Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Criteria for comparable overseas regulators

Enhanced international collaboration in the regulation of prescription medicines

Version 1.0, October 2016

TGA Health Safety Regulation

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Contents

Purpose and scope

The Therapeutic Goods Administration (TGA) is seeking comments on proposed criteria to identify comparable overseas regulators (CORs) as providers of assessment reports and possible work-sharing partners in the assessment of medicine registration applications.

We are specifically looking for feedback on:

- the proposed two-step process for identifying suitable opportunities for collaboration
- the individual criteria for identifying a COR (Stage 1) and considerations that are taken into account when a submission or assessment report is received (Stage 2)

The criteria outline key factors that need to be addressed to best realise the envisaged benefits of formal international collaboration. As these criteria are finalised, detailed guidance on how they will be applied to the work-sharing and COR-report processes will be developed.

This consultation focusses primarily on how these criteria will be applied within the prescription medicines context. However, they could also potentially be applied to biologicals (cell and tissue therapies) and registered over-the-counter medicines as part of future considerations. Complementary medicines and medical devices are not included within the scope of this consultation.

Background

The Independent Panel conducting the Review of Medicines and Medical Devices Regulation[1] (MMDR) made recommendations aimed at streamlining the TGA's assessment and registration processes and improving timely access by Australian consumers to new medicines.

The MMDR review recommended that the TGA should make greater use of assessments from comparable overseas regulators (CORs) in its own processes. In using international assessment reports, the TGA would continue to make the final regulatory decisions, ensuring that quality and safety are not compromised and that the Australian context is taken into account.

In its 2016 Budget announcement, the Australian Government noted that through the use of overseas reports from CORs, these reforms have the potential to reduce medicine assessment times by up to three months.[2]

The MMDR review also recommended that the TGA better utilise opportunities to work-share with CORs. Through work-sharing we aim to improve efficiencies in our review processes, develop a more streamlined entry for applicants to enter multiple international markets and potentially enable earlier access to medicines for Australian consumers.

Currently, applications for new medicines may include reports from other regulatory agencies. These are voluntarily provided by the applicant as supplementary information; the information may not be a complete set of reports, it can originate from any agency and does not undergo any review by the TGA prior to submission. Such information may be referred to during the assessment of the dossier but does not replace a de novo evaluation. This practice would not be affected by the introduction of a formal process where use of overseas reports from CORs would replace de novo evaluation by the TGA.

[1] <http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation>
[2] <http://www.health.gov.au/internet/budget/publishing.nsf/Content/budget2016-factsheet23.htm>

To enable the benefits identified by the MMDR review to be realised, the TGA will need to set up new business processes to formalise these collaboration activities. In addition, it is important that confidence in the regulatory actions undertaken by the TGA, including independent decision making processes and transparency of those decisions, is maintained.

To ensure clarity and consistency in processes, the MMDR review also recommended that the TGA develop and apply transparent criteria for identifying CORs. Consequently, this paper expands on the draft criteria outlined in the MMDR recommendations and outlines how these would be applied within:

- a process where a sponsor supplies a complete suite of COR reports as part of a medicine registration application and
- a work-sharing process for applications simultaneously submitted to the TGA and a COR.

International engagement

Adoption of international standards

The TGA has long-standing practices in place that govern its extensive adoption of, and alignment with, international standards. They are largely produced by multilateral groups of experts into which we have a significant level of input. The criteria proposed in this consultation paper are not intended to revisit these, but instead utilise the work that has been accomplished already.

Cooperative agreements

For many years, we have been involved in information-sharing and other activities with a number of overseas regulators and we have agreements and Memoranda of Understanding (MOUs) with many of them.

Importantly, many of these agreements include provisions about the confidentiality of shared information. Under the current Australian therapeutic goods legislation, these cooperative relationships underpin our ability to release and share information and provide an avenue for dialogue between regulators.

Global coalitions

In addition to arrangements between individual countries, we are involved in a number of global initiatives relating to regulation of medicines. These aim to avoid duplication of efforts and promote informed, risk-based allocation of agencies' resources.

Most notably, we are an active participant in the International Coalition of Medicines Regulatory Authorities (ICMRA). The ICMRA provides leadership in confidence building and greater collaboration between regulators. In addition to capacity building, specific working groups have been convened to progress information sharing and communication between agencies.

Another important coalition is the Australia-Canada-Singapore-Switzerland Consortium (ACSS). Again, a number of working groups have been established with the goal of creating greater alignment between these similar agencies.

We will continue to work with international counterparts through these existing arrangements, supporting our move to implementation of formal work-sharing activities. The criteria proposed

in this paper are intended to describe these relationships and set a framework for future cooperative arrangements.

How will COR relationships be utilised?

COR report-based assessments

Applicants can use these criteria to identify suitable assessment reports that are available from an agreed COR. These reports can then be included in an application to us for a new prescription medicine, in addition to submission of the complete dossier.

We could then conduct an abridged evaluation of the dossier, focussing on the Australian-specific Module 1 data, and a review of the COR reports. Depending on the quality and scope of the overseas reports provided to us, the need to evaluate the submitted data within the dossier can be reduced to a greater or lesser degree.

This process would be used for assessing:

- New chemical and biological entities
- Extension of indications
- Generic medicines
- Biosimilars

This process can be implemented with the adoption of new business rules and practices within the existing legislative framework.

Work-sharing

Work-sharing is where a medicine application dossier is submitted simultaneously to two (or more) regulators and is then jointly assessed as described below. The joint proposal would need to be submitted by related companies in each country with the express consent of each to the work sharing.

Work-sharing will be based on each agency taking responsibility for the assessment of a discrete section of the dossier. For example, Module 3 would be assessed by Agency A, Module 4 assessed by Agency B and Module 5 by either agency or potentially by both. Work-sharing on applications for new generic medicines is also envisaged, with division of Module 3 and bioequivalence data as appropriate in individual cases.

At the completion of the assessment, reports would be exchanged directly between the agencies. Each agency then follows their own independent decision-making processes – including the right to refer to expert advisory bodies.

This process would be used for assessing:

- New chemical and biological entities
- Extension of indications
- Generic medicines
- Biosimilars

A number of logistic factors will be considered in applying the criteria to the two processes.

For work-sharing, the timing and availability of COR and TGA resources to conduct simultaneous assessments are key to a successful work-sharing activity and need to be determined prior to lodgement.

Additional considerations

Expedited approval

As part of the response to the MMDR recommendations, we plan to create two expedited processes (subject to the necessary legislative changes being made). The first would result in new medicines that meet certain strict criteria being evaluated in a reduced timeframe ('priority review').

The second process would result in new medicines that meet certain strict criteria being given time-limited approval ('provisional approval'). Criteria for this process include evidence of early data indicating that its availability would provide a significant benefit to the treatment of Australian patients.

The use of overseas reports or work-sharing arrangements with a COR could be utilised in these pathways.

Over-the-counter medicines

Once the criteria have been established for prescription medicines, we will consider whether these criteria could usefully be applied in the registration of OTC medicines.

Proposed criteria

Summary

The criteria developed to identify these collaborative activities are designed to be applied through a two-stage process.

The first stage sets out the preliminary criteria that confirm that there is sufficient similarity between the overseas agency and us to support collaborative work of this nature.

The second stage outlines the parameters that we would consider about the suitability of:

- a particular submission to be evaluated using work-sharing or
- assessment reports from another regulator (COR reports) to be used in the TGA evaluation process.

Individual criteria may apply, equally or to varying degrees, to both these activities or may be specific to either the use of COR reports or work-sharing.

Stage 2 criteria apply to a specific activity, either work-sharing or use of overseas reports, when it is being considered in relation to a particular submission. These are assessed at the time the submission is received from an applicant but can also inform first stage considerations.

Stage 1: Identification of a comparable overseas regulator

Stage 1 criteria describe how closely the overseas agency's regulatory framework aligns with that of the TGA.

CRITERION	COR report process	Work-sharing
1. The COR's regulatory framework should be similar to that of the TGA in terms of what must/must not be taken into account in making regulatory decisions.	Required	Required

The regulatory framework of a COR must be comparable to ours to ensure that confidence is maintained in the Australian regulatory system. Regulatory responsibilities between the COR and us should align to ensure that medicines are of appropriate quality, safety and efficacy. For example, CORs should conduct similar pre- and post-market regulatory activities, including pharmacovigilance programs and full *de novo* assessments of the type of applications that are of interest to us (i.e. new chemical or biological entities, extensions of indication, generic medicines and biosimilars).

This framework will also need to take account of legislated requirements in both countries (including matters such as confidentiality, intellectual property, transparency and conflict of interest).

CRITERION	COR report process	Work-sharing
2. The TGA must have established a formal and robust framework for cooperation with the COR.	Desirable	Required

Formal and robust frameworks between regulators can include MOUs and exchanges of letters.

This criterion is particularly important for work-sharing activities, where links between agencies must allow clear, open, secure communication on regulatory issues and transmission of confidential information. Such communication must be compatible with each nation's international and domestic obligations. Where reports are supplied to us by an applicant, a robust framework with a COR would also give us the ability to seek clarification on those reports.

CRITERION	COR report process	Work-sharing
3. The COR must use similar international guidelines and standards to the TGA.	Required	Required

The COR should have established processes to evaluate dossiers containing scientific data in accordance with ICH guidelines and a system of peer review and referral for independent expert advice in relation to their assessments. Adoption of ICH guidelines and pharmacopoeial standards is essential to ensure that our data requirements and assessments reflect agreed international best practice.

In applying this criterion, we could consider how the overseas regulator adopts standards such as the European Pharmacopoeia, British Pharmacopoeia and United States Pharmacopeia as

these standards are legislative requirements in Australia. Any differences in how these international standards are adopted will need to be understood to best make use of overseas assessments.

CRITERION	COR report process	Work-sharing
4. The COR should be able to conduct their business and release reports in English.	Required	Required

For the COR report based process, the Australian sponsor must have access to the assessment reports in English to provide these to us as part of the medicine application. This is necessary to ensure that neither time nor accuracy is lost in translation.

For work-sharing, it is important that our evaluators are able to communicate in English with those who conduct the assessments.

Stage 2: Application-specific considerations

Stage 2 criteria focus on the specifics of a particular application. Once an overseas regulator has been identified as either a source of assessment reports or a work-sharing partner, the following considerations will be applied to determine whether proposed use of the COR reports or work-sharing can proceed.

For both processes the following factors will be crucial:

- comparability of the medicines and
- the nature of the assessment process undertaken by each agency.

All relevant criteria would need to be addressed to allow COR reports to be utilised or work-sharing activities to be initiated with a COR.

Comparability of the medicines

CRITERION	COR report process	Work-sharing
5. Identical indications are proposed for the medicines (including dosage regimen and route of administration).	Desirable	Required

With respect to the proposed indication, broadly similar population demographics, disease profiles, and expectations regarding public health outcomes should apply to both Australia and the COR. Any differences would need to be identified and justified by the applicant.

If assessment of the application is being done as part of a work-sharing exercise, the proposed indications for the medicines in each jurisdiction should be identical.

CRITERION	COR report process	Work-sharing
6. The medicine for which Australian registration is sought is identical to that approved by, or submitted to, the COR (i.e. dosage form, strength, formulation and manufacture).	Desirable	Required

For overseas assessment reports to be of most value as part of the COR report-based process, they must relate to the same medicine. If not identical, any differences between the medicine that has been submitted for registration in Australia and that which was the subject of the COR assessment report must be clearly understood.

Differences in characteristics such as formulation, manufacture, and indications are possible in situations where the application to us is made some time after approval by the overseas regulator. The details of any such differences must be provided to us so their possible impact on the safety, quality and efficacy of the medicine can be ascertained and subsequently reflected in registration decisions, approved Product Information and Risk Management Plan.

If assessment of the application is being done as part of a work-sharing exercise, the proposed medicines should be identical in terms of quality.

Nature of the assessment reports

CRITERION	COR report process	Work-sharing
7. Assessment reports should be prepared using methodology, guidelines and standards consistent with those used by the TGA.	Required	Required

To ensure the most benefit from work-sharing and the COR report process, the overseas assessment reports should be based on a methodology that is consistent with that used by the TGA. A key consideration in this criterion is whether the assessment reports have the required scope. For example, in the case of clinical assessments, we would consider what studies and analyses have been included, and for each of these, the data cut-off for analysis.

Differences in methodology need not prevent the use of the assessment reports. However, we would consequently need to be provided with additional information to address any gaps or concerns, reducing the benefit of using an overseas report.

CRITERION	COR report process	Work-sharing
8. Assessment reports must be un-redacted and complete.	Required	Required

As part of the COR report-based process, the Australian applicant is responsible for providing the reports to us at time of lodgement of the application.

To reduce the need to refer to dossier data, reports must be un-redacted and complete. These complete reports should include correspondence related to the application (e.g. questions asked of, and deliberations by, advisory bodies).

CRITERION	COR report process	Work-sharing
9. The TGA must be able to use assessment reports and any supplementary information generated during the evaluation process as part of Australian Public Assessment Reports.	Required	Required

We are committed to producing Australian Public Assessment Reports (AusPARs) as a key transparency initiative in the interests of the Australian public. Therefore, we need to be able to use overseas reports and work-sharing information as part of this initiative.

Reports that are provided to us should not be subject to any restrictions on use or disclosure by the TGA other than those which would apply to any material provided in an application dossier (e.g. these reports must be able to be used as the basis for published AusPARs).

Overseas regulator confidentiality provisions may also affect our ability to publish information generated through work-sharing arrangements in AusPARs. In considering a work-sharing application, we will therefore be informed by the formal relationship established with the overseas source regulator, specifically in relation to confidentiality provisions.

Questions

- Is the proposed two-step process for identifying suitable opportunities for collaboration appropriate?
- Are the individual criteria under Stages 1 and 2 appropriate?

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	SOMS/SEB	October 2016

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