Medicines regulation

Regulating medicine manufacturers: is an on-site inspection the only option?

The Australian approach to meeting inspection demands

On-site inspections of manufacturing and testing sites for medicines are resource-intensive for both regulators and manufacturers, especially as an increasing number of sites are located outside regulatory authorities’ territories. To maximize the impact of limited resources, it is therefore good regulatory practice to leverage available evidence from other agencies as part of a risk-based inspection planning process.

The Australian Department of Health’s Therapeutic Goods Administration (TGA) has been using a risk- and reliance-based approach in inspection planning for some time. This article describes the TGA’s pathways for granting good manufacturing practice (GMP) clearance.

Background

A cornerstone of effective medicine regulation is ensuring that the medicines available within a market meet appropriate quality standards. To this end, a national regulatory authority (NRA) will assess product quality data during pre-market assessment. Generally, this involves assessment of quality data provided as part of the application dossier (1) by the applicant, and an onsite inspection of the product manufacturer against compliance with the applicable Good Manufacturing Practice (GMP) standards, such as those developed by WHO and used in its Prequalification Programme (2,3) or those of the Pharmaceuticals Inspection Convention/Pic/S.

Where the manufacturer has been previously inspected and approved by the NRA, an onsite assessment may be avoided if the manufacturing steps are the same. If the product is approved for supply, the NRA monitors the manufacturer’s compliance with applicable GMP standards via regular inspections, either announced or unannounced.

A key objective of a GMP inspections programme is to provide the NRA with a proactive mechanism for identifying and preventing quality related medicine safety risks. Once a manufacturer is approved for supplying medicines to the market, re-inspections are usually conducted.

Authors:
Hongxia Jin, Nicola Carr, Harry Rothenfluh
Manufacturing Quality Branch, Therapeutic Goods Administration, Australian Department of Health
within a risk framework that takes into account product and process risks and manufacturer compliance history. (e.g. 5,6) The objective should be to conduct more frequent inspections of manufacturers with a higher risk profile. In contrast, where a manufacturer has demonstrated a high level of voluntary compliance with GMP standards over time, re-inspections could be conducted on a less frequent basis.

**Challenges in meeting demand for GMP inspections**

Maintaining an effective GMP inspections programme can be challenging for many reasons, including the following:

* Availability of appropriately trained and qualified staff
  Given the technical nature of the work involved in planning, conducting and closing out GMP inspections, GMP inspectors must have appropriate academic qualifications and professional experience.
  Factors that may impact on an NRA’s ability to build and maintain a team of appropriately experienced GMP inspectors include the presence of a domestic manufacturing industry, tertiary education institutions that offer suitable courses and the ability of a regulator to offer salaries that are competitive with those offered by industry.

* Inspecting international manufacturers
  Depending on the size and diversity of the domestic pharmaceutical market, NRAs may need to regulate a large number of domestic and/or overseas pharmaceutical manufacturers. In some countries, including Australia, there are many more international manufacturers than domestic manufacturers supplying the market.

Challenges associated with inspecting international manufacturers include travel costs and logistics, visa and other entry requirements, language barriers and inspector health and security risks.

**Demand for inspections outstrips capacity**

As the pharmaceutical supply chain becomes more complicated, the demand for GMP inspections can exceed the capacity of an NRA to meet that demand. In particular, with the emergence of contract manufacturing, multiple manufacturing sites may be associated with a single product. This can be mitigated to some extent by relying on the supplier qualification processes of the finished dosage form manufacturer.

Nevertheless, with increasing investment by international pharmaceutical companies in emerging medicine manufacturing economies, it is likely that the demand for GMP inspections will increase over time.

**Consequences of not meeting demand for GMP inspections**

The consequences of insufficient resources being available to meet the demand for GMP inspections include:

* Delayed access to new medicines by patients
  Delays in inspecting new manufacturers, or new manufacturing steps conducted by previously approved manufacturers, may delay product approvals. This may delay access of patients to new or essential medicines, which in turn may adversely impact on public health programmes.

* Reduced ability of the NRA to identify and manage medicine quality risks
  Failure to conduct GMP inspections within risk-based re-inspection timeframes reduces...
the NRA’s ability to identify manufacturing failures that may affect the safety profile of medicines. This increases the risk that patients may be exposed to medicines that do not meet applicable specifications and quality standards. Such medicines pose a risk to consumers as they may not achieve the desired health outcomes. Further, in the case of medicines used to treat infectious diseases, substandard medicines may promote the emergence of resistant strains of the infectious agent.

Lengthy approval times may deter investments and imports
Delays in approval times may be a disincentive for foreign investors to build manufacturing capacity in target countries. It may also be a disincentive for local distributors to apply for permits to import and supply medicines made by international manufacturers. This in turn may limit access to medicines that patients need.

Meeting the challenge: The Australian approach
The Australian Department of Health's TGA is responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods in Australia.

Under Australian law an applicant seeking pre-market approval of a medicinal product must supply evidence demonstrating that each manufacturer involved in the manufacture of the product has acceptable manufacturing and quality control procedures in place. It is also a condition of ongoing product approval that such evidence is supplied on request.

The TGA conducts GMP inspections of all Australian manufacturers of medicines. For manufacturers located outside of Australia, the applicant must obtain a TGA GMP clearance for each site, that specifies which manufacturing steps for the required dosage forms can be undertaken.

TGA conducts 80–120 inspections of international manufacturers and about 150–200 inspections of Australian manufacturers every year. However, the Agency does not have the resources to maintain a regular inspection programme for every international manufacturer that supplies API and/or finished product to the Australian market. The TGA has developed a risk-based desktop assessment process that relies on information from recognized regulators. This process has reduced the number of overseas on-site inspections to be performed.(7)

There are two types of desk top assessments that TGA conducts to make a decision about whether to issue a TGA GMP clearance to the international manufacturer:

Mutual Recognition Agreement Pathway
The TGA accepts GMP Certificates issued by a country with which Australia has a Mutual Recognition Agreement (MRA), based on an inspection within their own borders. Evaluation under the MRA pathway includes an assessment of a current GMP Certificate to identify the manufacturing site, to ensure an equivalent GMP standard is applied, and to verify that the scope (manufacturing steps and dosage forms) is relevant to the product to be supplied in Australia.

Compliance Verification Pathway
TGA may also accept evidence from the following:
- An MRA regulatory authority, for inspections performed outside their own borders; or
- the U. S. FDA, for inspections performed inside or outside its own border; or
Australian approach to meeting inspection demands

**Table 1 – Evidence required for Compliance Verification Assessments**

<table>
<thead>
<tr>
<th>Evidence required for Compliance Verification Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All non-sterile dosage forms &amp; APIs</strong></td>
</tr>
<tr>
<td>Current GMP Certificate</td>
</tr>
<tr>
<td>A list of all regulatory inspections conducted within the past 3 years, and a copy of the most recent inspection report</td>
</tr>
<tr>
<td>Details of any regulatory actions in the past 3 years</td>
</tr>
<tr>
<td>Site Master File, Quality Manual or equivalent</td>
</tr>
<tr>
<td>GMP agreement between the sponsor and the manufacturer(a)</td>
</tr>
<tr>
<td>List of products intended for supply in Australia</td>
</tr>
<tr>
<td>Copy of the procedures for release for supply of products included in the Clearance application(a)</td>
</tr>
<tr>
<td>Validation Master Plan</td>
</tr>
</tbody>
</table>

(a) not required unless requested
(b) or principal manufacturer and laboratory/sterilizer

- a recognized regulatory authority of a country with which Australia does not have an MRA (e.g. PIC/S members), for inspections performed within their own borders.

This pathway requires additional data to be supplied by the applicant (**Table 1**). A Compliance Verification assessment includes a detailed assessment of a recent GMP certificate and an inspection report prepared by an overseas regulatory agency recognized by the TGA, together with supporting manufacturing documentation supplied by the applicant or international manufacturer. The extent of the assessment process depends on the regulatory evidence required and increases with product risk and the complexity of manufacture.

The MRA and Compliance Verification assessments may result in a TGA decision to:
- issue a GMP Clearance, valid for a specified period, based on the date of the last on-site inspection performed by the recognized regulator;
- issue a GMP Clearance, valid for a specified period but with one or more conditions; or
- not issue a GMP Clearance where the evidence does not support the scope of the GMP Clearance application.

---

1 https://www.picscheme.org/en/members
TGA currently has MRA (or equivalent arrangements) with the European Union and several other jurisdictions covering 29 countries, and recognizes evidence from an additional 17 regulatory authorities.

Where there is no suitable evidence available from a recognized regulator to support a GMP Clearance application, the TGA will perform an onsite inspection of the international manufacturing site. The TGA always reserves the right to inspect an international manufacturing site regardless of what other evidence is available, particularly if issues have been identified during the compliance verification assessment or if there are concerns about the site’s GMP compliance.

Conclusions
The TGA’s GMP clearance system was created in the early 2000s to facilitate the efficient and effective management of the Agency’s regulatory compliance programmes and reduce the regulatory burden on industry. The widespread use of GMP clearances has significantly reduced the number of overseas TGA inspections required. The Agency is also undertaking an increasing number of joint inspections with other regulators and is contributing to the development of information-sharing mechanisms through the International Coalition of Medicines Regulatory Authorities (ICMRA). These initiatives are consistent with the principle adopted by the Australian Government that “if a system, service or product has been adopted under a trusted international standard or risk assessment, no additional requirements should be imposed for approval in Australia,” unless it can be demonstrated that there is a good reason to do so.”

References
5 PIC/S. A recommended model for risk-based inspection planning in the GMP environment. PI 037-1. 1 January 2012.
7 TGA. Australian Regulatory Guidelines. Good Manufacturing Practice (GMP) clearance for overseas manufacturers.

2 http://www.icmra.info