Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Guidance on licensing/certification inspections

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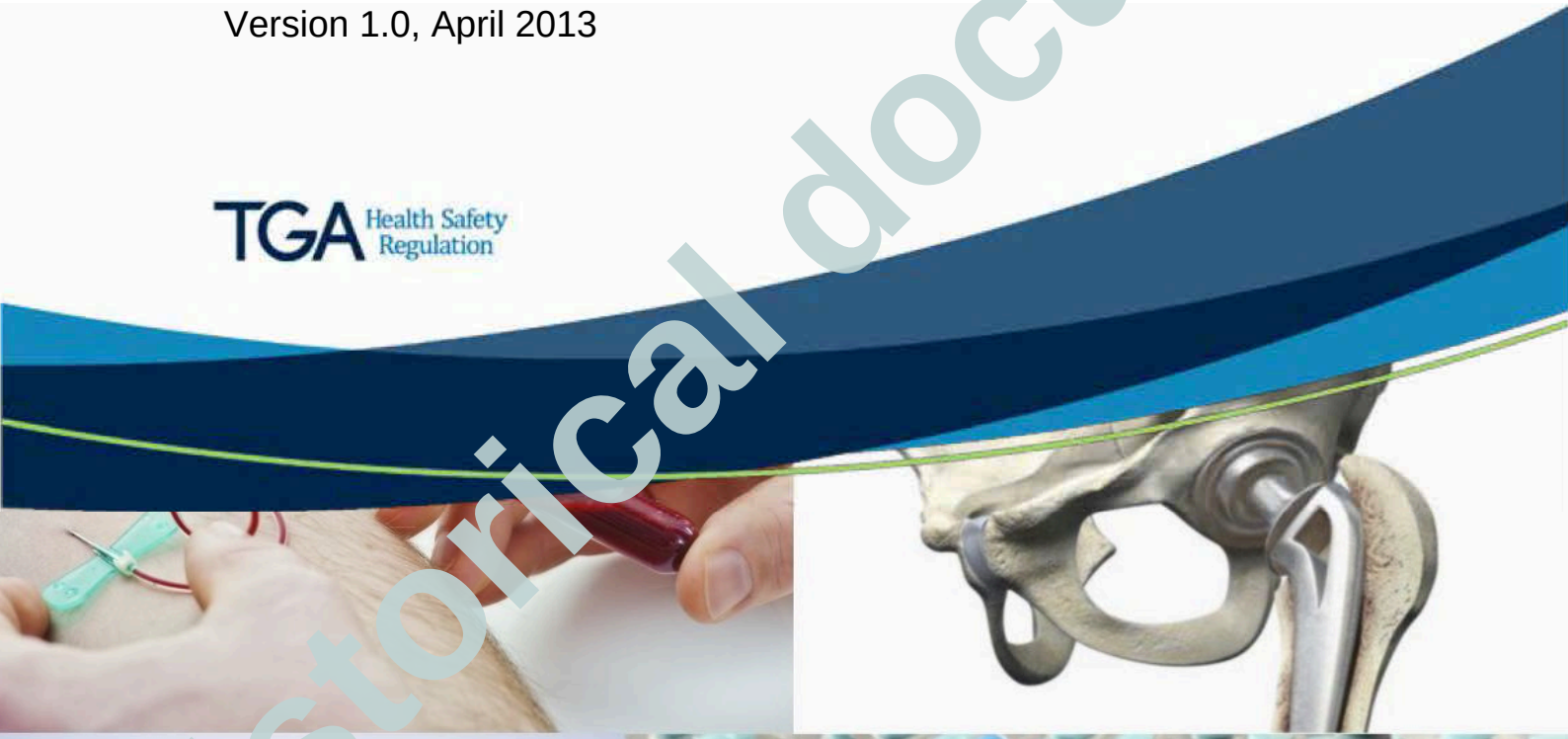
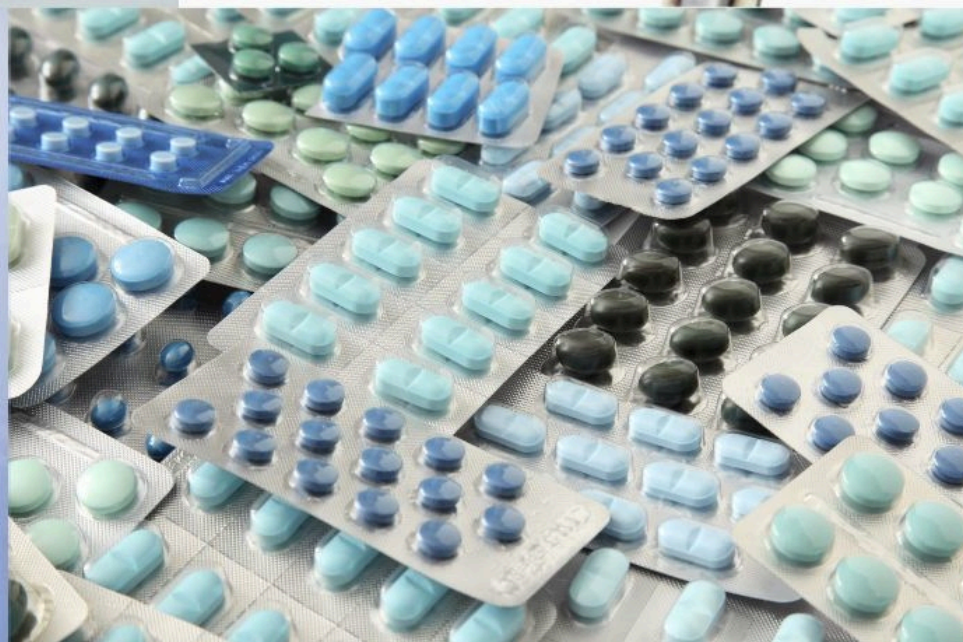
TGA Health Safety Regulation





About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act* 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
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Introduction

The Office of Manufacturing Quality

The Office of Manufacturing Quality (OMQ) is responsible for assessing compliance with Good Manufacturing Practice (GMP) and Quality Management System (QMS) standards of Australian and overseas manufacturers of therapeutic goods in accordance with the *Therapeutic Goods Act 1989* (the Act) and the Therapeutic Goods Regulations 1990 (the Regulations), including:

- Inspecting and licensing of Australian manufacturers of therapeutic goods for supply in Australia and for export
- Assessment and approval of overseas manufacturers supplying therapeutic goods to Australia
  - Note: Assessment of an overseas medicine manufacturer's compliance can be performed either by on-site inspections or through GMP clearance for overseas manufacturers. This Guideline focuses on the inspection program of domestic and overseas manufacturers of therapeutic goods. Guidelines regarding the GMP clearance program are provided in the Australian Regulatory Guidelines Good Manufacturing practice (GMP) Clearance for Overseas Manufacturers
- Special inspections to investigate problem reports and recalls of therapeutic goods.

This Guideline focuses on the inspection program of domestic and overseas manufacturers but excludes the processes for the inspection of manufacturers regulated under the Biologicals Framework. These include human tissues and human cellular therapy products.

The OMQ inspection program

General

The TGA performs inspections of Australian manufacturers of therapeutic goods to ensure that they meet an acceptable standard of GMP or comply with QMS standards, as legislated in the Act and Regulations, including the Manufacturing Principles and the Therapeutic Goods Orders.

The Act requires that overseas manufacturers of medicines and other therapeutic goods that are not medical devices, supplied in Australia, meet an acceptable standard of GMP comparable to that required for Australian manufacturers. If acceptable documentary GMP evidence cannot be provided, the TGA will undertake on-site inspections in the same manner as that conducted for the Australian manufacturers.

Manufacturers of medical devices supplied in Australia must demonstrate that Conformity Assessment Procedures have been applied to demonstrate that a product conforms to the essential principles of safety and performance. Manufacturers implement a quality management system based on recognised standards and have the system assessed by the TGA or a recognised conformity assessment body (overseas manufacturers only). Sponsors must declare that manufacturers have met their obligations and be able to provide relevant technical and quality management system documentation to support this claim.

When requested, the TGA is able to issue GMP or QMS certificates to approved manufacturers.

International involvement of the TGA includes development and maintenance of agreements with overseas authorities, participation in the development of international standards, and training of overseas inspectors. These international agreements may mean that the TGA can accept the results of an inspection from an overseas regulatory authority as outlined in the Australian Regulatory Guidelines Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers.

The TGA conducts inspections on a third party basis only and is independent of all manufacturers inspected.

Regulating medicines manufacture

Australian manufacturers of all types of therapeutic medicines must be licensed under Part 3.3 of the *Therapeutic Goods Act 1989* and must comply with the principles of GMP, unless specifically exempted. Overseas manufacturers of medicines imported into Australia must comply with an equivalent standard of GMP.

Medicines assessed as having a higher level of risk (prescription medicines, some non-prescription medicines) are evaluated for quality, safety and efficacy and are registered on the Australian Register of Therapeutic Goods (ARTG). Medicines having a lower risk (consumer medicines purchased over the counter such as complementary medicines including vitamins) are assessed for quality and safety. In assessing the level of risk, factors such as the effects and side effects of a product, potential harm through prolonged use, toxicity and the seriousness of the medical condition for which the product is intended to be used, are all taken into account.

Licensing or certification of medicines manufacturers, or the verification of compliance of overseas medicine manufacturers, is part of the assessment of medicines for their inclusion in the ARTG. Once approved for marketing in Australia, medicines on the ARTG can be identified by the AUST R number (for registered medicines) or an AUST L number (for listed medicines) that appears on the packaging of the medicine.

Regulating medical devices manufacture

Australian manufacturers of medical devices, and other specified manufacturers of devices incorporating a medicine or biological material, must be issued with a Conformity Assessment Certificate under Part 4 of the *Therapeutic Goods Act 1989*. Their quality management systems must comply with a recognised QMS standard.

All other overseas manufacturers must have evidence of the application of the conformity assessment procedures. This evidence is usually in the form of an equivalent assessment undertaken by recognised conformity assessment bodies.

All medical devices must have been demonstrated, and declared, by their manufacturer to conform to the Essential Principles of Safety and Performance for medical devices. The design of a medical device with a higher risk (pacemakers, coronary stents or incorporating a medicinal substance or biological material) is required to be independently assessed for conformity. Technical documentation for medical devices of lower risk (powered and non-powered hospital equipment, blood bags, and surgical instruments) is sampled during a quality management system inspection. The risk classification of devices is determined from the duration of use, the degree of invasiveness, the location of use and whether or not the device relies upon a source of energy.

Once approved for marketing a medical device is included in the ARTG. It is not required to bear the inclusion number on the labelling or packaging, however the name and address details of both the manufacturer and sponsor must be provided with the device.

Manufacturers are required to implement a comprehensive post market vigilance and adverse incident reporting program.

The licensing/certification process

Australian medicines manufacturers are required to obtain a licence to manufacture therapeutic goods (sometimes referred to as GMP licence). Overseas medicines manufacturers, where GMP clearance is based on a TGA inspection, obtain GMP Certification when passing a TGA inspection.

Australian and some types of overseas medical device manufacturers, selected by legislation, are required to obtain Conformity Assessment Certification.

The following section outlines the usual steps in the licensing or certification from initial enquiry through to the granting of the licence or certificate. The process has been standardised across all the industry streams. The sequence of these steps is as follows:

1. Application received
2. Application review
3. On-site inspection
4. Corrective action if applicable
5. Follow-up
6. Inspection close-out
7. Licensing/certification decision
8. Ongoing inspection activities

The application

The TGA will respond to applications received via the e-application process. As indicated in the application form, full details of the manufacturer including the types of products that are manufactured at each location to be licensed or certified need to be included.

A licence application (for Australian medicines manufacturers) must be accompanied by a declaration that none of the circumstances stated in Section 38(1)(g) of the Act applies to any person involved in the management of the manufacturer. A licence application also requires the nomination of persons responsible for Quality Assurance and Production. These individuals have specific responsibilities under the Act and Regulations, in particular to the Codes of GMP.

Applications for a Conformity Assessment certificates are processed by the Office of Devices Authorisation (ODA), as these certificates attest that product and QMS requirements have been met. Inspection of quality management system requirements is performed when an internal application is made to the TGA by ODA.

Application review

Upon receipt of an application, along with payment of the prescribed fee, an application will be allocated for review. The timing of the inspection may be negotiated at this point.

On-site inspection

The purpose of the inspection is to establish whether a manufacturer has implemented management systems and practices that comply with the relevant code, quality management system standard and regulations. This will be done by examining actual practices, documentation and records and comparing them against the manufacturer's policies and procedures and the relevant Code or QMS Standard requirements, which can be found in the Manufacturing Principles.

For further details regarding the on-site inspection, refer to the section 'The Inspection Process' of this document.

Licensing/certification

Licensing/certification decision

After confirmation that any necessary corrective actions have been taken, which may involve a follow up inspection, the findings and recommendations made in the inspection report are subject to an internal review process prior to a licence or certificate being granted.

Once the manufacturer has achieved the requirements for licensing or certification, the manufacturer will be issued with a Licence or Certificate.

Licence/certificate

When a medicines manufacturer has achieved licensing or certification, the TGA will provide a Licence to Manufacture or GMP Certificate respectively. The document includes important data such as the licence or certificate number, the site address and a description of the types of products and manufacturing steps authorised (for licences) or certified (for GMP certificates). A Schedule of Conditions may be included outlining the restrictions imposed on the Licence or Certificate.

Conformity assessment certificates are issued by the Office of Devices Authorisation (ODA). When ODA has completed any required product assessment, a Certificate indicating the manufacturer's name, site address and scope of products covered by the certificate, will be issued.

All licences and certificates remain the property of the TGA and must be returned upon request. Copies of certificates can be provided upon request and on payment of the applicable fee.

Displaying a licence

The licence to manufacture therapeutic goods and accompanying Schedule of Conditions must be displayed where the general public can view it.

Refusal of a licence or certificate

In the event that the manufacturer is unable to comply with the requirements of the relevant standard, the TGA may refuse to grant a licence or certificate. The decision to refuse licensing or certification, and the grounds for that decision, will be communicated to the manufacturer in writing. (Refer Sections 38 and 41EC of the Act).

Appeals and complaints

Appeals against licensing/conformity assessment certification decisions made by the TGA can be made in accordance with Section 60 of the Act. Instructions on how to make an appeal are provided in the letter advising the outcome of the licensing/conformity assessment certification decision.

Complaints against the service provided by the TGA may be made in writing and should be addressed to:

Head of Office
Office of Manufacturing Quality
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
AUSTRALIA

The TGA will investigate legitimate complaints, relevant to the products on the ARTG, from customers of the licensed or certified manufacturer. Licensed or certified manufacturers shall, at all reasonable times, provide representatives of the TGA with access to its premises and records for the purposes of investigating such complaints. The originator of a complaint will be advised of the outcomes, as appropriate.

Confidentiality

Information relating to an application or licensed/certified manufacturer is treated as confidential information by the TGA and staff, however, information may be released to other regulatory bodies following section 61 of the Act. In addition to that, information on inspection date(s) and final compliance rating may be published on the TGA website.

Details of the inspection are not released to sponsors who may have requested the inspection. The information is considered to be confidential between the manufacturer on the application and the TGA.

Post licensing/certification activities

Obligations of licensed/certified manufacturers

Following licensing or certification, there are a number of managerial responsibilities which the manufacturer will need to observe to maintain a licence or TGA certification. These are detailed in the Act and Regulations and include:

- Continued compliance with the relevant Code/Standard(s).
- Compliance with 'Conditions of licensing/certification' (see next section).
- Notification to the TGA of any significant changes in the structure and operations of the manufacturer to enable the impact of such changes to be evaluated.

Conditions associated with ongoing licensing/certification

The Act and Regulations contain details on the conditions associated with the licensing or conformity assessment certification of Australian manufacturers of medicines and medical devices.

The following sections contain the relevant requirements.

Medicines

Section	Section number
Granting a licence	Section 38
Term of the licence	Section 39
Conditions of the licence	Section 40/regulation 20
Variations by the Secretary	Section 40A
Variations by the licence holder	Section 40B
Revocation or suspension of licence	Section 41

Medical devices

Section	Section/Division number
Granting a conformity assessment certificate	Section 41EE
Refusal of application	Section 41EH
Conditions of the certificate	Division 2 of Part 4-4
Suspension of the certificate	Division 3 of Part 4-4
Revocation of the certificate	Division 4 of Part 4-4

The following conditions apply to the GMP certification issued to overseas medicines manufacturers as well as to certification of medical devices manufacturers:

- The certified manufacturer shall not in any way use the fact that certification has been granted to provide customers with misleading information regarding applicability of the certification outside the scope for which certification has been granted.
- Certificates of GMP Compliance issued to Australian medicines manufacturers are given a 3 years expiry. Other Certificates have an expiry period which reflects the intended re-inspection frequency and is based on the risk category of the products manufactured and the compliance rating determined at the close-out of the inspection.

For continuance of certification the TGA shall be satisfied that the following conditions are met:

- Continued compliance with these conditions of certification
- Continued compliance of the manufacturer with the relevant standard against which certification is held
- Payment by a Medicine sponsor, or a Medical Device manufacturer (or authorised representative), by the prescribed dates of all fees set by the TGA for continuance of certification.

Following certification, the certified manufacturer must:

- Maintain the facility and manufacturing operations in accordance with the applicable standard(s)
- Make personnel, records and facilities available for inspection by the TGA on the dates and at the times agreed and confirmed in writing by the TGA
- Provide the TGA with access to premises, facilities and records at any reasonable time for the conduct of inspections and periodic reinspections.

Following certification, the TGA will:

- Conduct inspections of the certified manufacturer's manufacturing facility at approximately 1 to 3 year intervals (depending on the risk of the products manufactured and the compliance level determined)
- Consider requests from the certified manufacturer for changes to the scope of the certification and evaluate such requests during inspections subject to payment of any additional costs associated with this evaluation process
- Notify the certified manufacturer in writing of any changes in the scope of certification
- Notify the certified manufacturer in writing of any inspection findings that require corrective action to maintain certification.

The licensed or certified manufacturer shall, in a time frame agreed with the TGA, rectify any deficiencies found during inspections that impact on the scope of the licence or certification of compliance with the relevant standard.

When a manufacturer's scope of licence, conditions or certification is reduced, the TGA shall issue revised licences, conditions and certificates and the manufacturer shall return all superseded licences, conditions or certificates.

Inspection and review activities

After licensing or certification the TGA conducts periodic on-site inspections of the manufacturer's facility. The frequency of these inspections may vary depending on the level of compliance demonstrated at the previous inspection(s) and the level of risk of the products manufactured.

For medical device manufacturers, surveillance inspections are conducted on a 12 monthly basis, with a full triennial inspection conducted in which the full management system is reviewed for continued compliance with the relevant Standard(s).

Inspections are scheduled within the TGA and the manufacturer is only advised shortly before the inspection is to be conducted. Unannounced inspections may be conducted if deemed necessary.

Any changes required to the manufacturer's scope of licence or certification can be processed within the ongoing inspection program. If the manufacturer wants to change or add to the products it is licensed to manufacture, an on-line application is completed.

General arrangements

Fees and charges

All fees and charges associated with licensing/certification and conduct of inspections can be found on the TGA website.

Performance measures and targets

The performance of the OMQ Licensing/Certification Inspection Program is published annually. The performance measures and targets for the program are provided in Appendix 1.

The inspection process

Inspections can be performed by single inspectors or inspection teams. In the case of a team inspection, the team will be led by a Lead Inspector bearing overall responsibility for the Inspection.

The Lead Inspector can be supported by appropriately qualified and experienced inspectors and, where required, technical specialists acting as advisors to the inspectors. Technical specialists bring to the Inspection Team current specialised knowledge of the activities being inspected and ensure that the inspection provides a relevant and practical review of aspects critical to the manufacture of therapeutic goods.

The inspection process is based on a 'paperless' approach, meaning that all communications relating to the inspection (announcement, report, close-out record and close-out letter) are issued as electronic documents only. Manufacturers are requested to submit any documents of which the inspector asks to take a copy, as e-documents only.

Definitions

The TGA uses the following definitions in relation to Inspection related terminology:

Inspection:

Systematic, independent and documented process for obtaining inspection evidence and evaluating it objectively to determine the extent to which the inspection criteria are fulfilled (ISO19011 – Clause 3.1)

> **Note**: When two or more inspecting organisations cooperate to inspect a single manufacturer, this is termed a joint inspection.

Inspection criteria:

Set of policies, procedures or requirements (ISO19011 – Clause 3.2)

> **Note**: Inspection criteria are used as a reference against which inspection evidence is compared.

Inspection evidence:

Records, statements of fact or other information, which are relevant to the inspection criteria and verifiable (ISO19011 – Clause 3.3)

Inspection findings:

Results of the evaluation of the collected inspection evidence against inspection criteria (ISO19011 – Clause 3.4)

> **Note**: Inspection findings can indicate either conformity or nonconformity with inspection criteria or opportunities for improvement.

Inspection conclusion:

Outcome of an inspection, provided by the inspection team after consideration of the inspection objectives and all inspection findings (ISO19011 – Clause 3.5)

Inspection scope:

Extent and boundaries of an inspection (ISO19011 – Clause 3.13)

> **Note**: The inspection scope generally includes a description of the physical locations, organisational units, activities and processes, as well as the time period covered.

Corrective action:

Action to eliminate the cause of a detected deficiency or nonconformity or other undesirable situation (ISO 9000 Clause 3.6.5)

Correction:

Action to eliminate a detected deficiency or nonconformity (ISO 9000 Clause 3.6.6)

> **Note**: There is a distinction between corrective action and correction. Corrective actions are made against an identified root cause, whereas corrections are made against individual examples of a core issue. A correction can be, for example, rework or regrade.
>
> There can be more than one root cause for any deficiency or nonconformity.
>
> A correction can be made in conjunction with a corrective action.

Deficiency:

Non-fulfilment of a requirement (for medicines inspections; ISO 9000 Clause 3.6.2)

Nonconformity:

Non-fulfilment of a requirement (for devices inspections; ISO 9000 Clause 3.6.2)

Objective evidence:

Data supporting the existence or verity of something (ISO 9000 Clause 3.8.1)

> **Note**: Objective evidence may be obtained through observation, measurement, test, or other means.

Preventive action:

Action to eliminate the cause of a potential deficiency or nonconformity or other undesirable potential situation (ISO 9000 Clause 3.6.4)

Recurring deficiency or nonconformity:

Deficiency or nonconformity that was also identified at a previous inspection for which apparently the corrective and preventative actions taken earlier were inadequate.

Inspection announcement

Although most inspections are announced, unannounced inspections may be performed where required. Inspections are announced via telephone (to the manufacturer or the sponsor) followed by an announcement letter to the manufacturer. Like all inspection correspondence, announcement letters are signed electronically and sent via email only.

Inspection preparation

Inspection preparation involves collection and review of all necessary documents and data relating to the manufacturer and the inspection. Preparation for inspection includes the following documents:

- Any applicable applications or variations
- Departmental files on the manufacturer (electronic and hard copy), for re-inspections in particular the previous two Inspection reports and Closeout records
- Manufacturing steps (Site Authorisations) and Conditions of the licence (domestic inspections) or certificates and clearances (overseas inspections)
- Recalls that have occurred since the previous inspection
- Outcomes of any product testing performed by the TGA Office of Laboratories and Scientific Services
- Regulatory issues
- Therapeutic goods entered into the ARTG and the related Marketing Authorisations
- Site Master File
- Documents provided by the manufacturer (or sponsor)

- An Inspection plan and an Inspection attendance sheet are prepared. The Inspection plan is handed to the manufacturer only at the start of the inspection.

Conduct of an inspection

Roles and responsibilities

The inspection may be performed by a single inspector or an inspection team. In case of an inspection team, the Lead Inspector manages the team and has oversight of all phases of the inspection. Where required, the inspection team may include specialists from other TGA Offices. Specialists have the same responsibilities as inspectors.

The team may be accompanied by guides or observers. Attendance of any guides or observers on initiative of the TGA will be communicated by the Lead Inspector to the manufacturer prior to the inspection. Guides or observers should not influence or interfere with the conduct of the inspection and are subject to confidentiality.

Guides or observers to the inspection on initiative of the manufacturer could be the manufacturer's key personnel or any witnesses on behalf of the manufacturer or interpreters arranged for by the manufacturer. When guides are appointed by the manufacturer, they should not influence or interfere with the conduct of the inspection. Guides should assist the inspection team, and act on the request of the inspection team.

Their responsibilities may include the following:

- Providing clarification or assisting in collecting information
- Ensuring that rules concerning site safety and security procedures are known and respected by the inspection team members
- Witnessing the inspection on behalf of the manufacturer
- Translating for the inspection team in the case of inspections involving foreign languages.

Observers may for example be representatives of other regulatory bodies. Observers may accompany the inspection team but must not influence or interfere with the conduct of the Inspection.

Opening meeting

On arrival at the manufacturer's premises, the Lead Inspector chairs an opening meeting with the manufacturer's management team. At this meeting:

- Members of the inspection team are introduced, including an outline of their roles
- The scope and objectives of the Inspection are confirmed
- The Inspection plan is discussed and confirmed
- A tentative time and date for the closing meeting and any interim meetings of the inspection team and the manufacturer's management are established
- The methods and procedures to be used to conduct the inspection are outlined

The manufacturer is advised they will be given sufficient opportunity to respond to potential issues identified. Opportunities typically include, but are not limited to:

- At the moment the issue is found
- At the daily debrief (if applicable)
- During the closing meeting
- After the closing meeting in appropriate cases
- Communication links between the Inspection team and manufacturer are established
- The language (English) to be used during the inspection is reconfirmed (especially for overseas Inspections)
- A record of attendance at the opening meeting is kept.

Collecting and verifying information

During the inspection, information relevant to the inspection objectives, scope and criteria, including information relating to interfaces between functions, activities and processes is reviewed by appropriate sampling and verified. The inspection evidence is based on samples of the available information. Inspections should be objective and related to the written current Code or Standard.

Unless a special inspection for a specific purpose, all areas relevant to the scope of manufacture are inspected for compliance with the relevant manufacturing standard specified in the current Manufacturing Principles. Any other regulatory requirement(s) that are relevant to GMP or QMS compliance are also included in the inspection (e.g. ARTG listing/registration, TGOs, Pharmacopoeias).

Shorter 'surveillance' inspections are only applicable to device manufacturers.

For medicine manufacturers critical elements include: validation (process, cleaning, QC test methods and computerised systems), complaints, deviations, change control, release for supply, starting material control and documentation/records.

Methods to collect information include:

- Interviews of personnel at all levels within the organisation
- Observation of activities, including reviewing and evaluating systems and procedures for compliance and effectiveness
- Review of documents, ie. a sufficient sample of records so that the number of records for each activity since the last inspection is adequately represented; reviewing logs and databases to show appropriate monitoring and trending has taken place
- Taking photocopies of documents or photographs.

It is a standard condition that licence holders allow documents to be copied and photographs to be taken (see s 40(4) of the Act). Where possible, electronic copies of documents are preferred.

Generating inspection findings

Inspection evidence is evaluated against the inspection criteria, ie relevant Code or Standard, to generate inspection findings. Inspection findings can indicate either compliance or non-compliance with the applicable standard in the *Manufacturing Principle*.

Full compliance with GMP/QMS requirements is expected. For example, where validation is required, this is expected for relevant processes for every product/product group and similarly it is expected that every starting material is properly tested according to GMP/QMS requirements and agreed interpretations. Every batch of every product must be made in full compliance with the applicable standard in the *Manufacturing Principle*.

Inspection conclusions

The inspection team confers prior to the closing meeting to:

- Review the inspection findings against the relevant Code or QMS Standard
- Review the evidence and any other information collected during the inspection, against the relevant Code or QMS Standard
- Agree on the inspection conclusions
- Prepare an overview of issues identified during inspection (i.e. the potential deficiencies/nonconformities)
- Discuss Inspection follow-up, if included in the Inspection plan.

The Inspection team considers the nature and significance of the deficiencies/ nonconformities identified and prepares a written overview of issues for presentation to the manufacturer during the closing meeting.

Closing meeting

- A closing meeting will be held at the end of the Inspection to present the inspection findings and conclusions. All items discussed are recorded and a copy of this record is provided to the attendees of the closing meeting.
- The Lead Inspector will provide a verbal overview of the inspection and its outcome, and verbally detail any issues identified. Findings of special significance will be emphasised, particularly those regarded as issues that could result in action to suspend or revoke the licence or certificate.
- Any diverging opinions regarding the inspection findings and conclusions between the inspection team and the manufacturer are discussed and if possible resolved. If not resolved, all opinions will be recorded.
- In the case of a pre-licence inspection, the likely terms of the licence conditions are discussed and documented.
- A record of attendance is kept using the same record used during the opening meeting.

Inspection reports

Following the on-site inspection, the inspection team prepares a report which includes the inspection findings and a summary of the overall compliance of the manufacturer's operations against the requirements of the relevant Codes and Standard(s). Like all inspection correspondence, the Inspection report is signed electronically and issued via email to the manufacturer.

Inspection report template

The template of the TGA's Inspection reports is standardised and based on the internationally harmonised template PI013-3 provided by the Pharmaceutical Inspection Co-operation Scheme (PIC/S), refer to <http://www.picscheme.org>. However, this harmonised template allows for minor differences in format and approach, for example as a result of requirements from legislation or international agreements. The main difference is that the TGA's Inspection report template does not include a Conclusion section, as the conclusion is only drawn after review of the manufacturer's response during the close-out process, and consequently the conclusion is reflected as a 'final compliance rating' in the close-out letter (see below).

The TGA Inspection report template also allows for some minor differences between reports for the different TGA Inspection programs (medicines, APIs, medical devices, blood and tissue products etc.).

Inspection reports consist of five distinct sections:

- Inspection related data, including:
  - Details of the inspected site and activities carried out
  - Inspection details, including inspection type, scope, date and inspectors names and roles
  - Reference to the Manufacturing Standard used
- Introduction and summary of the inspection activities, including the purpose of the Inspection and the product range
- Description of inspection findings and observations. This section is typically subdivided into paragraphs referring to the chapters of the Manufacturing Standard used, as far as applicable to the manufacturer. This section also includes evidence sighted for closing out or downgrading previous inspection findings
- List of deficiencies/nonconformities observed. Manufacturers are required to respond to all deficiencies/nonconformities listed. The requirements and expectations for this response are outlined in the cover letter that is sent with the report
- The name and signature of the person authorising the report on behalf of the TGA.

The Inspection Report should not ordinarily vary from the verbal report presented to the manufacturer at the closing meeting and the record of items for discussion presented during the closing meeting.

Inspection reports are reviewed prior to being issued to the manufacturer. During this review, inspection findings are classified as critical/major/other (for medicines inspections) or major/minor (for devices inspections).

Classification of deficiencies/nonconformities

Deficiencies identified during medicines Inspections are classified as critical, major or other based on the internationally harmonised definitions provided by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) in their document PI013-3, refer to <http://www.picscheme.org>. Nonconformities identified during devices Inspections are classified as major or minor. The definitions of these classifications are also included in the Inspection report.

A **Critical Deficiency** is a deficiency when it is observed that:

- A practice or process has produced, or may result in, a significant risk of producing a product that is harmful to the user; and/or
- The manufacturer has engaged in fraud, misrepresentation or falsification of products or data.

Examples of Critical Deficiencies for medicine manufacturers are provided in Appendix 2. A critical deficiency is a serious situation that will result in regulatory action being considered. This classification is not applicable to Medical Device Inspections.

A **Major Deficiency/Nonconformity** is a non-critical deficiency/nonconformity that:

- Has produced or may produce a product which does not comply with its marketing authorisation (in some circumstances this could be critical); and/or
- Indicates a major deviation from the Code of GMP or QMS standard; and/or
- Indicates a major deviation from the terms of the manufacturing licence, GMP approval (overseas manufacturers), or Conformity Assessment Certificate; and/or
- Indicates a failure to carry out satisfactory procedures for release of batches; and/or
- Indicates a failure of the person responsible for QA/QC to fulfil his/her duties; and/or
- Consists of several other deficiencies/non conformities, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Examples of Major Deficiencies for medicine manufacturers are provided in Appendix 2.

Examples of Major Nonconformities for medical device manufacturers are provided in Appendix 3.

An **Other Deficiency Minor Nonconformity** is a deficiency/nonconformity that cannot be classified as either critical or major, but indicates a departure from the applicable standard.

Review panel

In the case where the inspection outcome is a provisional compliance rating of *unacceptable*, the inspection is referred to a Review Panel. The Review Panel is convened and chaired by a TGA manager who has not been involved in the inspection and consists of other inspectors (who also have not been involved in the inspection) and, where applicable, representatives of the Office(s) involved in the ARTG entry and/or the Office of Laboratories and Scientific Services. The Review Panel reviews the inspection, undertakes a risk assessment of the manufacturer and prepares recommendations to the Delegate for regulatory actions as applicable.

Inspection close-out

The manufacturer is required to respond to the deficiencies/nonconformities identified in the Inspection report. The process of manufacturer response and Inspector review of the response is called close-out.

Purpose and scope of close-out

The purpose of the close-out process is to ensure the manufacturer commits to perform appropriate corrective and preventative actions for each deficiency/nonconformity within an acceptable period. The close-out correspondence will record this commitment as well as the inspection team's comments and agreement. The close-out letter provides final approval of the close-out, including the close-out correspondence.

The scope of the close-out is limited to those deficiencies/nonconformities that are listed in the Inspection report. Manufacturers are not required to respond to any statements in the body of the report, but may comment on it if they consider a statement not reflecting the actual situation.

Corrections and corrective actions

One should be mindful of the definitions of a corrective action as opposed to a correction. A corrective action is an action intended to eliminate the root cause of the deficiency/nonconformity, and thus to prevent recurrence. A correction is an action to eliminate a deficiency/nonconformity, or the individual examples of a grouped deficiency/nonconformity.

Following medicines inspections, the manufacturer is required to identify the root cause of all deficiencies that are classified as either critical or major. Following devices inspections, manufacturers are required to identify the root cause for all nonconformities (both major and minor).

For each issue, the manufacturer's response should include action taken or proposed to be taken to correct the specific issue (including corrective action to prevent recurrence) and the completion date or, if relevant, target date for completion.

For deficiencies classified as critical or major (medicines inspections) and for all nonconformities (devices inspections) an identification of the root cause is also required. Where identification of the root cause is required, the response should include corrective action to the root cause as well as corrections to the individual examples identified.

For deficiencies classified as critical or major (medicines inspections) as well as for nonconformities classified as major (devices inspections), objective evidence is required, e.g. copies of amended documentation, photographs etc.

Close-out record

The Lead Inspector provides the manufacturer with an e-copy of a close-out record, which can be used by the manufacturer to provide the response.

Use of this template is not compulsory for the manufacturer.

Time lines for close-out

Where the Inspection report is normally issued within approximately four weeks of the inspection, the initial response is requested within four weeks of the date of issue of the Inspection report. This allows the manufacturer a total of approximately eight weeks from the closing meeting to provide a response.

The response is normally reviewed within approximately two weeks after receipt, but this might vary depending on inspector's travel.

If a subsequent response is required, the manufacturer is given an additional two weeks response time.

If a deficiency/nonconformity is in the process of being addressed but further time is needed to fully implement the corrective actions, the Lead Inspector may determine that the inspection be closed out with a requirement for progress reporting. Examples of circumstances in which progress reporting may be appropriate include but are not limited to: generation of stability data, generation of validation data, facility or equipment refurbishment updates etc.

Close-out letter

After all corrections and corrective actions have been accepted, the inspection is closed out by issuing a close-out letter. This letter refers to the correspondence regarding the corrections and corrective actions, indicates the final compliance rating assigned to the manufacturer as a conclusion to the inspection and refers to any proposed amendments to site authorisations or conditions. The compliance rating is used by the TGA as one of the parameters to determine the re-inspection frequency based on risk assessment. Like all inspection correspondence, the Inspection report is signed electronically and issued via email to the manufacturer.

Licensing/certification decision

In case of an initial inspection, a decision on licensing or certification is prepared after the close- out of the Inspection as described in the section licensing/certification process above. The same applies for inspections following applications for variation of a licence or certificate.

Enforcement actions

The Act includes provisions for regulatory action(s) in the case where a re-inspection demonstrates non-compliance of a licensed or certified manufacturer of therapeutic goods. A Licence to Manufacture may be revoked or suspended under the conditions outlined in Section 41 of the Act. For overseas medicine manufacturers, the GMP Certificate issued will be varied accordingly, particularly in relation to authorisations and conditions. A variation to the authorisations and conditions of a GMP Certificate will be reflected in the relevant GMP clearance(s). A GMP clearance may be cancelled if a manufacturer has contravened the authorisations provided by a certificate or breached a condition of a certificate.

Conformity Assessment Certificates may be suspended under the conditions outlined in Sections 41EM to 41EQ of the Act or revoked under the conditions outlined in Sections 41ER to 41EWQ of the Act.

General arrangements

Confidentiality

All information relating to an inspection is treated as commercial-in-confidence information by the TGA and staff. At no time are the details of the inspection released to sponsors who may have requested the inspection. The information is considered to be confidential between the manufacturer on the application and the TGA.

However, section 61 of the Act provides for the Delegate to release details of the inspection to other authorities, for example the World Health Organization, an authority of the Commonwealth, a State or a Territory or to a regulatory authority of another country.

Fees and charges

All fees and charges associated with licensing/certification and conduct of inspections can be found on the TGA website.

Appendix 1: Performance measures and targets

All timeframes are subject to the cooperation of manufacturers and sponsors, and in some cases, international regulatory authorities.

Periods are measured from the time that application is 'effective' and can be progressed by the TGA. Licence(s) will be withheld until satisfactory resolution of any deficiencies identified.

Timeframes assume sites are ready for inspection at the time of application – applications may be rejected if sites are not ready for inspection.

Application type outcomes	Measurement	Target timeframe
New Australian Licence Application	Application to Inspection Report	< 3 months
Variation to the scope, premises or conditions of licence (not requiring onsite assessment)	Application to Licence Issue	< 3 months
Re-inspection of Australian licensed premises	Inspection due date to Inspection report	6 months
GMP certificate or notarised copy of Licence	Application to Issue	< 15 working days
New Certificate of GMP Compliance - Initial inspection	Application to Inspection report	< 6 months
Certificate of GMP Compliance - Re-Inspection	Inspection due date to Inspection Report	< 6 months

Appendix 2: Examples of medicine inspection deficiencies

Critical deficiency

Examples of critical deficiencies include the following where it can be reasonably expected that the definition in this Guidance will be met. A critical deficiency is a serious situation that will result in regulatory action being considered.

- Lack of sterilisation validation (relevant to all sterile products)
- Inadequate segregation of manufacturing of high risk products, such as penicillins, cephalosporins, cytostatics, steroids, hormones, resulting in a risk of contamination (relevant to prescription medicine manufacturers but critical deficiency also if possibility of cross contamination to any other product)
- Evidence of gross pest infestation (relevant to all manufacturers)
- Falsification or misrepresentation of analytical results or records(relevant to all manufacturers)
- Raw materials not tested (including proper identification testing) to ensure compliance with specifications (relevant to all manufacturers)
- No master batch documents (relevant to all manufacturers)
- Absence, falsification or misrepresentation of manufacturing and packaging records (relevant to all manufacturers)
- Water system for sterile products not validated (for manufacturers of sterile products)
- Grossly unsuitable premises so that there is a significant risk of contamination (relevant to all manufacturers)
- Release of materials or finished product for a Registered medicine not meeting specifications. (For Listed medicines the assignment of a critical classification should first be discussed with the relevant regulator.)
- Release of blood or tissue product without acceptable mandatory test results (relevant to manufacturers of blood or tissue products)
- Incorrect labelling of blood or tissue product (relevant to manufacturers of blood or tissue products)
- No separation of quarantined and released blood or tissue products (relevant to manufacturers of blood or tissue products)
- No evidence that mandated recall processes have been complied with. (relevant to all manufacturers)

Major deficiency

Examples of major deficiencies include the following:

- Lack of validation of critical processes (applicable to all medicines, but could be critical for low dose/high potency products; particularly sterilisation processes for sterile devices)
- No or grossly inadequate air filtration to minimise airborne contaminants (applicable to all medicines manufacturers – could be critical if possible contaminants are a safety concern and critical for sterile medicines)
- Cleaning program not followed and evidence of dirty premises/equipment or non-validated cleaning procedures (may be critical if resulting contamination is a safety concern)
- No data available to establish the shelf-life of registered medicines (relevant to all manufacturers of registered medicines as it is their responsibility. This should be referred to the relevant product regulator)
- No data available to establish the shelf-life of sterile medical devices, medical devices that incorporate medicinal substances, biological materials or an energy source. (may be relevant to other manufacturers of medical devices as it is their responsibility. This should be referred to the relevant product regulator)
- Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed
- Design of manufacturing area that does not permit effective cleaning
- Insufficient manufacturing space that could lead to mix-ups
- No raw material sampling area for medicine manufacturers (could be classes as 'other' if adequate precautions are taken)
- Sanitary fittings not used on liquid/cream manufacturing equipment
- Stored equipment not protected from contamination
- Individuals in charge of QC/production not qualified by education, training and experience
- Inadequate initial and ongoing training and/or no training records
- Cleaning procedures not documented and/or no cleaning records
- Production equipment cleaning procedures not validated
- Reduced QC testing of raw materials without data to certify suppliers
- Incomplete testing of raw materials
- Test methods not validated
- Complex production processes for non-critical products not validated
- Unapproved/undocumented changes to master batch or equivalent documents
- Deviations from instructions not approved
- No or inadequate internal inspection program
- No proper release for supply procedure
- Product reworked without proper approval

- No system/procedures for handling complaints or returned goods
- Inadequate testing of packaging materials
- No ongoing stability program and/or stability data for all products not available
- Insufficient lighting in production or inspection areas
- Temporary devices used for equipment repair
- Containers from which samples have been taken not identified
- Equipment not properly maintained
- The temperature of critical temperature controlled storage areas not monitored and alarmed

Appendix 3: Examples of devices inspection nonconformities

Examples of major nonconformities include the following:

- Lack of validation of critical processes (sterilization validation for example)
- Evidence of gross pest infestation
- Falsification or misrepresentation of quality test results
- No or grossly inadequate air filtration to minimise airborne contaminants (where appropriate)
- Cleaning program not followed and evidence of dirty premises/equipment or un-validated cleaning procedures (maybe critical if resulting contamination is a safety concern)
- No stability program or equivalent to support the life of the product, where applicable. (For example, drug/device combinations)
- Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed
- Design of manufacturing area that does not permit effective cleaning
- Insufficient manufacturing space that could lead mix-ups (in particular with regards to segregation of sterilised and non-sterilised devices)
- No raw material sampling area (could be other if adequate precautions are taken)
- Sanitary fittings not used on liquid/cream manufacturing equipment
- Stored equipment not protected from contamination
- Individuals in charge of QC/Production not qualified by education, training and experience
- Inadequate initial and ongoing training and/or no training records
- Cleaning procedures not documented and/or no cleaning records
- Production equipment cleaning procedures not validated
- Reduced QC testing of raw materials without data to certify suppliers
- Incomplete testing of raw materials
- Test methods not validated
- Unapproved/undocumented changes to master batch documents
- Deviations from instructions not approved
- No or inadequate internal audit program
- No proper release for supply procedure
- Product reworked without proper approval
- No system/procedures for handling complaints or returned goods

- Inadequate testing of packaging materials
- Insufficient lighting in production or inspection areas
- Temporary devices used for equipment repair
- Containers from which samples have been taken not identified
- Equipment not properly maintained

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