Comments on TGA draft document: Evidence required to support indications for Listed medicines (Dr Ken Harvey)

Summary

I commend the TGA for preparing this draft document which builds on a previous draft report and consultation on Listed weight loss products. The new draft is much more comprehensive and provides greater clarity for industry and other stakeholders about relevant regulatory requirements. In addition, the difficulty that industry apparently has in interpreting regulatory guidelines should be minimised by the new requirement that a suitably qualified 'expert' must 'sign off' on a report detailing the evidence supporting the indications and claims made at the time of Listing. I wholeheartedly support the adoption of the document subject to some additional considerations being taken on-board. The latter are detailed below.

Excellent features of the draft document:[1]

- It reiterates the positive features (for industry) of the TGA's risk-based system for regulating Listed medicines: quick, easy and inexpensive market entry with no pre-market assessment.

  Sponsors self-certify that the ingredients are picked from a consolidated list that the TGA regards as relatively low risk; that their product is manufactured according to GMP standards; that the product only carry indications and claims for the symptomatic relief of conditions (but not for proscribed serious disease, disorders, or conditions), health maintenance, health enhancement and risk reduction, and that they hold evidence sufficient to substantiate that the indications and claims are true, valid and not misleading.

- It builds on the "Draft Guideline for Levels and Kinds of Evidence for Listed Medicines with Indications and Claims for Weight Loss" and the consultation that followed.[2]

- It addresses the assumption that non-compliance with existing regulatory requirements is due to lack of clarity in the current 2001 guidelines on evidence[3] and/or some companies do not have staff sufficiently skilled to apply them to their own products.

  It does this by specifying in more detail the characteristics and types of listable indications, the difference between scientific and traditional indications, evidence required to support them and the type of health benefit that indications may target.

  In addition, a key difference from current document is that the new draft states, "To ensure that the relevant body of evidence is comprehensively and objectively assessed, an 'expert'

[1] http://www.tga.gov.au/industry/cm-notices-evidence-guideline-draft-120423.htm
[2] http://www.tga.gov.au/archive/consult-cm-weightloss-090206.htm
[3] http://www.tga.gov.au/pdf/cm-evidence-claims.pdf

with sufficient clinical and critical appraisal skills to perform such a review must prepare a formal 'expert report' in an appropriate format".

The draft document provides excellent guidance for the 'expert' on how to search the literature, how to assess the relevance, quality and balance of the evidence found about a well characterised active ingredient(s) to listable indications, the health benefit claimed, the target population and the clinical trials reviewed.

- It notes the potential for apparent clashes between the conclusions of traditional and scientific evidence.
- The document also notes that multiple ingredient listed medicines are common. In order to establish relevance of an indication to a proposed medicine, all items of evidence included must involve the same combination of ingredients at comparable doses as the sole active ingredients. When combining ingredients, it is the sponsor's responsibility to ensure that the final formulation is rational and fully supported by evidence.
- Finally, the document provides an interesting appendix of TGA accepted monographs including ancient texts such as Boericke W (1927) Pocket Manual of Homoeopathic Materia Medica.

Additional considerations required:

- Many sponsors are well aware of existing regulations but choose to ignore them because it is profitable to do so, the risk of being brought to task is low and there are currently no effective sanctions for violating the rules. The Auditor-General's 2011 report into complementary medicines regulation revealed that post-market compliance audits carried out by the TGA consistently showed a high level of non-compliance with regulatory requirements; that prosecution is currently the only available option available to the TGA when administrative requests are ignored and yet the TGA has never instituted such action.[4] Numerous upheld complaints about the promotion of Listed medicines reiterate the high level of non-compliance with a key regulatory requirement: that sponsors must hold evidence to support the indications and claims made.[5]

[4] http://www.anao.gov.au/Publications/Audit-Reports/2011-2012/Therapeutic-Goods-Regulation-Complementary-Medicines/
[5] http://www.tgacrp.com.au/index.cfm?pageID=13&displayYear=2011

In addition, if a sponsor is subjected to a rare TGA post-marketing review they can (and do) withdraw the product themselves (thus aborting the review) and then promptly re-list the product (perhaps with slightly altered ingredients) at minimal cost.

In short, a system that relied on trust and occasional post-marketing audits had failed.

In light of the above, a major problem with this draft paper is the lack of any implementation plan or incentives or sanctions to encourage regulatory compliance. It was a major disappointment that the response to these concerns in "TGA reforms: A blueprint for TGA's future" was merely to state (with no time frame given) that, "The government will examine the regulatory impact of options for enhancing sanctions and penalties for repeated breaches of the compliance".[6]

Even if this draft paper is finalised, without appropriate and timely sanctions and penalties it is likely to have no impact on the regulatory non-compliance that is par for the course in this industry.

The government must immediately implement effective, timely and transparent sanctions and penalties for breaches of regulatory compliance including advertising breaches. These must include easily applied civil penalties including substantial fines and enforceable undertakings such as retraction orders.

- The draft guidelines are also silent on naming products, yet names often contain an implied claim for efficacy that is unsustainable when the evidence is reviewed, e.g. Fat Blaster, Fat Magnet, Undoit (5 pills undoes a Big Mac and fries), Horney Goat Weed, Intense Cleanse (2 day detox), etc.

  This problem needs to be addressed by a statement in the guidelines that the name of the product must not make an implicate claim unless this is substantiated by the 'expert' report.

- The draft report notes that, "If the processing used to prepare a particular herbal product is different to that used in studies, sponsors will need to hold evidence that the chemical profile of the active ingredient(s) is not substantially different from the preparation used in the studies to support the indication".

[6] http://www.tga.gov.au/newsroom/media-2011-tga-reforms-111208.htm

Currently, it is common for sponsors to promote phyto or therapeutic equivalence of any generic ingredients used, regardless of the fact that only certain well characterised preparations in specific commercial products have shown clinical efficacy.

Industry (and the TGA) has failed to educate consumers and health professionals that complementary medicines (especially herbals) are often complex products and the concept of therapeutic equivalence of generic ingredients that is applicable to PBS products does not apply to complementary medicines. Just as all red wine is not Grange Hermitage neither are all preparations of St John's Wort, or glucosamine for example, therapeutically equivalent.

The final report must emphasise that clinical trial results only apply to the specific, well characterised product that was tested; they CANNOT be automatically extrapolated to other products containing the same generic ingredient without good evidence of phyto or therapeutic equivalence.

- The draft document states, "The availability of evidence that disputes the efficacy of the preparation does not disprove the history of use and the traditional indication remains valid".

  While this may be true epistemologically it is not helpful practically for consumers and health professionals to be told that X "Contains ingredients traditionally used in Ayurvedic medicine to aid sleep" when more recent well conducted clinical trials have failed to show X has any more effect on insomnia than a placebo!

  In addition, the Australian Homeopathic Association states, "homeoprophylaxis has been used for 200 years in homeopathy and precedes modern vaccination. There are numerous documented examples of the successful use of homeoprophylaxis throughout history".[7] In this case, presumably a homeopathic 'expert' would allow the claim that "The Standard Childhood Homeoprophylaxis Program (based upon the ground-breaking research of Dr Isaac Golden) is traditionally used by homeopaths to prevent Whooping Cough, Pneumococcal Disease, HIB, Meningococcal Disease, Polio, Tetanus, Measles and Influenza"?[8]

  The following statement in the current 2001 guideline (page 11), MUST be added to the draft document "Should scientific evidence be contrary to the evidence based on

[7] http://www.homeopathyoz.org/downloads/MediaKit01-FAQs.PDF
[8] http://www.homeoprophylaxis.com.au/AboutHP/HPPrograms/tabid/1062/Default.aspx

traditional use, the claim used must reflect the truth, on balance of the evidence available".

- Finally, homeopathic medicines were conspicuous by their absence in the draft report apart from being listed in Materia Medica and repertory references. A previous consultation on the "Regulation of homoeopathic and anthroposophic medicines in Australia"[9] was never brought to a conclusion and many problems remain with this form of medicine. These include the ongoing promotion of homeoprophylaxis as an alternative to conventional immunisation,[10] the use of conventional medicines such as melatonin in commercial homeopathic sleeping pills preparations[11] (which is not in keeping with Hahnemann's so-called "Law of Similars") and numerous research that shows overall, homeopathic medicines are no more effective than a placebo.[12,13]

  In addition, homoeopathic preparations more dilute than a one thousand fold dilution of a mother tincture are currently exempt from Listing on the Australian Register of Therapeutic Goods (ARTG)[14] and thus escape the evidential requirements of the draft report.

  All medicines purporting to be prepared in the homeopathic or anthroposophic tradition, regardless of dilution, must be Listed on the ARTG and comply with regulatory guidelines for Listed medicines (including the important additions suggested above).

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[9] http://www.tga.gov.au/archive/consult-cm-homoeopathic-080901.htm
[10] http://www.accc.gov.au/content/index.phtml/itemId/1049609/fromItemId/142
[11] http://www.bioglan.com.au/common-needs/stressrelief/melatonin-90s/melatonin-90s.html
[12] https://www.mja.com.au/journal/2010/192/8/homeopathy-what-does-best-evidence-tell-us
[13] http://rheumatology.oxfordjournals.org/content/early/2010/11/08/rheumatology.keq234.abstract
[14] http://www.tga.gov.au/industry/cm-homoeopathic-preparations.htm#artg