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Health systems and Products, Pharmaceuticals
Health and Consumers Directorate-General
Unit SANCO/D/3,
BREY 10/112,
BE-1049,
Brussels

c.c.: Anton Norder (TGA)

Dear Sir/ Madam

Subject: Comment to Concept Paper - *Implementing Act on the Requirements for the Regulatory Framework Applicable to the Manufacturing of Active Substances of Medicinal Products for Human Use.*

The Australian Self-Medication Industry (ASMI) is the peak body representing companies involved in the manufacture and distribution of non-prescription consumer healthcare products in Australia.

ASMI appreciates this opportunity to provide comment toward the implementation of the requirements for the regulatory framework applicable to the manufacturing of active substances of medicinal products for human use.

ASMI do not propose to make comments from the perspective of Australian exporters of APIs to the EU. We are confident that the EMA already has experience of the equivalence of Australia's rules for GMP, the regularity of inspections and the effectiveness of GMP enforcement after the publicised success of the EMA , US FDA and TGA's *International API Inspection Pilot Programme.* Australian manufacturers of therapeutic goods and manufacturers of APIs must hold a TGA GMP License. The license is obtained based on TGA inspection and can only be maintained subject to regular inspection.

ASMI propose to make comment to the concept paper on the basis of the Mutual Recognition Agreement (MRA) between Australia and the EU and the need for maintenance of equivalence between MRA partners. We believe all our comments therefore fit under Consultation item No.5 – Any other issues not raised above.

The implications to the Australian regulatory environment are broad and stem from differences in the regulation of products in this market when compared with the regulation of similar products in the EU. These differences occur at the Therapeutic Good/Dietary Supplement/Food interface and the Therapeutic Good/Cosmetic interface. Particular products at these interfaces, vitamin and mineral supplements, herbal supplements, nutritional supplements and sunscreens, are regulated as therapeutic goods in Australia.

In Australia the majority of these products (dependent on level of claim and level of active) are classified as lower risk medicines. However in most markets these products are not classified as medicines and are regulated as foods/dietary supplements or cosmetics respectively. This is largely true also of the situation in the European Union (EU). While it is recognised that herbal substances can be registered as Traditional Herbal Medicines, herbal and vitamin and mineral substances may also be marketed as foods with food supplement claims even though they are presented in medicinal style dose forms and packaging with dosage instructions for use, which

would force the product to require listing as a medicine in the Australian environment. Schedule 4 of the *Therapeutic Goods Regulations 1990* identifies the Therapeutic goods required to be included in the part of the Register for listed goods. Section 7 of the *Therapeutic Goods Act 1989* allows the TGA to make a determination whether a product is or is not deemed a therapeutic good.

ASMI members concerns arising from the MRA between Australia and the EU are related to the significant implications of the minor differences in where the regulatory interfaces are drawn between the partners. They have the potential to have significant impact on TGA resources and costs to the Australian Complementary Medicine and Sunscreen industries, further impacting their viability to compete in export markets. If not appropriately managed the MRA may have unintended consequences. .

The TGA resource implications are explained in more detail below.

The Australian regulatory system does not include an equivalent of the 'Qualified Person'.
GMP Clearance of an overseas API or a finished dose form site of manufacture can be granted by the TGA to a sponsor (Marketing Authorisation holder) on the basis of GMP Compliance evidenced by any one of the following:

- A GMP Certificate issued by a country with which Australia has an MRA in relation to the relevant overseas manufacturing site.
- A Compliance Verification assessment (desk top audit) of a recent GMP inspection report of the relevant overseas manufacturing site prepared by a competent overseas regulatory agency acceptable to the TGA, together with supporting manufacturing documentation supplied by the sponsor or manufacturer.
- A GMP Certificate issued by the TGA following an on-site audit of the relevant overseas manufacturing site.

The TGA does not currently require sponsors to submit Clearance applications for APIs used in listed medicines or registered over-the-counter (OTC) and complementary medicines. Sponsors must ensure that any step of manufacture (e.g. blending of the active to create a direct compression grade of the material) undertaken outside of Australia is undertaken in GMP compliant facilities. This is a similar approach to that taken in the EU with GMP of 'atypical actives'.

The GMP Clearance application is separate to the product license application or variation to change, and must be maintained for currency approximately every 2 years. The GMP Clearances required for the steps of manufacture of a therapeutic good are linked to the Marketing Authorisation. Update to the GMP Clearance triggers the need for variation of the Marketing Authorisation.

The impact on the TGA audit resource to implement an equivalent regulatory framework for all active substances encompassing Listable Medicine actives or 'atypical actives' would be exponential for the following reasons:

1. Where listed medicines are classified as foods or cosmetics in the majority of countries, the 'actives' produced for their manufacture are therefore manufactured to a food or cosmetic standard. The TGA is faced with this issue for overseas manufacturers of listed complementary medicines, where they must audit or require a recognised competent authority to audit to the *PIC/S Guide for good manufacturing practice for medicinal products*. Looking at the key global production zones the current practicalities are:
    a. For cosmetics the country authorities generally have the power to inspect cosmetic product manufacturing facilities. Where Good Manufacturing Practice (GMP) Guidelines are available they are product based and do not provide comprehensive GMP requirements for active ingredient manufacture. They therefore would not meet any of the requirements for equivalence assessment. Therefore TGA would be required to Audit or require the competent authority to audit the facilities to the PIC/S for all listed sunscreen actives imported into Australia OR not allow the import of the active.
    b. For Herbal or Vitamin or Mineral actives the country authorities may have product based enforced codes of GMP or the requirement for HACCP ISO 9000. It is however unlikely that the existing standards would meet the requirements for

equivalence assessment. Therefore TGA would be required to Audit or require the competent authority to audit the facilities to the PIC/S Guide OR not allow the import of the active.

2. The TGA resource required to conduct audits would need to multiply to manage the increase in audit load.
3. The Australian Therapeutic Goods Act is fully cost recovered by fees levied on the industry. To fund the addition resource required by the TGA the annual fees and charges applied to sponsors would need to be significantly increased. The industry would additionally bear the costs of audits approximately every 2 years charged to the marketing authorisation holder or the manufacturing authorisation holder.The current costs for a 4 day overseas Audit by the TGA is of the order of $AUD 30-40K.

The existing GMP requirements, combined with the legislated quality standards Australia is required to comply with (British Pharmacopoeia, European Pharmacopoeia or United States Pharmacopeia) are adequate to control the quality of these types of active ingredients.

ASMI would therefore request that these matters of practicality surrounding listed or 'typical actives' are considered as part of this consultation with the suggestion they be exempt from the requirement. The small but significant regulatory differences between our markets have the potential to impose an increased regulatory and cost burden, unintentionally reducing the viability of one country's industry.

While the EC Concept Paper does not provide specific details of how the new requirements for imported APIs are proposed to work in practice, ASMI would like to make some comment based on experience of the practicalities of similar types of requirements within the Australian environment.

ASMI is unclear from the Concept Paper where the responsibilities for assessing the written confirmation from the 3rd country competent authority will lie:

1. the customs authority, preventing importation at the border or
2. the manufacturing authorisation holder, confirming the documentation on receipt of the goods and notifying medicines authorities where irregularities occur.

The 1st option raises significant process/logistics issues and if not well implemented and maintained has potential to disrupt the supply chain and create issues of medicine shortages.

ASMI also question:

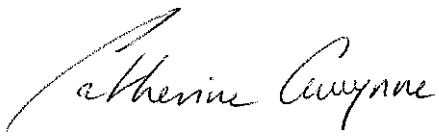
1. How the documentation is proposed to be confirmed as authentic? ASMI suggest the manufacturing authorisation holder may be best placed to confirm this.
2. What the resource implications are to the 3rd country competent authorities in issuing written confirmation when required for each shipment of each API. ASMI's members have advised that obtaining notarised copies of evidence of GMP from 3rd country competent authorities for a GMP clearance application to TGA was time consuming and complicated by lack of understanding on the part of the 3rd country competent authorities.
3. If the requirement for written confirmation with each shipment is waived and the responsibility for assessment of the written confirmation lies with the customs authority at the border, how will customs determine that equivalence of the 3rd country's competent authority has been established, covers this API's site of manufacture and is current.

Australia has strict customs and quarantine inspection requirements to protect native flora and fauna and our agriculture and livestock industries from entry of exotic pests and diseases. ASMI members, particularly those importing actives and excipients of natural origins have experience of the delays that can occur in the supply chain due to questions raised by customs inspectors even when the correct documentation accompanies shipment. Additionally members have experienced situations where customs inspectors wish to sample materials in non GMP facilities or irradiate materials to eliminate potential risks posed by materials. Where the required information cannot be provided within the required timeframe to customs the material is returned to the country of origin or incinerated.

Based on the concerns raised above, ASMI suggests that the process for obtaining and authenticating the written confirmation from the 3rd country competent authority may require further consultation once a detailed proposal is established.

ASMI hope our comments are helpful in contributing to the further development and implementation of this concept.

Yours faithfully



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