has announced much stricter rules for its experts' interaction with the drug industry (Cohen 2010). Under the new policy, experts will be asked a lot more questions.

As the TGA is totally funded by industry fees, it is of great importance that its policies on the disclosure and management of conflicts of interest are publicly available.

Recommendations

The TGA should publish its policies on the disclosure and management of conflicts of interest, not only for staff and members of advisory committees, but also external experts, advisors etc.

The TGA should establish and constantly maintain a database of declarations of conflict of interests from the members of various committees, scientific reviews, which must allow free and easy public access.

The TGA should scrupulously exclude conflicts of interest when it comes to meetings.

The TGA should release detailed minutes of the meetings of working groups and committees, including minority opinions, and published within a few weeks, along with the underlying documents being worked upon;

Commercial confidentiality

“Commercial in confidence” is too broadly defined in the Australian National Health Act and is the main barrier to improved transparency. The general interest's principle (transparency) and a private economical interest (confidential commerciality) should not be placed on the same level. Confidential commerciality cannot override the need to protect public health and deprive patients and health professionals of drug safety information. To overcome extensive secrecy, “*commercial in confidence*” must be redefined more restrictively.

A recent example of excessive secrecy due to the broad definition of commercial confidentiality in Australian laws was given by the Administrative Appeals Tribunal (AAT) decision involving an application for documents concerning the listing of the drug Strattera on the Commonwealth Government Pharmaceutical Benefits Scheme (see <http://foi-privacy.blogspot.com/2010/06/drug-secrecy-law-trumps-foi.html>). Martin Whitely, an ALP Member of state parliament in Western Australia, sought access under the Freedom of Information Act to documents held by the Pharmaceutical Benefits Advisory Committee about the listing of Strattera on the Pharmaceutical Benefits Scheme. One of Mr Whitely's campaigns since election in 2001 has been mistakes in diagnosis of attention deficit disorder, overuse of

prescription drugs to treat the condition and their side effects. Strattera has attracted attention in this regard. After consultations with the manufacturer Eli Lilly, and an internal review, the Department had decided to release two documents in full, to release parts of seven others and to claim two documents wholly exempt. The exemptions cited were section 43 (business affairs) and section 45 (information obtained in confidence). Lilly prior to the internal review had objected to disclosure of 8 of the 9 documents the Department had been prepared to release in full or in part. It did not object to release of one document, the Public Summary Document for Atomoxetine from a November 2006 Pharmaceutical Benefits Advisory Committee meeting. Mr Whitely took the matter to the Tribunal. In *Whitely and Department of Health and Ageing* [2010] AATA 338, the Tribunal was presented with an additional and compelling argument for refusal of access to all 11 documents in their entirety: the documents were exempt under section 38 of the act because disclosure was an offence under section 135A of the National Health Act, a provision listed in Schedule 3 of the FOI act. Secrecy provisions listed in schedule 3 of the FOI act in effect trump FOI rights of access. The Tribunal agreed, noting it had no power to grant access to the documents. This case shows how information relevant to public health is protected from disclosure by laws that do not require showing harm from disclosure.

Recommendations

The basic principle that “transparency should be the rule” needs to be clearly stated in all health acts. Information available within regulatory agencies should be freely available to any party that requests it. Exceptions to transparency, notably for “commercial in confidence”, must be defined and interpreted very strictly.

The definition of “commercial confidentiality” should be reviewed so that it does not undermine FOI rights of access.

Conclusion

The reduced capacity of the TGA to undertake additional activities to protect public health such as supporting independent pharmacovigilance studies and supporting communication and transparency is a serious concern. “Too costly” was the reason given when the TGA refused to provide CMI and PI on its website following a review that concluded that it was the best option for consumers and health professionals alike. The decision was then reverted after intense pressure of consumer organisations.

I am concerned that the recommendations of this panel review could be downgraded as “too costly”. Transparency has indeed a cost. It is the cost of the integrity, accountability, credibility and performance of the TGA. Performance indicators of the TGA should not focus exclusively on its speedy review of new medicines but on how well it ensures its role in ensuring the protection of the public and in informing the public quickly and comprehensively. Many transparency deficiencies at the TGA may not be only impaired by legal barriers such as the confidentiality provisions in health acts but also by a tradition of “secrecy” in governmental institutions. The TGA must undertake a cultural change as the society has changed. The Australian public has the right to know, transparency should be the rule and not the exception.

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