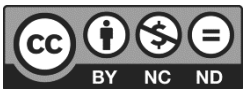
The Auditor-General
Audit Report No.30 2013–14
Performance Audit

Administering the Code of Good Manufacturing Practice for Prescription Medicines

Department of Health

Australian National Audit Office

ISSN 1036–7632
ISBN 0 642 81448 1 (Print)
ISBN 0 642 81449 X (Online)



Australian National Audit Office

Canberra ACT
7 May 2014

Dear Mr President
Dear Madam Speaker

The Australian National Audit Office has undertaken an independent performance audit in the Department of Health titled *Administering the Code of Good Manufacturing Practice for Prescription Medicines.* The audit was conducted in accordance with the authority contained in the *Auditor-General Act 1997*. Pursuant to Senate Standing Order 166 relating to the presentation of documents when the Senate is not sitting, I present the report of this audit to the Parliament.

Following its presentation and receipt, the report will be placed on the Australian National Audit Office's website—http://www.anao.gov.au.

Yours sincerely

Ian McPhee
Auditor-General

The Honourable the President of the Senate
The Honourable the Speaker of the House of Representatives
Parliament House
Canberra ACT

AUDITING FOR AUSTRALIA

The Auditor-General is head of the Australian National Audit Office (ANAO). The ANAO assists the Auditor-General to carry out his duties under the *Auditor-General Act 1997* to undertake performance audits, financial statement audits and assurance reviews of Commonwealth public sector bodies and to provide independent reports and advice for the Parliament, the Australian Government and the community. The aim is to improve Commonwealth public sector administration and accountability.

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Abbreviations

ABC	Activity Based Costing
Act	*Therapeutic Goods Act 1989*
ANAO	Australian National Audit Office
ANZTPA	Australia New Zealand Therapeutic Products Agency
ARTG	Australian Register of Therapeutic Goods
Code of GMP	Australian Code of Good Manufacturing Practice for Medicinal Products
Code of GWP	Australian Code of Good Wholesaling Practice for Medicines in Schedules 2, 3, 4 and 8
CRIS	Cost Recovery Impact Statement
CSO	Community Service Obligation
GMP	Good Manufacturing Practice
IGM	Inspection Group Manager
IT	Information Technology
KPI	Key Performance Indicator
MIS	Manufacturers Information System
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
OMQ	Office of Manufacturing Quality
PBS	Pharmaceutical Benefits Scheme

PIC/S	Pharmaceutical Inspection Convention/Cooperation Scheme
RMP	Risk Management Plan
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration

Glossary

Certification	The direct approval that an overseas manufacturer is compliant with Australian or equivalent manufacturing standards.
Close-out	The final phase of an inspection when a manufacturer addresses deficiencies and a final decision is made by the TGA on the manufacturer's level of compliance with mandated requirements.
Code of GMP	Australian Code of Good Manufacturing Practice for Medicinal Products. The Code sets out manufacturing principles and requirements relating to quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recalls, and self inspection.
GMP clearance	The required approval that all overseas manufacturers involved in the manufacture of a product supplied in Australia are compliant with Australian or equivalent manufacturing standards.
Licence	Authority to manufacture therapeutic goods granted to a manufacturer pursuant to Part 3-3 of the *Therapeutic Goods Act 1989*. Australian manufacturers must be licensed by the TGA prior to commencing the manufacture of therapeutic goods.
PIC/S	Pharmaceutical Inspection Convention/Pharmaceutical Inspection Cooperation Scheme. Two international instruments between national health authorities and pharmaceutical inspection authorities that facilitate networking, cooperation and harmonisation activities in the field of GMP. The TGA is one of 44 participating authorities.

Registered medicine	A medicinal product included in the part of the Australian Register of Therapeutic Goods known as 'registered goods', which are assessed as having a higher level of risk. Prescription medicines are a sub-category of registered medicines.
Sponsor	Australian importer, exporter and/or supplier of a therapeutic good. The sponsor is required to be a resident of Australia, or registered as a business in Australia.

Summary and Recommendations

Summary

Introduction

1. To safeguard the health of Australians, the *Therapeutic Goods Act 1989* (the Act) establishes a framework for regulating all therapeutic goods, including prescription medicines, that are manufactured or supplied in Australia. Prescription medicines[1] are those for which consumers require a prescription from an authorised medical practitioner or that are dispensed in hospital settings by authorised health care professionals, with community pharmacies dispensing 271 million prescriptions for such medicines in 2010. The Act makes provision for the Department of Health, through the Therapeutic Goods Administration[2] (TGA), to assess whether therapeutic goods have been manufactured in a way that provides the public with confidence about their safety, quality and efficacy. It is the responsibility of each prescription medicine manufacturer supplying the Australian market to adhere to the established regulatory standards. The Act also includes provisions enabling the TGA to recover the full cost of its regulatory activities through fees and charges on the manufacturers and sponsors[3] of therapeutic goods.

Good manufacturing practice

2. All therapeutic goods available in Australia must be manufactured in accordance with the Australian Code of Good Manufacturing Practice for Medicinal Products (the Code of GMP).[4] Good manufacturing practice (GMP) is a set of principles and objectives that seek to ensure products are manufactured consistently and to a standard appropriate for their intended use. Most countries, including Australia, have legislated that manufacturers of

1 In Australia, prescription medicines fall under a category known as registered medicines, which are assessed by the TGA as having a higher level of risk and are therefore individually examined for safety, quality and efficacy. Examples of prescription medicines include antibiotics, contraceptive pills, and strong painkillers.

2 The TGA is part of the Department of Health, notwithstanding its distinct branding.

3 The sponsor of a therapeutic good is a person or company who either exports the goods from Australia, imports them into Australia or manufactures them for supply in Australia or elsewhere.

4 Section 36 of the Act enables the Minister for Health to determine which principles will be observed in the manufacture of therapeutic goods supplied in Australia. The TGA currently administers the 2013 version of the Guide to Good Manufacturing Practice for Medicinal Products, issued by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

therapeutic goods must meet acceptable standards of GMP through the use of quality systems, controlled manufacturing processes, trained personnel, appropriate facilities and equipment, and documented procedures.

3. The TGA licenses Australian manufacturers that comply with the Code of GMP and requires overseas manufacturers to meet an equivalent standard before they can supply prescription medicines in Australia. When a manufacturer is not compliant with the Code of GMP, the TGA may adopt measures to reduce possible risks to public health and safety, including the restriction, suspension or cancellation of a manufacturer's licence or product approval. As at 30 June 2013, 1519 sites were approved to manufacture registered medicines (including prescription medicines) for supply in Australia. Of these, 154 were Australian sites licensed by the TGA, 327 were overseas sites inspected and certified by the TGA, and the remaining 1038 sites were certified by overseas regulators.

4. The TGA's Office of Manufacturing Quality (OMQ) has responsibility for licensing domestic manufacturers, and certifying overseas manufacturers, against the Code of GMP and implementing a risk-based program of surveillance inspections. The OMQ also grants GMP clearances to sponsors importing prescription medicines from overseas manufacturers that have been approved by a regulator with which Australia has formal recognition arrangements.

5. All therapeutic goods carry potential risks, many of which can originate in the course of manufacture. A robust framework for assessing and monitoring compliance with the Code of GMP assists in mitigating these risks. Key features of an effective framework include: mechanisms to assess and monitor compliance; procedures to support a quality system; and graduated responses to address non-compliance.

Audit objective and criteria

6. The audit objective was to assess the effectiveness of the Therapeutic Goods Administration's (TGA) application of the Code of Good Manufacturing Practice (Code of GMP) for prescription medicines.

7. To assist in evaluating the TGA's performance in terms of the audit objective, the ANAO developed the following high level criteria:

- only manufacturers who have been rigorously assessed as meeting the Code of GMP are eligible to supply prescription medicines in Australia;

- the TGA has a risk-based approach to monitoring compliance of prescription medicine manufacturers against the Code of GMP, to enable the TGA to target resources effectively and respond to priority risks;
- the TGA has implemented policies and procedures to respond to manufacturing non-compliance of prescription medicine manufacturers, which are proportionate to the risks presented; and
- the TGA's regulation of the Code of GMP is supported by appropriate structures and processes.

Overall conclusion

8. The Department of Health, through the TGA, administers the Australian regulatory framework for therapeutic goods, providing assurance to the community that prescription medicines, whether of Australian or overseas origin, are manufactured in accordance with a formal Code of Good Manufacturing Practice (Code of GMP). Experience has shown that risks arising during manufacture, such as ingredient substitution or breaches in the quality system, may have potentially serious consequences for patient and public health and therefore require the ongoing attention of manufacturers and regulatory authorities.

9. The TGA has been generally effective in applying the Code of GMP for prescription medicines manufactured or supplied in Australia. The TGA applies a well-developed and structured process for licensing and monitoring manufacturing sites in Australia, and has adopted a viable approach to the certification of overseas manufacturing sites, drawing on the work of selected overseas regulators. However, the audit identified a number of shortcomings in the TGA's administration of the Code of GMP which highlight the need for greater internal discipline and management attention to: strengthen the documentation of key decisions relating to licensing and certification processes; and enhance arrangements for information security and management. There also remains scope to realise the full benefits of TGA initiatives to: reduce duplicated effort in granting clearances for the supply of imported prescription medicine; and implement more equitable cost recovery arrangements.

10. The TGA licenses Australian manufacturing sites and certifies overseas manufacturing sites against the Code of GMP. These regulatory functions are

supported by standard operating procedures (SOPs), providing a good starting-point for the TGA's application of the Code of GMP. However, the ANAO's review of licensing and certification records indicated that TGA staff have not always documented key decisions or consistently maintained inspection files, as required by the SOPs. The TGA should strengthen its quality assurance processes to provide greater confidence that staff formally document key decisions, particularly when discretions are exercised, and maintain complete and accurate records to enhance the transparency and accountability of the licensing and certification process.[5]

11. The TGA monitors the ongoing compliance of licensed and certified prescription medicine manufacturers with the Code of GMP through a systematic and risk-based inspection program. The ANAO's review of inspection documentation indicated that while inspection procedures are mostly followed, there remains scope to refine aspects of the SOPs, which do not require inspectors to record the basis on which they have verified whether corrective and preventive actions identified during previous inspections adequately addressed deficiencies. Further, the timeliness of issuing inspection reports and closing out inspections is well below the TGA's targets.[6]

12. Manufacturing sites inspected by the TGA account for only one-third of sites supplying registered medicines (including prescription medicines) in Australia, with the remainder certified by overseas regulators. All prescription medicines supplied in Australia must have an Australian-based sponsor, who applies to the TGA for GMP clearance. At present, the TGA processes each clearance application individually, even where other sponsors have recently obtained clearances for the supply of identical products from the same manufacturing site. The OMQ advised the ANAO that approximately two-thirds of the effort spent processing clearance applications is a duplication of previous work, and it is considering a model to enable the reuse of current evidence of a manufacturing site's compliance with the Code of GMP in subsequent assessments of the same site. If adopted, this initiative will

5 At present, the OMQ's quality assurance process focuses on staff competencies and does not require detailed review of the way in which staff have documented the inspection and close-out process in accordance with standard operating procedures.

6 In the ANAO's random sample of 58 inspection reports, only 26 per cent were provided to the manufacturer within the four-week target timeframe. In a random sample of inspection close-outs, which have a target timeframe of between six to 14 weeks depending on the number of responses sought by OMQ, the ANAO calculated an average of 14 weeks for sites with 'good' or 'satisfactory' compliance and 41 weeks for those with a 'basic' compliance rating.

improve the efficiency of regulatory processes, to the benefit of industry and the TGA.

13. The TGA undertakes regulation of the Code of GMP on a cost recovery basis. However, the TGA's current fee structure for regulating compliance with the Code of GMP is such that domestic manufacturers with 'good' compliance[7] are cross-subsidising the effort spent by the TGA to regulate manufacturers with 'basic' compliance, as the licence fee is fixed and inspections identifying a high number of deficiencies require considerably more resources to finalise.[8] The TGA has acknowledged there is scope for improvement and advised that it plans to revise fees and charges in 2014–15, pending the outcome of a structural review of fees, charges and activity based costing.

14. The OMQ operates a Manufacturers Information System (MIS) intended to support the compliance program. However, the MIS does not capture key information required to monitor administrative performance and staff adherence to SOPs relating to the Code of GMP. Further, the compliance information contained in the MIS is not aligned with other TGA information holdings to ensure that publicly accessible information on prescription medicines is current and reliable. More generally, the OMQ has not assessed its IT network security controls against the risk of cyber intrusion. To enhance its operational effectiveness and the security of its data holdings, the OMQ should review its information management arrangements in support of the Code of GMP compliance program, particularly the MIS.

15. The ANAO has made two recommendations to improve the TGA's administration of the Code of GMP for prescription medicines, focussing on: strengthening processes for recording key decisions and maintaining inspection files, and refining the quality assurance process to support staff adherence to SOPs; and reviewing information management arrangements to more effectively support the OMQ's application of the Code of GMP and improve the security of data holdings.

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7 The TGA has a system for classifying each deficiency against the Code of GMP according to its potential risk and subsequently provides the manufacturer with a compliance rating of either 'good' (A1), 'satisfactory' (A2), 'basic' (A3) or 'unacceptable' (U).

8 The cost of domestic inspections is recovered through a fixed licence fee that includes a specified number of inspection hours, and an hourly fee once this allocation is exceeded. The TGA may not use all available inspection hours in the case of manufacturers with 'good' compliance.

Key findings by chapter

Licensing and Certifying Manufacturing Sites (Chapter 2)

16. The licensing and certification of regulated bodies enables regulators to manage regulatory risks by controlling entry to the market.[9] The TGA's licensing and certification functions are supported by a detailed set of SOPs, providing a good starting-point for the TGA's application of the Code of GMP.

17. Approximately 32 per cent of sites manufacturing registered medicines for supply in Australia are directly licensed or certified by the TGA through on-site inspections.[10] The ANAO's review of this initial inspection process indicated that some key decisions had not been supported by formal documentation, and electronic inspection files were not consistently maintained, in accordance with the TGA's SOPs. Further, quality assurance reviews are not structured to verify whether staff have fully documented the inspection process, in line with the TGA's requirements.

18. Approximately 68 per cent of the manufacturing sites supplying registered medicines in Australia are located and regulated overseas. These sites are certified by regulators with which Australia has a Mutual Recognition Agreement (MRA), Memorandum of Understanding (MOU) or cooperative arrangement.[11] As part of an international engagement strategy to mitigate the risk of 'unjustified approval of foreign manufacturing sites', the TGA participates in joint and concurrent inspections, conducts regular teleconferences and exchanges detailed annual reports in order to verify the standards applied by its MRA partners.[12] However, any differences observed during joint inspections are not documented and brought to management attention by TGA inspectors so that significant discrepancies in approaches and conclusions can be addressed through inter-agency coordination.

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9 ANAO Better Practice Guide—*Administrating Regulation*, March 2007, Canberra, pp. 43–49.

10 Of this figure, 10 per cent are located domestically and 22 per cent overseas.

11 Australia currently has MRAs with 22 European Union countries, and with Switzerland, Canada and Singapore. It also has a MOU with New Zealand, a cooperative arrangement with the United States and, informally, with the 14 PIC/S members who do not fall within the above categories.

12 TGA, *TGA International Engagement Strategy 2013–15*, Canberra, 2013.

Monitoring Compliance Of Licensed And Certified Manufacturing Sites (Chapter 3)

19. The TGA monitors the compliance of licensed and certified prescription medicine manufacturers through a systematic and risk-based program of on-site inspections. An inspection frequency matrix is used to determine the frequency of these inspections, having regard to the risks associated with: the product type; the manufacturing process; and the manufacturer's compliance rating from the previous inspection.

20. Compliance monitoring is also supported by a detailed set of policies and procedures to guide staff in scheduling, planning and conducting manufacturer inspections, as well as classifying levels of compliance. The ANAO's review of inspection documentation indicated that while inspection procedures are mostly followed, there remains scope to refine aspects of the SOPs. While most inspections allocate time to verify whether previous deficiencies have been addressed, there is currently no requirement to record the basis of this assessment and therefore limited means to subsequently evaluate the adequacy of corrective and preventive actions and inform future inspection teams.

Addressing Deficiencies In Compliance (Chapter 4)

21. Almost all inspections conducted on sites manufacturing prescription medicines identify at least one deficiency against the Code of GMP.[13] To respond appropriately to the risks presented by compliance deficiencies, the TGA has developed graduated responses to support its risk-based compliance strategy.

22. The TGA's general approach is to use lower level responses to address most deficiencies and reserve enforcement measures for serious non-compliance or when lower level responses are failing to achieve the desired outcome.[14] The TGA employs a risk-based strategy, known as inspection close-out, that allows most manufacturers to continue production while also correcting deficiencies. An inspection cannot be closed out until the

13 In the five years to 30 June 2013, 96 per cent of inspections of sites manufacturing prescription medicines identified at least one deficiency against the Code of GMP, with 60 per cent identifying at least one major deficiency.

14 The TGA advised the ANAO that in the five years to 30 June 2013, it had not brought legal proceedings against any manufacturer of prescription medicines regarding non-compliance with the Code of GMP.

lead inspector reviews and accepts information from a manufacturer on the corrective actions it proposes to address deficiencies. However, the timeliness of issuing inspection reports and closing out inspections is well below the TGA's targets. Further, while the TGA's approach has been generally effective and has helped avoid disruption to manufacturers' business operations, its approach to compliance has not led to improvements in the case of several domestic manufacturing sites with a history of 'basic' compliance, with one of these sites dropping from 'basic' compliance to a provisional rating[15] of 'unacceptable' at one inspection.

23. Where required, review panels are convened following an inspection to provide an independent assessment and recommendation to the delegate on an approach to address 'unacceptable' compliance.[16] In a minority of cases, the TGA does pursue stronger enforcement measures but advised the ANAO that, with the exception of legal proceedings, it does not collect information on administrative compliance measures, including those recommended by review panels, centrally. The TGA could therefore not advise the ANAO on the number or type of actions previously used to address sites with a history of compliance that has been less than 'satisfactory'. Accordingly, the TGA is not well placed to evaluate the effectiveness of actions taken to address poor levels of compliance. A Compliance Unit established by the OMQ in late 2012 for the purpose of addressing such sites has made limited progress to date, and there would be benefit in TGA management revisiting this approach.

Supporting the Compliance Program (Chapter 5)

24. The TGA's current fee structure for regulating compliance with the Code of GMP results in some regulated Australian manufacturers paying significantly more per hour of inspection effort than others. The TGA has recognised that its cost recovery arrangements for regulating compliance with the Code of GMP are in need of revision, and advised the ANAO that it plans to revise the structure of fees and charges over three years from 2014–15.

25. The OMQ's primary IT system supporting its compliance program, the Manufacturers Information System (MIS), was built on legacy platforms and

15 A compliance rating is provisional until the inspection has been closed out and a final compliance rating is assigned.

16 An inspection report is referred to a review panel before it is finalised if: there is a provisional compliance rating of 'unacceptable'; the manufacturer's response cannot be accepted; or the lead inspector or their manager consider it useful to determine if a follow-up procedure is required.

has not been fully modified to meet business requirements. Consequently, it does not capture key management information required to monitor performance and adherence to SOPs, and the TGA should enhance the system to record the dates on which inspection reports are sent, manufacturers' responses are received and inspections are closed out. The TGA has not assessed its IT network security controls relating to OMQ's data holdings to ensure that commercially sensitive information is protected against cyber intrusion, and should review relevant system controls. Further, the compliance information contained in the MIS is not aligned with information held on the Australian Register of Therapeutic Goods (ARTG)[17] to ensure that publicly accessible information on prescription medicines is current and reliable.

26. The TGA reports on its regulatory performance through the Department of Health's Portfolio Budget Statement. The TGA identified three quantitative key performance indicators (KPIs) for 2013–14, one of which relates to the timeliness of inspections.[18] The TGA has acknowledged the limitations of its current KPIs and has advised that it plans to develop revised performance measures by December 2015.

Summary of agency response

27. The Department of Health's covering letter in response to the proposed audit report is reproduced at Appendix 1. The Department of Health's response to the proposed audit report is set out below:

> The Department of Health notes the audit report and agrees with the recommendations.

17 The Australian Register of Therapeutic Goods (ARTG) is a register published on the TGA website containing information about all therapeutic goods approved for supply in Australia.

18 The 2013–14 KPI relating to the performance of the manufacturing compliance program measures the 'Percentage of licensing and surveillance inspections completed within target timeframes'.

Recommendations

Recommendation No.1

Paragraph 2.10

To provide additional assurance on the integrity of the Therapeutic Goods Administration's (TGA) process for assessing compliance with the Code of GMP, the ANAO recommends that the Department of Health improve existing processes for, and oversight of:

- recording key decisions and maintaining inspection files, according to standard operating procedures; and
- staff adherence to standard operating procedures, through the TGA's quality assurance reviews.

Department of Health response: *Agreed*.

Recommendation No.2

Paragraph 5.44

To improve the security and utility of the Office of Manufacturing Quality's (OMQ) information management arrangements, the ANAO recommends that the Department of Health enhance the OMQ's processes for:

- capturing management information, including key dates relating to the inspection process, and whether quality assurance reviews have been undertaken;
- aligning the manufacturing information held on the Australian Register of Therapeutic Goods with that held by the OMQ; and
- protecting commercially sensitive information held by the OMQ.

Department of Health response: *Agreed*.

Audit Findings

1. Introduction

This chapter provides background information on therapeutic goods, the Code of Good Manufacturing Practice and the regulatory framework, as applied by the Therapeutic Goods Administration. It also outlines the audit objective and criteria, as well as the structure of subsequent chapters.

Background

1.1 Therapeutic goods are products for human use in preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury. They include a range of medicines, medical devices, blood, tissues and biologicals.

1.2 Consumers expect the therapeutic goods they obtain from the Australian market to be manufactured in a way that assures their safety, quality and efficacy. They also expect the timely availability of new therapeutic goods. For these reasons and the associated risks, the Australian Government regulates all therapeutic goods through the *Therapeutic Goods Act 1989*.

1.3 Generally, regulated therapeutic goods supplied in Australia fall into three categories:

- *registered medicines*—registered medicines are assessed as having the highest level of risk and are individually examined for safety, quality and efficacy. They include all prescription medicines[19], most over-the-counter medicines[20] and some complementary medicines[21];
- *listed medicines*—listed medicines contain pre-approved, low risk ingredients and are subject to a less rigorous assessment. They include some over-the-counter medicines and most complementary medicines; and
- *medical devices*—these are items used on humans for therapeutic benefit and which generally have a physical or mechanical effect on the body or are used to measure or monitor functions of the body. They are

19 Prescription medicines are those for which consumers require a prescription from an authorised medical practitioner or that are dispensed in hospital settings by authorised health care professionals.

20 Over-the-counter medicines for self-treatment are available from pharmacies, with selected products also available in supermarkets and health food stores.

21 Complementary medicines include vitamin, mineral, herbal, aromatherapy and homeopathic products.

classified according to their level of risk and assessed on a basis applicable to devices.

1.4 Prescription medicines supplied on the Australian market are manufactured domestically and internationally. As at 30 June 2013, there were 154 sites approved to manufacture registered medicines in Australia and 1365 overseas manufacturers supplying imported registered medicines.

1.5 In 2011–12, the export value of Australia's pharmaceutical industry was $4.6 billion, with imports amounting to $10.7 billion. The overall industry turnover in Australia was estimated at $23.6 billion in 2011–12[22], with community pharmacies dispensing 271 million prescriptions in 2010.

The regulatory framework

Legislation

1.6 As noted in paragraph 1.2, the primary legislation authorising the regulation of therapeutic goods in Australia is the *Therapeutic Goods Act 1989* (the Act). From 1990, the Act established a national framework to regulate the safety, quality, efficacy and timely availability of therapeutic goods that are used in or exported from Australia.[23] Accordingly, its provisions apply to prescription medicines and the quality of their manufacture.

1.7 The Minister for Health has responsibility for the Act while the Therapeutic Goods Administration (TGA), a part of the Department of Health[24], administers the regulatory framework.

1.8 The main parts of the Act cover:

- the licensing of Australian manufacturers of therapeutic goods;
- the determination of standards for therapeutic goods, including the manufacturing principles to be observed in their manufacture; and

22 Department of Industry, *Pharmaceuticals Industry Data Card 2013* [Internet], Industry, Canberra, 2013, available from <http://www.innovation.gov.au/INDUSTRY/PHARMACEUTICALSANDHEALTHTECHNOLOGIES/PHARMACEUTICALS/Pages/PharmaceuticalsIndustryDataCard.aspx> [accessed August 2013].

23 *Therapeutic Goods Act 1989*, s. 4: Objects of Act, p. 21, available from <www.comlaw.gov.au> [accessed 3 September 2013].

24 The Department of Health was known as the Department of Health and Ageing prior to a machinery of government change in September 2013.

- the maintenance of an Australian register of therapeutic goods which are approved for import, export and supply.[25]

1.9 A range of subordinate legislation supports the Act, including the *Therapeutic Goods Regulations 1990*, which prescribe matters necessary for carrying out the Act. For example, regulations have been enacted on: the registration or listing of therapeutic goods; the licensing of manufacturers; the examination, testing and analysis of goods; the charges and fees associated with these activities; and the formation of expert advisory committees.[26]

Licensing and certification of manufacturers

1.10 The Act requires that Australian manufacturers of prescription medicines obtain a licence before they can legally manufacture products approved for supply in Australia or for export.[27] Overseas manufacturers of prescription medicines are also required to meet equivalent standards, whether they have been certified by the TGA or an overseas regulator, before the importer (known as a 'sponsor') is granted clearance to supply in Australia. To be eligible for a licence or clearance, the applicant must demonstrate that the facility in which the goods were manufactured is compliant with the designated manufacturing principles.[28]

The Code of Good Manufacturing Practice

1.11 Good manufacturing practice (GMP) is a set of principles and procedures which, when applied by manufacturers of therapeutic goods, helps to ensure a consistently high level of manufacturing quality. Section 36 of the Act enables the Minister for Health to determine which principles will be observed in the manufacture of therapeutic goods supplied in Australia, namely the designation of a specific code of GMP.[29]

1.12 Since 2002, Australia's manufacturing principles have been based on the Guide to Good Manufacturing Practice for Medicinal Products, commonly

25 Therapeutic Goods Bill 1989, *Explanatory Memorandum.*

26 *Therapeutic Goods Regulations 1990*, Parts 3, 4, 5, 7 and 6, respectively.

27 Manufacture includes, but is not limited to: production, processing, assembling, packaging, labelling, storage, sterilising, testing and release for supply (refer section 3, p. 9).

28 *Therapeutic Goods Act 1989,* s. 40(4)(a), p. 239.

29 The manufacturing principles relate to: the standards to be maintained, equipment and premises to be used, the qualifications required of persons employed in the manufacture of therapeutic goods, the manufacturing practices and other matters relevant to the quality, safety and efficacy of therapeutic goods.

referred to as the Code of GMP.[30] The Code of GMP is issued by the international Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)[31], of which Australia is a member.

1.13 For the purpose of assessing compliance with the Act and the Code of GMP, persons authorised by the Secretary of the Department of Health, namely inspectors, are permitted to enter and search any premises where therapeutic goods are manufactured. The authorised person may inspect, examine, take measurements, obtain samples and take images or recordings of anything on the premises relating to the manufacture of therapeutic goods.[32]

Administering the framework

The Therapeutic Goods Administration

1.14 The role of the Therapeutic Goods Administration (TGA) is to administer the regulatory framework established by the Act, in order to regulate the manufacture and supply of therapeutic goods in Australia.

1.15 The TGA has operated on a full cost recovery basis since 1998–99. Through fees and charges imposed on manufacturers and sponsors of therapeutic goods, the TGA seeks to recover the costs of all activities within the scope of the Act. These activities include: pre-market product assessment; licensing of manufacturers; post-market monitoring; and enforcing compliance with legislative requirements.

1.16 Within the TGA, specific responsibility for assessing and monitoring compliance with the Code of GMP falls to the Office of Manufacturing Quality (OMQ), positioned in the TGA's Monitoring and Compliance Group.[33] The OMQ's framework for regulating the manufacturing quality of prescription medicines has two main operational elements:

- the licensing of domestic manufacturers and certification and clearance of overseas manufacturers against the Code of GMP; and

30 The TGA currently administers the 2013 version of this Guide.

31 The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly known as PIC/S) is a cooperative arrangement between national regulatory authorities aimed at achieving global harmonisation in the field of GMP.

32 *Therapeutic Goods Act 1989*, s. 46, pp. 112 and 425–27 and s. 49, pp. 434–35.

33 The OMQ is responsible for administering Part 3-3 (Manufacturing of therapeutic goods) of the Act.

- implementing a risk-based compliance program of manufacturer surveillance inspections.

1.17 In 2012–13, four new Australian licences were granted for registered medicine manufacture, 29 overseas registered medicine manufacturing sites were certified by the TGA and 3644 clearances for therapeutic goods were approved. A total of 53 inspections were conducted on prescription medicine manufacturing sites, both domestically and overseas.

Previous relevant ANAO performance audits

1.18 This audit continues the ANAO's examination of aspects of the TGA's regulatory functions. The ANAO has most recently undertaken an audit of the TGA's regulation of complementary medicines, Audit Report No.3 2011–12 *Therapeutic Goods Regulation: Complementary Medicines*. The ANAO last reviewed the TGA's application of the Code of GMP in Audit Report No.18 2004–05 *Regulation of Non-prescription Medicinal Products*.

Audit objective, criteria and scope

1.19 The audit objective was to assess the effectiveness of the Therapeutic Goods Administration's application of the Code of Good Manufacturing Practice (Code of GMP) for prescription medicines.

1.20 To assist in evaluating the TGA's performance in terms of the audit objective, the ANAO developed the following high level criteria:

- only manufacturers who have been rigorously assessed as meeting the Code of GMP are eligible to supply prescription medicines in Australia;
- the TGA has a risk-based approach to monitoring compliance of prescription medicine manufacturers against the Code of GMP, to enable the TGA to target resources effectively and respond to priority risks;
- the TGA has implemented policies and procedures to respond to manufacturing non-compliance of prescription medicine manufacturers, which are proportionate to the risks presented; and
- the TGA's regulation of the Code of GMP is supported by appropriate structures and processes.

Audit methodology

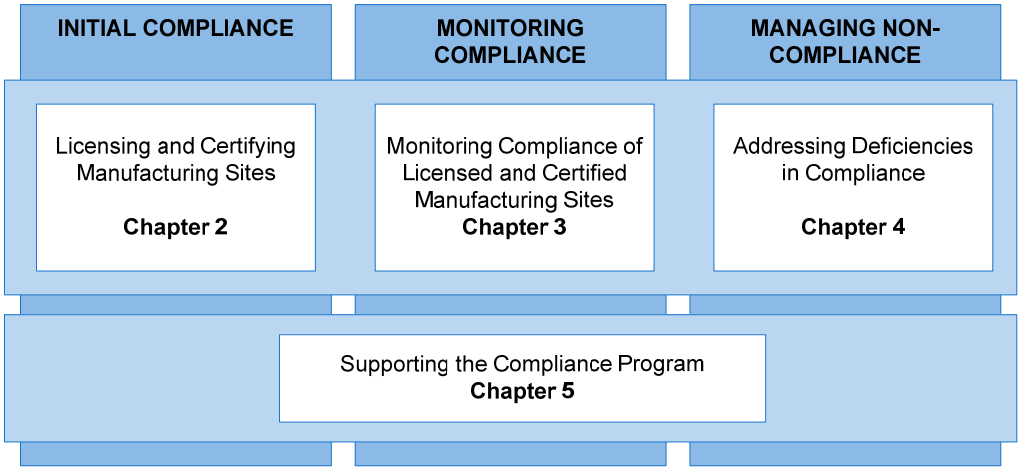
1.21 In undertaking the audit, the ANAO: interviewed senior and operational TGA and Department of Health staff, state and territory government health divisions and non-government stakeholders; observed two TGA compliance inspections; reviewed key documents relevant to the administration of the compliance program, and analysed performance and financial data; and conducted qualitative and quantitative analysis of the compliance program and supporting information management systems.

1.22 The audit was conducted in accordance with the ANAO's Auditing Standards at a cost to the ANAO of $532 399.

Structure of report

1.23 Figure 1.1 provides a diagrammatic summary of the structure of subsequent chapters.

Figure 1.1: Structure of report



Source: ANAO.

2. Licensing and Certifying Manufacturing Sites

This chapter addresses the effectiveness of the TGA's approach for assessing manufacturers' compliance, to provide confidence that only manufacturers that have been rigorously assessed as meeting the Code of GMP are able to supply prescription medicines in Australia.

Introduction

2.1 As a basis for providing assurance that the manufacture of therapeutic goods supplied in Australia aligns with the Code of GMP, the TGA requires that manufacturing sites are initially licensed or certified against the Code of GMP, with certification carried out either by the TGA or an overseas regulator.

2.2 Australian manufacturers of therapeutic goods are required under the Act to hold a manufacturing licence listing the type(s) of product, the authorised manufacturing steps and any conditions. A licence usually relates to a single manufacturing site but can include secondary sites according to guidelines issued under section 38A of the Act.[34] Licences issued by the TGA are ongoing, provided that the manufacturer remains compliant with the Code of GMP and pays an annual licence charge.

2.3 Overseas manufacturers supplying the Australian market are outside the jurisdiction of the Act. Instead, the Act requires the TGA to gain assurance that 'if a step in the manufacture of the good has been performed outside Australia ... the manufacturing and quality control procedures used in the manufacture of the goods are acceptable'.[35] This requirement forms the basis for the TGA's GMP clearance process, through which the OMQ assesses manufacturing compliance with the Code of GMP for manufacturing steps carried out overseas. The TGA assesses each clearance application according to the location of the manufacturing site and the risk associated with the product. This assessment can range from a check on the validity of the GMP certification through to a TGA on-site inspection.

34 TGA, *Therapeutic Goods (Multi-Site Manufacturing Licenses) Guidelines of 2010,* TGA, Canberra, 2010.

35 *Therapeutic Goods Act 1989*, s. 25(1)(g).

2.4 Table 2.1 identifies the distribution of licensed and certified registered medicine manufacturing sites, as at 30 June 2013, according to type of assessment.[36] This shows that the TGA is responsible for conducting inspections on approximately one-third of the manufacturing sites supplying registered medicines to the Australian market; the balance are certified by overseas regulators.

Table 2.1: Licensed and certified registered medicine manufacturing sites as at 30 June 2013

Type	Number	Percentage
Australian sites licensed by the TGA	154	10
Overseas sites inspected and certified by the TGA	327	22
Overseas sites certified by overseas regulators	1038	68
Total	**1519**	**100**

Source: TGA.

2.5 To assess the effectiveness of the TGA's framework for ensuring that only manufacturers who have been rigorously assessed as meeting the Code of GMP are able to supply prescription medicines in Australia, the ANAO examined the process and timeliness for:

- licensing of Australian manufacturers;
- assessing certifications by overseas regulators; and
- certifying overseas manufacturers.

Licensing of Australian manufacturing sites

Processing licence applications

2.6 Applicants for new licences to manufacture prescription medicines are subject to initial inspections to determine whether the facility complies with the Code of GMP. In the four years to 30 June 2013, seven licence applications to manufacture prescription medicines were received by the TGA, all of which were approved. The TGA's licensing process, from application review to final decision, is supported by standard operating procedures (SOPs) and designed

36 Prescription medicines are a subset of registered medicines. The TGA's information technology systems are not configured to easily extract information on prescription medicine manufacturing sites as they reflect the two categories of therapeutic goods outlined in the legislation: registered and listed.

to provide assurance that the products manufactured in the facility will be safe, reliable and of consistent high quality. The SOPs specify the process and documentation required to support the TGA's decision to grant a licence, including where key documentation should be filed.

2.7 The ANAO reviewed the documentation relating to the four licences issued to Australian manufacturers of prescription medicines in 2012–13 and found that procedures were mostly followed. However, the inspection files had not been consistently maintained, in accordance with SOPs. As a result, in each case, the formal decision record was incomplete or missing, as were a number of key documents to support these decisions. The ANAO assessed a further sample of certification decisions on five overseas manufacturing sites and found that the inspection files were inconsistent with the requirements in the SOPs. Such documentation is particularly important when discretion is exercised. At one of the domestic sites, the TGA made a discretionary decision not to conduct an inspection of a manufacturer's new site prior to issuing the licence. The absence of documentation meant that it was not possible to determine whether this discretion had been exercised on the basis of a well-considered risk assessment.

2.8 The quality review process provides some potential to identify and address shortcomings in record-keeping. The TGA introduced a new basis for undertaking quality reviews in mid-2013 after identifying limitations in its previous approach (see paragraph 3.47). The TGA has acknowledged that not all its inspectors consistently comply with the records management requirements of its SOPs and advised that it intends to address this through additional training for inspectors and business coordination staff in the application of the OMQ's Quality Management System.

2.9 Given that licences are ongoing, the decision to grant one must be based on adequate consideration of the site's compliance with the Code of GMP and the associated manufacturing and product risks. Strengthening its quality assurance processes will enable the TGA to provide greater confidence that staff formally document key decisions, particularly when discretion is exercised, and maintain complete and accurate records to enhance accountability and transparency of the licensing and certification process.

Recommendation No.1

2.10 To provide additional assurance on the integrity of the Therapeutic Goods Administration's (TGA) process for assessing compliance with the Code of GMP, the ANAO recommends that the Department of Health improve existing processes for, and oversight of:

- recording key decisions and maintaining inspection files, according to standard operating procedures; and
- staff adherence to standard operating procedures, through the TGA's quality assurance reviews.

Department of Health's response:

2.11 *The department agrees with this recommendation.*

Effort and timeliness

2.12 In the scheduling of an initial licensing inspection, a preliminary estimate of the inspection effort[37] is determined based on the product profiles and the manufacturing processes involved. The actual average effort[38] used to undertake initial licensing inspections over the five years to 30 June 2013 was 12.3 person-hours, significantly below the 43.8 hours of actual average effort used for re-inspections. Inspections undertaken for new licence applications typically take place prior to the production of medicines and therefore have a smaller inspection scope.

2.13 The TGA has published a target timeframe of less than three months to process a new Australian licence, from the date of application to the provision of the inspection report.[39] However, since the OMQ does not centrally record the date the inspection report was sent, it has limited means to monitor its performance against this target.

2.14 The ANAO interviewed one of the seven Australian manufacturers that had been licensed in the four years to 30 June 2013. This manufacturer was positive about the licensing process, advising that the inspector conducting the

37 Inspection effort is the measure of resources required to undertake an on-site inspection. It is measured in person-hours: (the days spent on-site) x (number of inspectors) x (8 hrs per day).

38 The actual effort is determined following the on-site inspection.

39 TGA, *Guidance on licensing/certification inspections*, TGA, Canberra, 2013.

initial inspection had been very communicative about the requirements of the Code of GMP and had closed out the inspection within the target timeframe.

Certification by overseas regulators

2.15 Australian-based sponsors of therapeutic goods manufactured overseas must demonstrate the manufacturer's compliance with an equivalent standard of GMP in order to supply in Australia. Compliance can be determined through an on-site TGA inspection or by an overseas regulator. GMP clearances can be granted to the sponsor when the manufacturer has a current GMP certificate issued by one of the following overseas regulators:

- a regulatory authority in a country with which Australia has a Mutual Recognition Agreement (MRA).[40] Australia currently has MRAs with 22 European Union countries and Switzerland, Canada and Singapore[41];
- Medsafe (New Zealand) with which the TGA has a Memorandum of Understanding (MOU);
- the United States Food and Drug Administration (FDA) with which the TGA has a cooperative arrangement for the exchange of GMP and other information[42];
- a regulatory authority that is a member of PIC/S. There are fourteen countries with PIC/S membership that do not fall within the above categories.[43]

2.16 The OMQ issues GMP clearances for a set period of time. This is based on a due date six months after the manufacturing site's GMP certificate expires or is subject to compliance review.[44]

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40 MRAs are treaties between Australia and other countries that are enforceable under international law. The countries have been assessed as having GMP standards equivalent to Australia and the agreements provide for the mutual recognition of compliance assessments.

41 See Appendix 1 for the full list of countries.

42 The arrangement between the TGA and US FDA is governed by an exchange of letters from October 2007. It facilitates TGA's access to the FDA's database to enable checking of a manufacturer's compliance status.

43 All but one of the MRA countries' regulators, along with the TGA, Medsafe and the US FDA are members of PIC/S. See: Therapeutic Goods Administration, *Australian Regulatory Guidelines Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers, 17th Edition*, TGA, Canberra, 2011, p. 14.

44 The practice of issuing clearances for the length of the GMP certificate plus six months allows time for the next inspection to occur and the GMP certificate to be issued, which the sponsor can then use to make an application to renew their GMP clearance.

2.17 The level of assessment the TGA undertakes for clearance applications depends on the category of the overseas regulator, and the location of the manufacturing site. In particular:

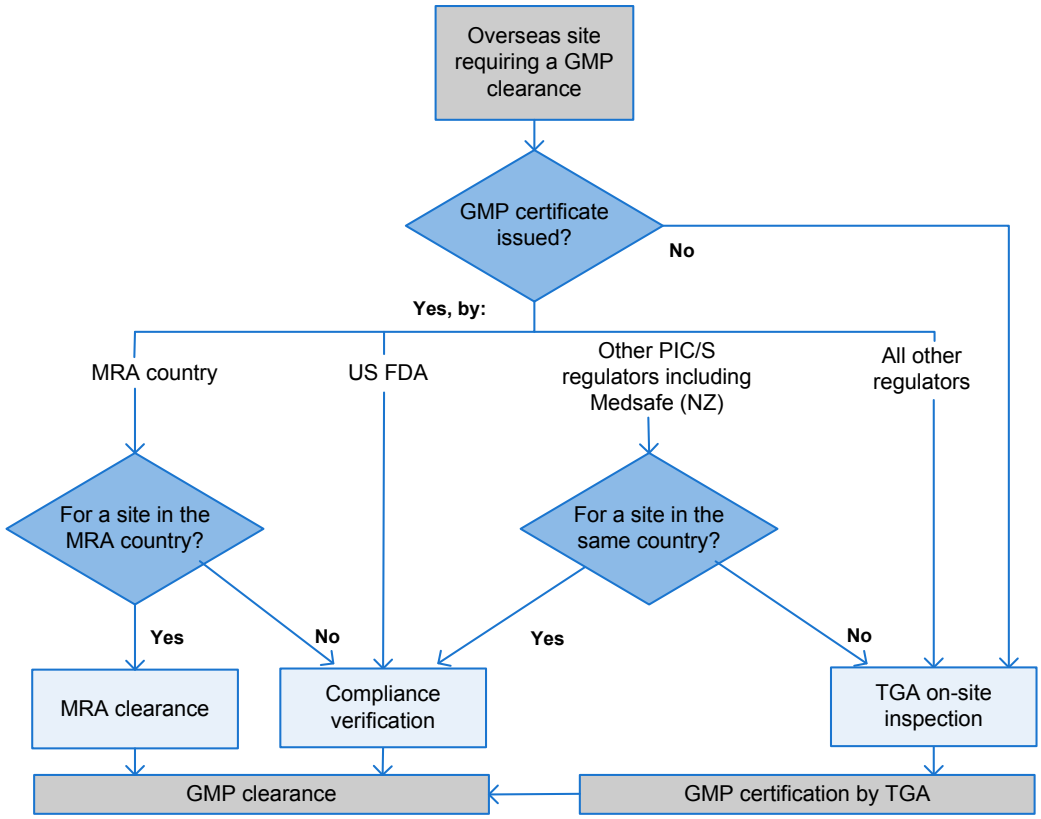
- if certification was undertaken by an MRA regulator on a site in their own country, the TGA will not conduct an independent assessment;
- if the site was certified by one of the other bodies listed at paragraph 2.15, the TGA conducts a desk assessment, known as a compliance verification, of the following:
  - evidence that the manufacturer has a current GMP certificate issued by one of the above regulators; and
  - necessary supporting documentation, including detail of all regulatory inspections and any product alerts, warning letters, import alerts, and recalls due to defects.

2.18 The OMQ reserves the right to inspect manufacturers, irrespective of other evidence provided. For example, if the TGA is alerted to any compliance issues or if it is inspecting an adjacent manufacturer, it may choose to undertake an inspection.[45]

2.19 The usual pathways to obtaining GMP clearance for overseas manufacturers of prescription medicines are outlined in Figure 2.1.

45 TGA, *Australian Regulatory Guidelines Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers, 17th Edition*, TGA, Canberra, 2011, pp. 7 and 15.

Figure 2.1: Pathways to GMP clearance for prescription medicines



Source: ANAO analysis of TGA information.

Obtaining assurance on the standard of overseas regulators

2.20 Table 2.1 shows that a significant proportion (68 per cent) of sites manufacturing registered medicines for supply in Australia are certified by overseas regulators. This presents a risk, to be managed by the TGA, as to the quality of the processes applied by overseas regulators.

2.21 The OMQ obtains its primary assurance on the standard of overseas regulatory activity through PIC/S and will only accept certifications by regulators who are members of PIC/S.[46] Before a regulatory authority can become a member, they are subject to an initial inspection by representatives of current PIC/S members to verify that they have appropriate systems and

46 The exception is certifications undertaken by the regulator in Luxembourg. These certifications are covered by the MRA with the European Union.

procedures in place to apply an inspection regime comparable to that of existing PIC/S members.

2.22 Nonetheless, a high level of trust underpins the MRAs to which Australia is signatory as these arrangements, along with MOUs and PIC/S membership, do not guarantee regulatory equivalence. The TGA, in common with many other national regulators, faces the challenge of how best to obtain assurance on the standards applied by other regulators. The need to obtain adequate assurance is underscored by industry trends, which have seen the therapeutic goods industry become increasingly globalised in recent years. Consequently, GMP clearances represent a growing proportion of the OMQ's regulatory workflow.

2.23 The OMQ advised the ANAO of one PIC/S member regulator whose regulatory approach does not fully align with the TGA's and, consequently, sponsors of products manufactured in that country are often provided clearances with conditions attached. A further example highlighting the risks associated with reliance on overseas regulator's certifications involves an African manufacturer with GMP clearance to supply prescription medicines in Australia on the basis of certification by a regulator within the European Union. When the TGA conducted its own inspection of the manufacturer, it identified a number of critical deficiencies and subsequently suspended all current clearances and denied a certificate of GMP compliance.

2.24 The key risks to be managed with respect to overseas regulators' approval of foreign manufacturing sites will differ depending on the type of clearance (see Table 2.3). Where an MRA is in place, the risks relate to lack of visibility around the regulator's inspection scope, outcomes and capabilities. Where a compliance verification is conducted, the risks include limited knowledge of the physical site under inspection and incomplete knowledge of how the regulator applies standards of GMP. Further, the clearances granted to overseas manufacturing sites following a TGA inspection are dependent on available resources for the inspection, which may affect the depth of assessment. The TGA also recognises that additional risks may arise in the context of manufacturing in emerging economies.

2.25 The ANAO observed in its 2004 audit on the regulation of non-prescription medicines that the TGA did not have an effective means of monitoring the regulatory equivalence of countries with which it has GMP

agreements.[47] Since then, the TGA has developed the following plans to obtain assurance on the standard of overseas regulators:

- International Engagement Strategy 2013–15[48] — a high level strategy that identifies target goals, associated risks and performance indicators relating to the TGA's engagement with overseas regulators; and
- OMQ Risk Management Plan — which recognises the risks of reliance on overseas regulators for the approval of foreign manufacturing sites.[49] It currently rates the risk of unjustified approval of these sites as having a 'moderate' consequence and 'unlikely' likelihood, generating an overall risk rating of 'medium', in line with the target risk.

2.26 Some of the activities identified by the OMQ to maintain the current risk level associated with reliance on overseas regulators include attendance at joint training and/or education events, participation in joint inspections and regular liaison with regulators to ensure alignment of assessment policies and approaches. Examples of this include:

- regular teleconferences with MRA partners and the exchange of annual reports detailing any changes to regulatory processes;
- ongoing collaboration with Health Canada to achieve mutual assurance on a number of regulatory matters, including the GMP standards applied by new PIC/S members[50];
- participation between 2008–10 in a pilot program to rationalise international GMP inspections of active pharmaceutical ingredients with the aim of fostering cooperation and mutual confidence[51]; and
- participation in the teams responsible for conducting a PIC/S pre-acceptance inspection, as well as involvement in the PIC/S membership re-inspection program.[52]

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47 ANAO Audit Report No.18 2004–05 *Regulation of Non-prescription Medicinal Products,* p.44.

48 TGA, *International Engagement Strategy 2013–2015*, Canberra, 2013.

49 The risk is poor quality, unsafe medications being imported into Australia. The increased reliance on other regulatory authorities in approving foreign manufacturers is identified as contributing to the risk.

50 In 2004, when 12 countries were admitted to the EU, Health Canada and the TGA agreed to conduct reviews of the compliance approach of each new regulatory authority and share this intelligence.

51 European Medicines Agency, *Final report on the International API Inspection Pilot Program*, EMA, London, 2011.

52 For example, a senior inspector in OMQ recently formed part of the PIC/S pre-acceptance inspection of the Japanese regulator, the Pharmaceutical and Medical Devices Agency.

2.27 In addition to the activities outlined above, the OMQ's site inspections have occasionally coincided with compliance inspections conducted by other regulators and this has led to an informal collaboration between the inspection teams. The OMQ does not centrally record such occurrences but was able to identify at least two examples of concurrent inspections, in addition to four planned joint inspections, over the previous three years. These interactions with other regulators present valuable opportunities for the OMQ to observe differences in approach and the alignment of standards between the TGA and its overseas counterparts. However, there is currently no means of capturing the lessons learnt from these observations and using those lessons to obtain assurance on the standards applied by overseas regulators. The ANAO therefore suggests that the OMQ systematically record and analyse the observations made by inspection teams following their on-site interaction with overseas regulators. Subsequently, observed differences should be brought to the attention of TGA management so that significant discrepancies in approaches and conclusions can be addressed through inter-agency coordination.

Processing clearance applications

2.28 Reflecting the increasingly global nature of therapeutic goods manufacturing, the OMQ approved 4103 clearance applications in 2011–12, and 3644 applications in 2012–13 (covering all therapeutic goods). The number of clearance applications can vary considerably in any one year, with a fall in applications of over 20 per cent between 2008–09 and 2009–10, followed by a significant increase of 61 per cent from 2010–11 to 2011–12. As shown in Table 2.2, the OMQ's level of processing, as reflected through its approval or rejection of applications, has largely kept pace with these fluctuations.

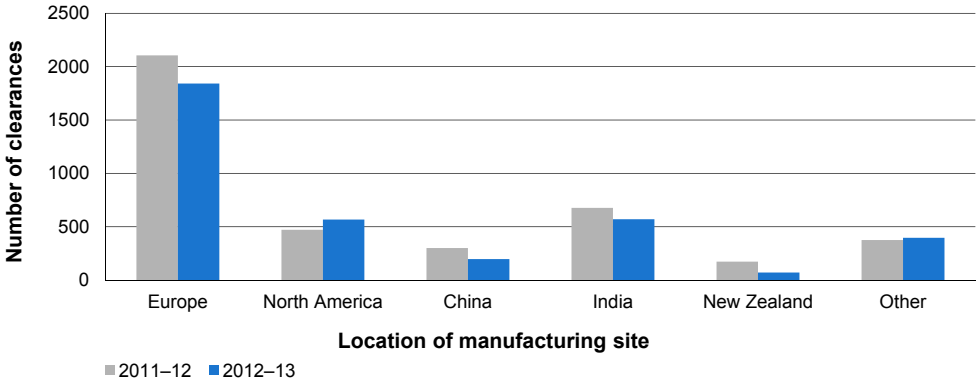
Table 2.2: Clearances for overseas sites manufacturing therapeutic goods for Australia 2008–09 to 2012–13

Clearance application status	2008–09	2009–10	2010–11	2011–12	2012–13
Applications received	3170	2511	2418	3900	3941
Approved (A)	3266	3163	3362	4103	3644
Rejected (B)	13	8	18	232	92
Applications finalised (A)+(B)	3279	3171	3380	4335	3736

Source: OMQ internal performance reporting information for 2011–12 and 2012–13.
Note: The OMQ processed a large backlog of clearances in 2009–10, 2010–11 and 2011–12.

2.29 Figure 2.2 shows the distribution of clearances conducted in 2011–12 and 2012–13 by location of manufacturing site.

Figure 2.2: Approved clearances for all therapeutic goods by location of manufacturing site



Source: OMQ internal performance reporting information for 2011–12 and 2012–13.

Note: The 'other' category primarily comprises manufacturing sites in the following countries: Japan, Israel, Singapore, Taiwan, Mexico, South Africa, Argentina, Brazil and Korea.

2.30 The OMQ's level of assessment on each clearance application is based on an evaluation of the risk associated with the different categories of clearance and is identified within the relevant SOP. Table 2.3 outlines the characteristics of the different types of clearance.

Table 2.3: Clearance categories for therapeutic goods based on certification by overseas regulators

		Compliance Verification	
	Category A	Category B	Categories C and D
Description	Certified by MRA regulator in own country	Non-sterile production	Sterile production (C) Testing laboratories/ sterilisers (D)
Applications/ renewals approved in 2012–13: no. (%)	1575 (49%)	1348 (42%)[A]	316 (9%)[A]
Assessed by:	Administrative assessor (APS 6)	Administrative assessor (APS 6) with reference to an inspector if discrepancies/ significant deficiencies identified	GMP inspector
Target timeframe	Within 15 business days.	Within 30 business days.	Within 90 business days.
Reviewed for completeness and accuracy by:	SOP: Peer review of two assessments/day/ assessor In practice: 'minimal'.	SOP: 100% peer reviewed with selected application reviewed by the clearance coordinator (EL 1). In practice: 'minimal', with the ANAO noting review of a rejected application.	SOP: 100% review by the clearance coordinator or Inspection Group Manager. The ANAO was unable to determine the extent to which this occurred in practice as the OMQ does not centrally record this information.[B]

Source: TGA.

Note A: These figures include the small number of Category B applications required to be referred to inspectors under Categories C and D.

Note B: Of the 50 clearances examined by the ANAO, five were Category C and D applications but two were letters of access to previous clearances. While the OMQ was able to provide examples of the types of checks the remaining three clearances were subject to, they were unable to provide the sign-off sheets for these clearances.

2.31 As outlined in Table 2.3, over 90 per cent of clearances are approved by administrative assessors with minimal review of completeness and accuracy. Based on a sample of 50 clearances processed in the five years to 30 June 2013, the ANAO determined that the OMQ's assessment of clearance applications was largely consistent with the level of checking required by the relevant SOPs with respect to completeness and accuracy.[53]

53 In this analysis, the ANAO examined the extent to which the OMQ's assessment of clearance applications: accurately identified the category according to the type of regulator; checked required dosage forms and manufacturing steps; and were undertaken by inspectors when they involved sterile manufacture.

Timeliness

2.32 As shown in Table 2.3, the TGA has set timeliness standards for the processing of overseas clearance applications from the receipt of application, supporting documentation and payment of fees.[54] Table 2.4 shows the extent to which the TGA has met these targets.

Table 2.4: Timeliness of clearances for overseas sites manufacturing therapeutic goods for Australia, certified by overseas regulators 2012–13

Category	Met target (%)	Median processing time of those that do not meet target (business days)
A (<15 business days)	91	21
B (< 30 business days)	85	79
C & D (< 90 business days)	75	161

Source: TGA.

2.33 The OMQ largely meets its timeliness target for applications for sites certified by MRA regulators in their own country (Category A). The OMQ also has a reasonable achievement of timeliness for applications requiring compliance verification (Category B). However, for the nine per cent of applications that required assessment by a GMP inspector, 25 per cent of applications did not meet the 90 day timeliness target, and had a median processing time of 71 days over the target. The OMQ advised that the causes for such delays include:

- on-site inspection commitments of the inspector and/or the reviewer;
- delays in receiving additional information; and
- complexity of the information provided by the manufacturer.

2.34 As such delays may have commercial implications for sponsors supplying prescription medicines to Australia, the ANAO suggests that the OMQ advise sponsors when the timeframe is likely to exceed 90 days.

54 TGA, *Australian Regulatory Guidelines Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers, 17th Edition*, TGA, Canberra, 2011, p. 38. These timeliness standards were set by the TGA a number of years ago; the basis on which they were set is not known by current TGA staff.

Initiatives to improve the efficiency and effectiveness of the clearance processes

2.35 Currently, around 90 per cent of all therapeutic goods supplied in Australia are manufactured overseas. Under the legislation, if an Australian sponsor wishes to import a therapeutic good for supply in Australia, a separate application is required for each of the overseas manufacturers involved in the product supply chain.[55] Overseas manufacturers can supply products, or be involved in the manufacturing steps, for a number of therapeutic goods supplied in Australia, through various Australian sponsors.

2.36 In May 2013, the OMQ estimated that there were 5500 current clearances covering around 2000 manufacturers, indicating a sponsor to manufacturer overall ratio of almost three to one. This distribution varies significantly. In particular, approximately 70 per cent of manufacturing sites have two or more individual clearances, and about eight per cent have five or more. One overseas manufacturing site was the subject of more than 20 individual clearances.

2.37 Under current arrangements, the OMQ processes each clearance application separately, irrespective of previous assessments, resulting in duplicated effort. Furthermore, if a manufacturer has not been certified by the TGA or an MRA partner, the sponsor is required to submit documentation for compliance verification. In some cases, the manufacturer has been unwilling to share this information with the sponsor for commercial-in-confidence reasons and will therefore only submit directly to the TGA. To address this, the OMQ initiated a pilot program in 2007 in which it held the site information for five participating manufacturers so that the sponsor, with a letter of access from the manufacturer, could request the TGA to use this information to assess their clearance. Over the course of the pilot, which concluded in 2009, approximately 100 clearances were granted on the basis of letters of access.

2.38 Since 2012, the OMQ has been exploring options to extend this model to address the duplication of clearance processing effort. In February 2014, the OMQ proposed to the TGA Executive a model whereby clearance applications could be processed drawing on previous assessments of the same manufacturing site. If adopted, this initiative would improve the efficiency of

55 *Therapeutic Goods Act 1989*, ss. 25 and 26A.

regulatory processes by significantly reducing duplicated effort and contributing to the timely processing of clearances.

Certification of overseas manufacturing sites by the TGA

2.39 For a portion of overseas manufacturing sites from which a sponsor intends to import prescription medicines to Australia, the TGA determines GMP certification through an on-site inspection. The TGA will conduct these inspections when:

- the site has been assessed by a PIC/S regulator that is not from an MRA country or the United States, and is not located in the regulator's country;
- the site has been GMP certified by a regulator that is not a member of PIC/S; or
- the site does not have any GMP certification.

2.40 Once the TGA has determined, through an on-site inspection, that the manufacturing site is compliant with the Code of GMP, the TGA issues a clearance to the sponsor/s. Unlike licences, GMP certifications are subject to expiry. Typically, the expiry range is between one and three years from the date of the last on site inspection and is linked to the level of assessed risk.

2.41 Table 2.5 shows the activity relating to overseas sites applying for GMP certification over the five years to 30 June 2013.

Table 2.5: Overseas registered medicine manufacturing sites certified by the TGA 2008–09 to 2012–13

Activity	2008–09	2009–10	2010–11	2011–12	2012–13
Initial applications received	12	17	27	58	16
Renewal applications received	15	20	17	37	28
Approved	26	35	56	50	29
Rejected[1]	1	0	0	2	1

Source: ANAO analysis of TGA data

Note: Approved and rejected sites include both initial and renewal certifications. In any one financial year, applications and renewals received will not necessarily equal the total number approved and rejected, given the lag between the receipt of applications and the inspection.

Effort and timeliness

2.42 The actual average effort used to undertake inspections for initial certification purposes was 42.4 person-hours[56] over the last five years. This is similar to the average effort used for certification re-inspections, 49.8 person-hours. Unlike Australian sites, where initial inspections are undertaken prior to production, overseas sites are typically in production at the time of TGA's on-site inspection. Comparable effort is therefore required for both the initial and renewal inspections.

2.43 The TGA has set a standard of less than six months as the target timeframe for a new certificate of GMP compliance for overseas sites, from date of application to provision of the inspection report.[57] This is three months longer than for initial inspections of domestic manufacturers. The OMQ has identified that this extra time is required given the lead time involved in planning for an efficient overseas site visit. The main Information Technology (IT) system used by the TGA to administer the Code of GMP, the Manufacturers Information System (MIS), does not have a field to directly record the date the inspection report is sent and therefore has limited means of monitoring its performance against this target. Rather, the TGA monitors and reports against its performance in conducting inspections within six months of a certification application.

2.44 Across all overseas manufacturing sites that applied for GMP certification in 2012–13, the OMQ achieved this secondary target in only 74 per cent of applications. The OMQ advised that there are a number of reasons for such a low achievement rate including time lags to gain approval for overseas travel and unforseen factors that can affect visa processing. In order to accurately inform sponsors of the time required to achieve certification of an overseas manufacturing site, the ANAO suggests that the OMQ review its ability to meet this performance target and advise sponsors of any delays.

56 The measure of person-hours is defined at footnote 37.

57 TGA, *Guidance on licensing/certification inspections*, TGA, Canberra, 2013, p.24.

Conclusion

2.45 The licensing and certification of regulated bodies enables regulators to manage regulatory risks by controlling entry to the market. The TGA's licensing and certification functions are supported by a detailed set of SOPs, providing a good starting-point for the TGA's application of the Code of GMP.

2.46 Approximately 32 per cent of sites manufacturing registered medicines for supply in Australia are directly licensed or certified by the TGA through on-site inspections. The ANAO's review of this initial inspection process indicated that some key decisions had not been supported by formal documentation, and electronic inspection files were not consistently maintained, in accordance with the TGA's SOPs. Further, quality assurance reviews are not structured to verify whether staff have fully documented the inspection process, in line with the TGA's requirements.

2.47 Approximately 68 per cent of the manufacturing sites supplying registered medicines in Australia are located and regulated overseas. All prescription medicines supplied in Australia must have an Australian-based sponsor, who applies to the TGA for GMP clearance. At present, the TGA processes each clearance application individually, even where other sponsors have recently obtained clearances for the supply of identical products from the same manufacturing site. The OMQ advised the ANAO that approximately two-thirds of the effort spent processing clearance applications is a duplication of previous work, and it is considering a model to enable the reuse of current evidence of a manufacturing site's compliance with the Code of GMP in subsequent assessments of the same site. If adopted, this initiative can be expected to improve the efficiency of regulatory processes, to the benefit of industry and the TGA.

2.48 The manufacturing sites supplying registered medicines in Australia that are located and regulated overseas are certified by regulators with whom Australia has a MRA, MOU or cooperative arrangement. As part of an international engagement strategy to mitigate the risk of 'unjustified approval of foreign manufacturing sites', the TGA participates in joint and concurrent inspections, conducts regular teleconferences and exchanges detailed annual reports in order to verify the standards applied by its MRA partners. However, any differences observed during joint inspections are not documented and brought to management attention by TGA inspectors so that significant discrepancies in approaches and conclusions can be addressed through inter-agency coordination.

3. Monitoring Compliance of Licensed and Certified Manufacturing Sites

This chapter assesses the extent to which the TGA implements a risk-based approach to monitoring compliance of prescription medicine manufacturers with the Code of GMP.

Introduction

3.1 Following the issuing of GMP licences and certifications, the OMQ monitors manufacturers' continued compliance with the Code of GMP through a systematic program of routine inspections. The frequency of these inspections is risk-based, having regard to the risks associated with product type, manufacturing process and the manufacturer's compliance rating from the previous inspection. Changes at the manufacturing site may also warrant an inspection. Both domestic manufacturers and sponsors of products manufactured overseas are required to advise the TGA when they implement significant changes, including: new trading names; product alterations; the establishment of new manufacturing sites; and changes to the manufacturing steps or technology used.

3.2 Table 3.1 outlines the number of compliance inspections undertaken on prescription medicine manufacturing sites over the past five financial years.

Table 3.1: Compliance monitoring inspections of prescription medicine manufacturing sites 2008–09 to 2012–13

	2008–09	2009–10	2010–11	2011–12	2012–13
Australian licensed sites — compliance inspections (numbers)					
Planned	36	34	35	28	26
Non-routine	1	4	4	9	6
Overseas certified sites — compliance/renewal inspections (numbers)					
Planned	15	17	25	27	16
Non-routine	2	0	0	0	1
Total inspections	**54**	**55**	**64**	**64**	**49**

Source: ANAO analysis of TGA data.

3.3 The ANAO assessed the extent to which the TGA implements a risk-based approach to monitoring compliance of prescription medicine manufacturers with the Code of GMP, enabling the TGA to target resources

effectively and respond to priority risks. To focus this assessment, the ANAO examined:

- the risk basis for monitoring compliance;
- scheduling inspection activities; and
- the inspection process, including: resourcing; communication with manufacturers; inspection preparation; collection of evidence; and assessment of deficiencies.

The risk-based approach to monitoring compliance

Timing of routine inspections

3.4 The OMQ uses an inspection frequency matrix to determine the frequency of compliance inspections of licensed Australian manufacturing sites and for renewing overseas manufacturing site certifications. This is based on the inherent risk of the product and manufacturing processes, as well as the manufacturer's compliance rating from the immediately preceding inspection. Based on this, the frequency interval for compliance re-inspections is set between 12 to 36 months.

3.5 Examples of the risks, as determined by the OMQ, associated with products and manufacturing processes relevant to prescription medicines are:

- high risk: sterile medicines, including biotechnology active pharmaceutical ingredients, and non-sterile medicines containing antibiotics, steroids or antineoplastics (anti-cancer drugs);
- medium risk: other non-sterile medicines; and
- low risk: labelling/packaging, analysis/testing, and storage.[58]

3.6 The manufacturer's compliance rating for the immediately preceding inspection is also used to determine the re-inspection interval. At each inspection, the OMQ identifies any deficiencies against the Code of GMP and classifies these as critical, major or other, according to the internationally

58 TGA, *Manufacturer Inspections — Product/Process Risk Classifications*, [Internet], TGA, 2013, available from <http://www.tga.gov.au/industry/manuf-inspections-risk-classifications.htm> [accessed 2 December 2013].

harmonised definitions developed by PIC/S.[59] The number and type of deficiencies are then used to determine the manufacturer's compliance rating, as outlined in Table 3.2.

Table 3.2: Manufacturer compliance levels

	Rating	Basis for the rating
Acceptable	A1 (good)	Few deficiencies were found, which are of a relatively minor nature.
	A2 (satisfactory)	Few major deficiencies (not more than five) and/or a larger number of minor deficiencies were found. No critical deficiencies were found.
	A3 (basic)	A large number of major (more than five, not more than 10) and/or a large number of minor deficiencies were found. No critical deficiencies were found.
Unacceptable		One or more critical deficiencies and/or a large number of major deficiencies were found.

Source: Therapeutic Goods Administration, *Manufacturer Compliance History* [Internet], TGA, Canberra, 2013, available from <http://www.tga.gov.au/industry/manuf-compliance-history.htm> [accessed 30 July 2013].

3.7 The compliance rating is used in conjunction with the product and manufacturing risk rating to determine the manufacturer's re-inspection interval, as shown in Table 3.3.

Table 3.3: Inspection frequency matrix

	Compliance rating			
	Acceptable			Unacceptable
	A1	A2	A3	
Risk category	Re-inspection interval in months			
High	24	18	12	Determined by review panel[(A)]
Medium	30	20	12	Determined by review panel
Low	36	24	12	Determined by review panel

Source: Therapeutic Goods Administration, *Manufacturer Inspections — A Risk Based Approach to Frequency* [Internet], TGA, Canberra, 2013, available from <http://www.tga.gov.au/industry/manuf-inspections-frequency.htm> [accessed 30 July 2013].

Note A: Review panels are convened where the provisional compliance rating of a manufacturer is 'unacceptable'. The review panel makes a recommendation regarding how best to proceed.

59 Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, *PIC/S Inspection Report Format*, PIC/S, Geneva, 2007, p.4, available from <http://www.picscheme.org/publication.php> [accessed 30 July 2013].

Adherence to the procedure for setting inspection frequencies

3.8 Particular re-inspection frequencies are specified as a means to manage the risk of non-compliance. It is important that these intervals are adhered to as a means of focussing regulatory resources and maintaining the integrity of the regulatory process. The ANAO examined a random sample of 60 inspections conducted on sites manufacturing prescription medicine over the five years to 30 June 2013 to determine the extent to which the re-inspection interval was based on the product and manufacturing risk, and the previous compliance rating. This analysis showed that the re-inspection interval had been correctly identified for 100 per cent of the sampled inspections.

The effectiveness of re-inspection intervals

3.9 The OMQ has adopted a strategy of site re-inspections as part of a risk-based approach to managing potential non-compliance. Under such a strategy, the frequency of re-inspections should be aligned to the assessed risk. At any particular manufacturing site that is not subject to a production change, the inherent risk based on product and manufacturing process will remain the same. The ANAO assessed the extent to which the compliance program is effective, by determining the degree to which the current frequency of re-inspections results in improved compliance ratings for sites with 'basic' and 'unacceptable' compliance, and maintenance of compliance ratings within the 'good' and 'satisfactory' range. For all prescription medicine manufacturing sites that were subject to two or more inspections in the five years to 30 June 2013, the compliance rating resulting from an inspection was compared with that from the subsequent inspection. The result from the ANAO's analysis is shown in Table 3.4.

Table 3.4: Changes in compliance rating from subsequent inspections 2008–09 to 2012–13

Compliance status	Movement in compliance rating (%)[A]		
	A1	A2	A3
Improved	Not applicable	29	54
Same	52	58	44
Declined	48	13	2
Total	**100**	**100**	**100**

Source: ANAO analysis of TGA data.

Note A: Two subsequent inspections were undertaken on sites with a compliance rating of 'unacceptable'. One was an overseas site, which lost its certification for a period, and the other was a domestic site with a provisional rating of 'unacceptable' compliance prior to a close-out inspection. An improvement in compliance rating was subsequently assigned for both sites.

3.10 Table 3.4 shows that for 46 per cent of inspections that identified a large number of major deficiencies at the first inspection and therefore 'basic' compliance, subsequent inspections identified a similarly large number of major deficiencies. In one case, a new critical deficiency was identified. These inspections were on 13 separate manufacturing sites, 10 of which were located in Australia. Seven of the Australian sites were subject to three or more inspections; in each case the inspection interval was set at 12 months or less.

3.11 The ANAO examined the re-inspection reports for the seven domestic manufacturing sites with sequential 'basic' compliance ratings to determine the extent to which new or recurring major deficiencies were the reason for poor levels of compliance across inspections. Fourteen subsequent inspections were assessed. Of the seven sites, the ANAO identified the following:

- three sites had not addressed a significant proportion of the deficiencies previously identified, despite a requirement for the manufacturer to outline satisfactory corrective and preventive actions to address these deficiencies prior to closing out the previous inspection;
- two sites continued to have a significant number of deficiencies across inspections, but these were different deficiencies from those previously identified; and
- two sites showed improvements in the number of deficiencies, and previous deficiencies were no longer apparent.

3.12 Table 3.4 also shows that for 54 per cent of inspections (on 31 separate sites) that identified a large number of major deficiencies, manufacturers improved their compliance results in subsequent inspections.[60] Re-inspections were mostly set at 12-monthly intervals.

3.13 The ANAO's analysis indicates that the re-inspection intervals are effective in maintaining 'satisfactory' compliance with the Code of GMP. However, for a small number of sites, regular re-inspections either do not lead to significant improvements in particular major deficiencies or prevent new ones from arising, suggesting that the threat of regular re-inspections may not provide sufficient incentive for sites with 'basic' compliance to improve manufacturing standards.

60 Seventeen sites were in Australia, with 14 located overseas.

3.14 In September 2010, the TGA undertook an internal review of its inspection frequency matrix. Within recognised data limitations, the TGA could not determine whether varying the frequency of manufacturer inspections based on product and manufacturing risk categories made a difference in compliance outcomes for individual manufacturing sites. However, varying the inspection frequency based on original compliance ratings did subsequently lead to improvements in compliance. The TGA identified the need to undertake ongoing review and assessment of its inspection frequency model, including regular reviews of the manufacturing risk profile. Although no reassessment has been completed to date, the TGA advised the ANAO that it has initiated a review of its risk-based inspection model, including an assessment of the inspection frequency matrix.

Non-routine inspections

3.15 In addition to routine re-inspections, the OMQ conducts risk-based non-routine (special) inspections of manufacturing sites. Risks identified by the TGA as triggers for a non-routine inspection can include: adverse events; significant production changes; product recalls; laboratory testing[61]; feedback and inspection results from other regulators; or emerging trends that the OMQ identifies as a risk.

3.16 In the five years to 30 June 2013, the OMQ conducted 27 non-routine inspections of prescription medicine manufacturers. This involved 16 separate sites, with all but two located in Australia.[62] Four of these sites were subject to multiple non-routine inspections, with one having a history of 'basic' compliance ratings, as well as a provisional compliance rating of 'unacceptable' for a period of two months.[63] Of the seven Australian manufacturing sites that have maintained or fallen below 'basic' compliance across consecutive inspections (see paragraph 3.10), all were subject to non-routine inspections.

3.17 Of the sampled inspections, the main reason for conducting non-routine inspections was to check that corrective action to address deficiencies had been

61 The TGA's Office of Laboratories and Scientific Services (OLSS) undertakes laboratory testing of therapeutic goods to determine compliance with regulatory and technical standards. Abnormal test results that indicate an issue that may originate in manufacture can trigger an inspection.

62 TGA only conducts non-routine inspections on overseas sites on advice from the manufacturer regarding changes to manufacturing processes or key personnel; these are announced inspections.

63 A further inspection was scheduled two months later, at which time the rating was revised to 'basic'.

undertaken or was underway by the manufacturer prior to closing out an inspection. Other reasons included: the manufacturer seeking a licence variation; a joint inspection with an overseas regulator; and advice from the manufacturer of an adverse product test undertaken by an overseas regulator. In each of these cases the manufacturer was advised in advance of the inspection.

3.18 In response to a 2004 ANAO audit recommendation that the TGA undertake a cost-benefit analysis of conducting random unannounced compliance inspections[64], the OMQ performed an assessment in 2010. This assessment indicated that in the previous five years, less than one per cent of domestic inspections across all manufacturing sites had been unannounced and recommended an increase, given the potential benefits identified. In particular, it was noted that inspectors would more easily be able to assess GMP compliance, especially when there was an intention by the manufacturer to hide activities or deceive inspectors.

3.19 The ANAO's sample testing indicated that the number of unannounced inspections on prescription medicine manufacturing sites has not increased since this recommendation was made. The TGA advised that a number of factors influence its decisions to conduct random unannounced inspections. These include: the disruption and cost to the company involved; availability of data and key site personnel required to liaise with inspectors; potential delays for inspectors once on-site; and the potential of some manufacturing processes not to be operational during the inspection. The OMQ advised that it now considers that resources can more effectively be targeted to other regulatory activities and advised the ANAO that it will generally only conduct unannounced inspections where there is evidence of an actual or potential breach of the Code of GMP.

Scheduling inspection activities

3.20 The TGA conducts re-inspections as part of its approach to managing the risk associated with non-compliance. In order to be effective, the OMQ should be undertaking these inspections in line with the set frequency interval, unless there has been a change in circumstances.

64 ANAO Audit Report No.18 2004–05 *Regulation of Non-prescription Medicinal Products,* p. 68.

The TGA's process for scheduling inspections

3.21 Inspections of manufacturing sites are undertaken within six inspection groups in the OMQ. Each inspection group specialises in the manufacture of a particular product type: medicines (including prescription medicines), medical devices and blood, tissue and cellular therapies. Four of these inspection groups, each overseen by an inspection group manager (IGM), specialises in the manufacture of medicines. A further inspection group, known as the Compliance Unit, was established in late 2012 to address manufacturers with a history of compliance that has been less than 'satisfactory'. This unit also coordinates inspections or desk top reviews arising from intelligence on adverse findings or complaints related to manufacturing.

3.22 The MIS stores information relating to the last inspection, specifically when it was conducted and the number of months until the next inspection, as determined by the inspection frequency matrix (see Table 3.3). For each re-inspection, it is therefore possible to determine in advance the due date, inspection duration, number of inspectors, and whether specialists are required. These parameters are set at the close-out of the previous inspection.

3.23 On a six-monthly basis, an automated scheduling system generates a schedule for the inspections due in the upcoming six months. This process includes the allocation of a default lead inspector and team members, reflecting the inspection duration and effort required. A list of inspections is assigned to each inspector. The IGMs work with their inspectors to schedule dates for each inspection that take account of assigned inspection priority[65], make adjustments to the team to account for individual needs and the rotation of lead inspectors, and appoint technical specialists as required. All inspections are expected to be completed within the six-month period.

3.24 Generally, domestic manufacturers are advised that an inspection has been scheduled two to four weeks before the start date. This is intended to allow manufacturers sufficient time to provide the inspector(s) with the background information they require and ensure that key personnel at the facility will be available for the inspection. Overseas inspections have an increased lead time, of two to three months, due to the time required to organise travel and have it approved.

65 The priority rating takes account of factors such as the manufacturer's risk profile, sterility, compliance history and input from the other regulatory streams within the TGA.

Outcome of the TGA's scheduling approach

3.25 For inspections of domestic and overseas prescription medicine manufacturing sites, the ANAO estimated the average frequency interval set by the TGA for each compliance rating. The ANAO also calculated the deviation between when a re-inspection was due based on the assigned frequency interval and when the re-inspection commenced.[66] The results of these analyses are provided in Table 3.5.

Table 3.5: Inspection intervals for prescription medicine manufacturing sites 2008–09 to 2012–13

		Inspection intervals (months)		
		A1	A2	A3
Australian sites	Average inspection intervals as set (A)	29.1	20.3	11.7
	Average deviation from planned to actual site re-inspection start (B)	3.2	3.8	1.5
	Average inspection intervals as implemented ((A)+(B))	**32.3**	**24.1**	**13.2**
Overseas sites	Average inspection intervals as set (A)	29.6	20.1	12.3
	Average deviation from planned to actual site re-inspection start (B)	3.6	4.6	3.1
	Average inspection intervals as implemented ((A)+(B))	**33.2**	**24.7**	**15.4**

Source: ANAO analysis of TGA data.

3.26 Table 3.5 shows that for both domestic and overseas prescription medicine manufacturing sites, the TGA's re-inspection intervals are significantly longer than those set to manage compliance risks. While the TGA's process may result in some variation within a six-month window between when an inspection is due and when it is conducted, there should be little, or no, average deviation.

3.27 For most manufacturing sites, the OMQ's practice of implementing re-inspection frequency intervals greater than those set by its risk matrix has not had a negative impact on maintaining compliance with the Code of GMP. This suggests that the frequency intervals at Table 3.3 could potentially be increased to reflect actual practice with limited impact on compliance. Such a

66 This analysis did not include sites that were subject to non-routine (special) inspections, given that the inclusion of a non-routine inspection affects the scheduling of subsequent inspections.

revision could allow the OMQ to more accurately determine its inspection resourcing requirements.

The inspection process

Resourcing inspections

Background, training and overall resourcing

3.28 Inspectors in the OMQ typically have five or more years experience in the therapeutic goods industry prior to joining the TGA. The manufacturing stream to which they are allocated (medicines, medical devices or blood, tissues and cellular therapies) is determined by their experience, training and competency level. On commencement, inspectors undertake induction training designed to familiarise them with the OMQ's regulatory activities and the role they perform as inspectors. This is supported by an OMQ Inspector Training Manual, and followed up by an annual training program and witnessed inspections to test competencies. A number of inspectors considered that the OMQ's ongoing training could be improved to better equip them for the challenges associated with compliance inspections. The ANAO considers that this may be a factor contributing to inconsistent interpretation of the Code of GMP by OMQ inspectors, as noted later in paragraph 3.36. During the course of the audit, amendments were being made to the structure and content of the training program, with potential to address these concerns.

3.29 At the time of the audit, the OMQ employed four senior inspectors, 11 inspectors and eight associate inspectors to undertake inspections of all sites manufacturing medicines. In addition, each IGM had at least one medicine inspection team, and the inspectors in the OMQ's Compliance Unit also conduct inspections of medicine manufacturing sites.

Determining the resource levels required for each inspection

3.30 The resource level required for each inspection is determined by the inspection duration and number of inspectors required, set at the completion of the previous inspection.

3.31 The TGA conducted 420 inspections of prescription medicine manufacturing sites over five years to 30 June 2013, with an average of 5.5 person-days spent on-site for each inspection. This is within three per cent of the estimated on-site resource requirements, indicating that the OMQ is effective in estimating its field resource requirements.

Rotation of inspectors

3.32 Rotation of lead inspectors is an important aspect of quality assurance for the compliance program. It can provide a peer review function, albeit spread across an extended time period, and allow inspectors with differing expertise to assess compliance with the Code of GMP. It is also a means to manage the risks of fraud, collusion and regulatory capture and to ensure that the lead inspector, who writes the inspection report, is not influenced by their previous findings at a particular manufacturing site.

3.33 In determining the inspection team, the OMQ takes a number of factors into account, including: conflicts of interest, the site and inspector's location, expertise required and familiarity with particularly large or complex sites. Further, the OMQ has a strategy whereby inspectors will not lead more than two consecutive inspections at a site. In the five years to the end of June 2013, inspections were conducted on over 226 individual prescription medicine manufacturing sites[67], both domestically and overseas. Table 3.6 shows the extent to which these sites were subject to consecutive inspections with the same lead inspector.

Table 3.6: Prescription medicine manufacturing sites with the same lead inspector on consecutive inspections 2008–09 to 2012–13

	Location of sites (numbers)	
	Australia	**Overseas**
Individual manufacturing sites which were subject to two or more inspections over the period	68	51
Sites subject to two consecutive inspections with the same lead	14	6
Sites subject to three or more consecutive inspections with the same lead	5	0
Percentage of sites subject to consecutive inspections with the same lead (%)	**27.9**	**11.8**

Source: ANAO analysis of TGA data.

3.34 Table 3.6 shows that domestic sites are much more likely to be subject to consecutive inspections with the same lead inspector than those overseas. Of

67 Note that while 420 inspections of prescription medicine manufacturing sites were undertaken in this period, they involved only 226 manufacturing sites.

the domestic sites, the OMQ met its strategy of no more than two consecutive inspections with the same lead inspector in 94 per cent of inspections.

3.35 When re-inspections have been undertaken over the last five years, 56 per cent on average have resulted in a change of compliance rating. When the lead inspector has undertaken consecutive re-inspections of a site, the rate of change to the compliance rating drops to 36 per cent. This provides an indication that, on average, the compliance rating of a site is more likely to change if the lead inspector changes. While the ANAO was not able to determine the reasons for this difference, the result indicates an increased risk that lead inspectors are less willing to objectively question the previous conclusion for an individual site they have inspected.

3.36 The importance of lead inspector rotation was observed by the ANAO on a site visit during an inspection. The lead inspector queried the compliance of a system against the Code of GMP, where the system had been considered compliant by previous lead inspectors. A further manufacturer advised the ANAO that a subsequent inspector had informed them that the manufacturer did not need to have in place some of the processes that a previous inspector had insisted were a requirement of the Code of GMP. While there may be a range of reasons for these differences, including changes to the Code of GMP, differing interpretations and miscommunication between manufacturers and inspectors, it highlights the importance of exposing manufacturers to different inspectors when possible.

3.37 The OMQ intends to implement a reporting tool (see paragraph 5.26) with the potential to identify inconsistent application of the Code of GMP. While this tool has some potential to highlight and manage regulatory risks when it is not practical to rotate the lead inspector, it is not a substitute for alternative assessments of a site. The OMQ further advised the ANAO that as part of its new scheduling approach introduced in late 2012, IGMs and senior inspectors were cognisant of the need to rotate lead inspectors and applied active measures to do so. The OMQ also identified its intention to develop an automated signal to alert management when lead inspectors are concurrently assigned to re-inspect the same manufacturing site. The ANAO suggests that the OMQ expedite the development of automated signals and regularly assess the effectiveness of its approach to rotating lead inspectors, given its importance in managing the risks of fraud, collusion and regulatory capture.

Communication with industry on the Code of GMP and the TGA's compliance approach

3.38 The OMQ provides guidance to manufacturers and sponsors on the requirements of the Code of GMP and its compliance approach through a number of avenues, including: the TGA website[68], printed materials and face-to-face.[69] The TGA's website includes links to the Code of GMP and relevant legislation (the Act and subsidiary legislation), as well as guidance on how licensing and certification inspections are undertaken[70], and on how to obtain clearances for overseas manufacturers.[71] Manufacturers and sponsors are also able to subscribe to a range of information regularly released by the TGA, including on new or updated guidelines.[72]

3.39 Most manufacturers interviewed as part of the audit advised that the website can be difficult to navigate[73] and that they usually asked inspectors during a compliance inspection for copies of the TGA's documented requirements. They also regarded the inspections as opportunities to raise questions and remain informed on the Code of GMP and the TGA's administration. The TGA launched changes to its website in November 2013, in order to enhance its communication with industry and the public.

Inspection preparation

3.40 The TGA has a documented SOP for the preparation of an inspection. This includes a review of the previous two inspections (as applicable) to determine previously identified deficiencies against the Code of GMP and any product recalls and complaints, particularly those that may arise from a manufacturing process. The lead inspector is required to develop a standardised inspection plan, based on a template, that considers the corrective actions for previous deficiencies, as well as relevant recalls and complaints.

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68 TGA, *Industry*, [Internet], TGA, Canberra, 2013, available from <http://www.tga.gov.au/industry/index.htm> [accessed 28 November 2013].

69 As opportunities arise, the TGA will present at industry seminars and conferences.

70 TGA *Guidance on licensing/certification inspections*, TGA, Canberra, 2013.

71 TGA, *Australian Regulatory Guidelines Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers, 17th Edition*, TGA, Canberra, 2011.

72 TGA, *Subscribe to Updates* [Internet], 2011, available from <http://www.tga.gov.au/newsroom/subscribe.htm> [accessed 28 November 2013].

73 One manufacturer out of the six interviewed on this subject advised the ANAO that the TGA's website was 'structured and written well'.

The SOP provides a sound basis for undertaking an inspection that focuses on the known risks of manufacturing processes at the site.

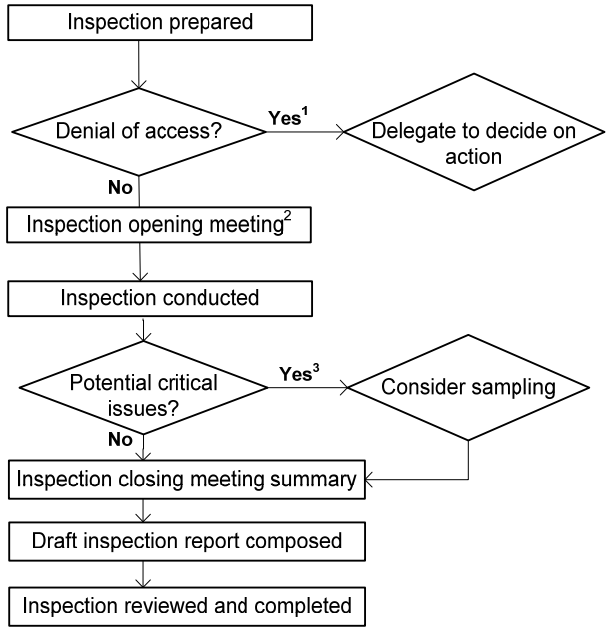
3.41 The ANAO analysed a random sample of eight inspection plans to determine the extent to which inspections were consistently planned against the SOP and whether they allocated time to verify corrective actions. Of the eight inspections, there was limited documentation on one as the TGA had not taken the lead on either the previous or subsequent inspections for one of these sites. Of the remaining seven, the planning documentation indicated that six of the seven inspections had been prepared consistently with the SOP. The remaining inspection plan did not allocate time during the inspection to verify corrective actions as required in the close-out records from the previous inspection. This can occur legitimately when the inspection scope differs between inspections.

3.42 The ANAO's analysis showed that the OMQ has a structured, consistent approach to planning its inspections, and largely intends to monitor the corrective actions for previously identified deficiencies by verifying them at subsequent inspections.

On-site inspection process

3.43 The OMQ also has a SOP for undertaking the on-site inspection process, supported by a template to record findings in a structured and consistent way. The standard process for conducting an on-site inspection is outlined in Figure 3.1.

Figure 3.1: Conducting an inspection



Source: TGA.

Note 1: If access for an inspection is denied by the manufacturer, the Head of OMQ (as delegate) is able to revoke the manufacturer's licence.

Note 2: At the inspection opening meeting, the inspector explains the purpose, scope, process and timelines of the inspection, including procedural fairness processes and the means to make a complaint or provide feedback.

Note 3: Product sampling is required if a request is received prior to the inspection from another area of TGA, or a critical deficiency is identified.

3.44 The TGA's documented process for undertaking an on-site inspection includes a significant component for communicating with the manufacturer, aimed at informing them about the Code of GMP requirements, the inspection process and its findings, particularly if deficiencies against the Code of GMP are recurring issues. Significant communication was observed by the ANAO when accompanying the TGA on two on-site inspections, consistent with the documented procedure.

3.45 The ANAO reviewed the inspection reports from a sample of five inspections[74] to determine whether they reflected the SOP, focussing particularly on the extent to which they verified the implementation of corrective actions, as required by the previous inspection close-out. Each of

74 This sample is a subset of the sample discussed at paragraph 3.41.

these inspections had allocated time in their plans to verify corrective actions and each report had been completed in line with the required format, including a declaration by the lead inspector that the inspection had been undertaken in line with the SOPs and that the all deficiencies from the previous inspection had been corrected.

3.46 Only two of the five inspection reports specifically addressed the adequacy of corrective actions, while the remaining reports did not address any of the previous deficiencies. It was therefore not possible to determine whether these inspections had verified corrective actions on-site, according to their plan. The report template currently does not prompt a write-up of the assessment of corrective actions. Given that previous inspection close-outs identified the need to verify corrective actions, recording these findings supports the transparency and accountability of the regulatory function. The ANAO suggests that the TGA amend the reporting template to prompt inspectors, where applicable, to address the adequacy of corrective actions in their inspection reports.

3.47 The OMQ undertakes quality assurance testing on a sample of inspections based on a review of the inspection report and accompanying documents. The OMQ introduced a new basis for undertaking such reviews during the course of the audit in mid-2013, related to the lead inspector's competency. In particular, for each inspector leading an inspection, if reviews of five consecutive inspections and reports have been found to be consistent with the relevant SOPs, work instructions and the training manual, with no or minimal changes to deficiency ratings, the inspector is considered competent. Thereafter, the inspection reports that he/she is responsible for are subject to review every six months. Such a process is risk-based, and provides the potential for efficient and effective quality assurance. These reviews were recorded at the IGM level and therefore there was limited means to determine the extent to which this process is being adhered to on a whole-of-office basis.

3.48 All five of the inspection reports examined by the ANAO were completed prior to the introduction of the new risk based process in mid-2013. Only two of the five inspection reports were subject to quality assurance review and the basis for selecting these reviews had not been documented. Based on the ANAO's analysis of a limited sample prior to the introduction of a new quality assurance process, there was not a high degree of assurance that inspections had been undertaken in line with the OMQ's procedures, particularly where these required an assessment of the corrective actions

identified at previous inspections. The new basis for undertaking quality reviews provides potential for improvement. Given previous limitations, the ANAO suggests that the OMQ introduce central recording of such reviews to assist in ensuring their implementation against the required procedure.

Assessment of deficiencies

3.49 As part of the inspection process, the inspection team records deviations against the Code of GMP and classifies them as follows:

- critical deficiency: a deficiency in a practice or process that has produced, or may result in, a significant risk of producing a product that is harmful to the user[75];
- major deficiency: a non-critical deficiency that:
  - has produced or may produce a product which does not comply with its marketing authorisation; and/or
  - indicates a major deviation from the Code of GMP and/or the terms of the manufacturing licence or GMP approval for overseas manufacturers; and/or
  - indicates a failure to carry out satisfactory procedures for release of batches; and/or
  - indicates a failure of the person responsible for quality assurance/control to fulfil his/her duties; and/or
  - consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such; and
- other deficiency: a deficiency that cannot be classified as either critical or major, but indicates a departure from GMP. A deficiency may be 'other' either because it is judged as minor or because there is insufficient information to classify it as major or critical.[76]

3.50 The OMQ's documented advice to manufacturers is that deficiencies are classified according to the risk associated with the product and

75 A critical deficiency is also recorded when the inspection team finds that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.

76 One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer.

manufacturing steps and could subsequently vary, leading to circumstances whereby an otherwise major deficiency may be categorised as critical. In addition, a recurring deficiency may be rated at a higher classification.

3.51 Manufacturers are initially advised on potential deficiencies at the time of the inspection closing meeting and subsequently informed in writing to provide a formal response on their proposed corrective action. The number and classification of deficiencies results in a compliance rating which, together with the risk rating, determines the frequency with which the TGA will re-inspect the site. An accurate and consistent rating of deficiencies therefore supports effective implementation of the TGA's risk-based approach for monitoring manufacturing standards.

3.52 The classification of deficiencies is largely left to the judgement of inspectors. In 2004, the ANAO observed inconsistent assessments of the same system by different inspectors, resulting from broad definitions of the deficiency classification and an overall lack of guidance on the classification of deficiencies for various types of manufacturers.[77] At the time, however, there was some guidance in the form of examples in the SOP documentation. The current guidance on deficiencies is similarly broad, but the SOP no longer includes examples on deficiency classification, although these are referenced through training documents. The guidance provided to inspectors has not improved since 2004, notwithstanding the identified need to address inconsistent assessments by inspectors.

3.53 Some inspectors interviewed observed that assessment against the Code of GMP relied on the prior knowledge and experience of inspectors and an expectation that they will assume responsibility for their own development. This approach raises the risk of inconsistency in the judgement of inspectors at a critical stage of compliance processing. As previously noted, the ANAO observed, and was advised of instances of, variations in interpreting the Code of GMP between inspectors. The OMQ has planned improvements to the training program (see paragraph 3.30), which may improve consistency in the assessment of deficiencies.

3.54 As discussed at paragraph 3.47, the OMQ undertakes quality assurance testing on a sample of inspection reports. While found to be relatively limited

77 ANAO Audit Report No.18 2004–05 *Regulation of Non-prescription Medicinal Products,* p.72 and Recommendation No.8.

prior to the introduction of a new process, quality assurance reviews provide the potential to improve consistency in assessment of deficiencies across inspectors, the importance of which was recognised by inspectors themselves. No changes were made to deficiency assessments following the two quality assurance reviews examined.

Conclusion

3.55 The TGA monitors the compliance of licensed and certified prescription medicine manufacturers through a systematic and risk-based program of on-site inspections. An inspection frequency matrix is used to determine the frequency of these inspections, having regard to the risks associated with: the product type; the manufacturing process; and the manufacturer's compliance rating from the previous inspection.

3.56 Compliance monitoring is also supported by a detailed set of policies and procedures to guide staff in scheduling, planning and conducting manufacturer inspections, as well as classifying levels of compliance. The ANAO's review of inspection documentation indicated that while inspection procedures are mostly followed, there remains scope to refine aspects of the SOPs. While most inspections allocate time to verify whether previous deficiencies have been addressed, there is currently no requirement to record the basis of this assessment and therefore limited means to subsequently evaluate the adequacy of corrective and preventive actions and inform future inspection teams.

4. Addressing Deficiencies in Compliance

This chapter assesses the extent to which the TGA has implemented policies and procedures to address deficiencies in the compliance of prescription medicine manufacturers with the Code of GMP.

Introduction

4.1 Over the five years to 30 June 2013, 96 per cent of inspections conducted on sites manufacturing prescription medicines have identified at least one deficiency against the Code of GMP, with almost 60 per cent having at least one major deficiency. The frequency of deficiencies identified by classification across the two inspection types is shown in Table 4.1.

Table 4.1: Deficiencies identified at sites manufacturing prescription medicine 2008–09 to 2012–13 (Percentage of inspections)

Classification	Initial Inspections	Planned Re-inspections	Total	(Number)
Critical	1.8	0.8	1.1	(5)
Major: More than 10	0.9	4.9	3.6	(15)
Major : 6 to 10	7.1	8.9	8.4	(31)
Major: 1 to 5	42.0	49.0	46.8	(168)
Other: More than 10	35.7	49.0	44.8	(162)
Other: 1 to 10	58.0	48.2	51.3	(185)
1 or more deficiency of any classification	93.8	97.2		96.1
(Number of inspections)	(112)	(247)		(359)

Source: ANAO analysis of TGA data.

Notes: 1. An inspection can result in the identification of deficiencies across two or more classifications (critical, major or other). The category 'one or more deficiency of any classification' is therefore not based on the total of the inspections in the separate categories.

2. Non-routine inspections have not been included in the table. The deficiencies recorded are not consistent with the risk rating for most inspections of this type.

4.2 The incidence of major deficiencies indicates that the TGA requires an effective means of addressing deficiencies in compliance. Better practice in administrative regulation indicates that a regulator should:

- have a graduated response to non-compliance proportionate to the risks presented;
- be transparent, consistent and timely in decision-making regarding actions to address non-compliance;
- monitor the implementation and effectiveness of enforcement actions to address the most serious risks; and
- provide the regulated entities with the right to a fair hearing including the ability to appeal or make a complaint relating to the decision.[78]

4.3 The ANAO assessed the extent to which the TGA has implemented policies and procedures to respond to deficiencies in prescription medicine manufacturers' compliance with the Code of GMP, which are proportionate to the risk presented. To focus this assessment, the ANAO examined:

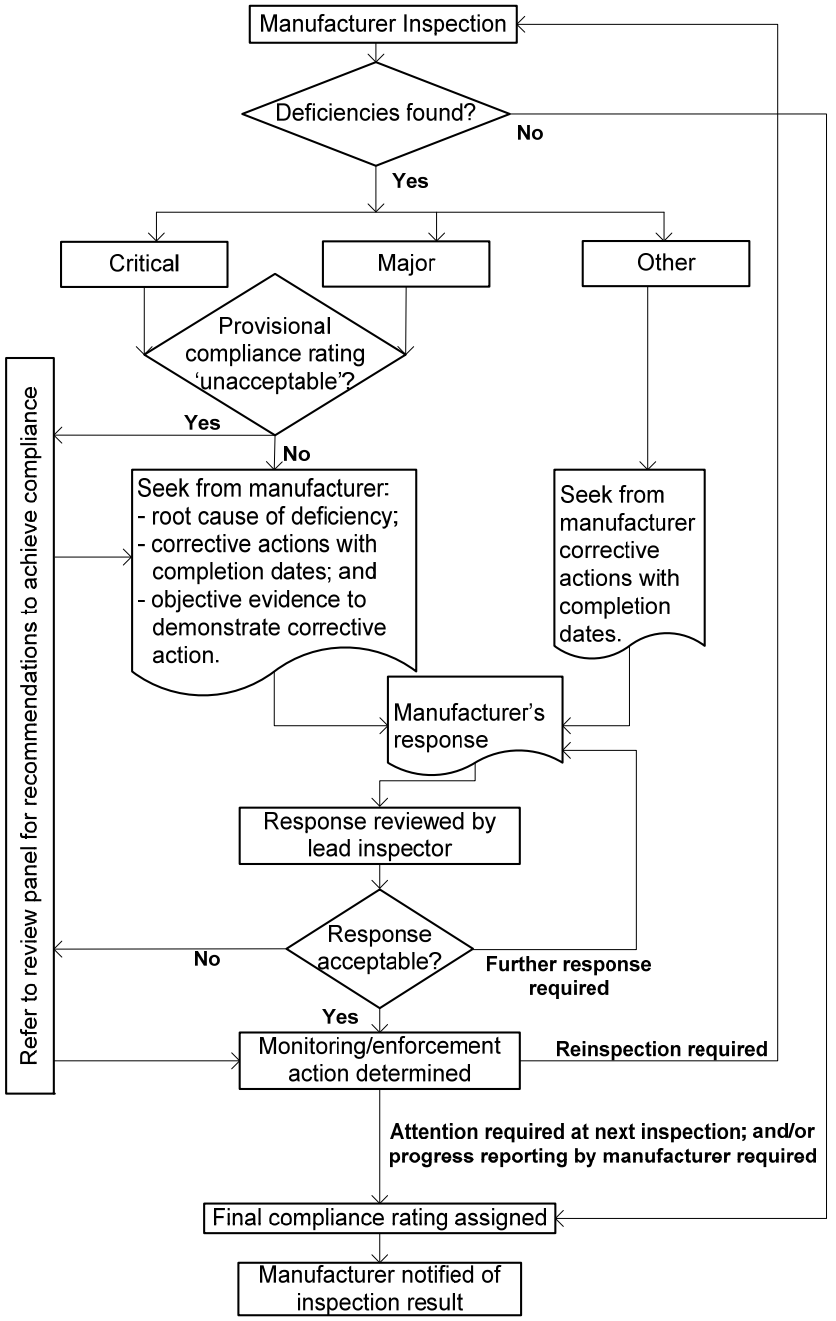
- the TGA's management of the process to finalise inspections, from reporting to the inspection close-out;
- the implementation and management of enforcement actions; and
- the management of complaints and appeals by manufacturers.

Managing the process to finalise inspections

4.4 The process leading to the finalisation or close-out of an inspection is outlined in Figure 4.1.

78 ANAO Better Practice Guide—*Administrating Regulation*, March 2007, Canberra, pp. 31–32, 63–71.

Figure 4.1: Process from identification of deficiencies to finalising the inspection



Source: ANAO analysis of the OMQ's standard operating procedures.

4.5 Once the lead inspector has classified each deficiency and drafted the inspection report, it is forwarded to the manufacturer, seeking a response within four weeks. For each deficiency classified as critical or major, the manufacturer is required to identify its root cause and provide objective evidence of corrective action taken or proposed to be taken to address the deficiency, as well as dates for completion. On receipt of an acceptable response, the lead inspector finalises the manufacturer's compliance rating and closes out the inspection. At this point the manufacturer is advised in writing of the inspection outcome and their level of compliance with the Code of GMP. The OMQ also advises on any planned monitoring such as: progress reporting; review of corrective actions at the next inspection; or enforcement action (see paragraphs 4.19 to 4.24). Such a process provides procedural fairness for manufacturers and helps avoid unnecessary disruptions to the manufacturer's business as most manufacturers are able to continue production while correcting deficiencies.

4.6 The OMQ sets the following target timeframes for finalising inspections:

- four weeks from the end of the on-site inspection to issuing the inspection report; and
- six to eight weeks from issuing the inspection report to the inspection close-out if only one manufacturer's response is required, with an additional four weeks for each subsequent response.

4.7 Senior inspectors conduct quality assurance reviews on the close-out process by assessing the relevant documentation on a selected sample of inspections. The OMQ advised the ANAO that, prior to 1 July 2013, individual IGMs did some informal close-out reviews but these were not recorded. From that time, the OMQ introduced a risk-based review process, similar to that for quality reviews on inspection reports. In particular, close-out reviews are undertaken for every inspection conducted by an individual lead inspector until five consecutive close-outs are considered to meet the required standards. Thereafter, close-out reviews on that lead inspector's work are undertaken six-monthly. As with the quality reviews for inspection reports, there is limited means to determine the extent to which this process is adhered to on a whole-of-office basis, as the reviews are undertaken and recorded at the IGM level.

4.8 To determine the timeliness of issuing the inspection report, the ANAO examined a random sample of 70 inspection reports for inspections conducted since 1 July 2008. Of these, 12 were not dated. Of the remaining 58, only

15 reports (26 per cent) were completed within the four-week target timeframe. The average elapsed time from the end of the site inspection to issuing the inspection report for the remaining 74 per cent of reports was 63 days, more than double the target timeframe.

4.9 A random sample of the close-out process examined 25 inspections conducted in the five years to 30 June 2013 to assess the extent to which the close-out process was undertaken in accordance with the SOP. The OMQ was able to provide the close-out records for 22 of these inspections. Of the remainder, one could not be located, one did not identify any deficiencies and was therefore closed out on-site, and the third inspection close-out was combined with another re-inspection and not available as a separate document. Of the 22 close-out reports available, the ANAO assessed the following to determine consistency with the SOP:

- deficiencies addressed;
- the root cause of major deficiencies identified; and
- objective evidence provided of remediation for major and critical deficiencies.

4.10 In each of the 22 close-out records, the documentary evidence reviewed by the ANAO showed that the OMQ had adhered to the SOP with respect to each requirement.

4.11 The ANAO also examined two separate random samples (totalling 30 inspections) to determine the extent to which target timeframes were adhered to, from the point of issuing the inspection report to closing out the inspection. The first random sample was of 16 inspections with 'satisfactory' or 'good' compliance ratings. The average time for closing out these inspections from issuing the inspection report was 14 weeks, as compared to the target of six to 16 weeks, depending on the number of times that the OMQ seeks further responses from the manufacturer. The second random sample was of 14 inspections with a 'basic' compliance rating. The average time for closing out these inspections from issuing the inspection report was 41 weeks, against the same target of six to 16 weeks.[79] Currently, there is no means of centrally recording and monitoring the timeliness of manufacturers' responses, as this

79 There is evidence that the close-out for the second sample was undertaken very soon after the receipt of the final response from the manufacturer.

information is managed at the IGM level. Performance against targets is a key accountability measure and should be available as part of management reporting processes.

4.12 The TGA's process to finalise inspections allows procedural fairness for manufacturers. However, for most inspections, the timeliness of this process significantly exceeds the target timeframes, particularly when closing out inspections with a large number of deficiencies.

Review panels

4.13 A three person review panel is convened on a case by case basis to undertake an independent review of inspections and to make recommendations to the delegate on an approach to achieve manufacturer compliance. A review panel includes at least two OMQ inspectors, and is chaired by an IGM. New requirements for the use of review panels were introduced in 2010. An inspection report is referred to a review panel before it is finalised if:

- there is a provisional compliance rating of 'unacceptable';
- the manufacturer's responses cannot be accepted; or
- the lead inspector and the IGM consider it useful to determine if a follow-up procedure is required.

4.14 Review panels are able to make recommendations to the delegate on: monitoring arrangements; conditions on the licence or certification; and rejecting or revoking a licence or certification. While the delegation for the first two recommendations rests with the IGM, rejecting or revoking a licence or certification is determined by the Office Head of OMQ.

4.15 The OMQ has convened review panels 16 times since 2010, following adverse inspection findings at domestic and overseas sites manufacturing registered medicines. The OMQ was not able to determine the number of times review panels were convened prior to 2010, as details were not centralised. The OMQ advised that while the MIS has a function to record review panel meetings and references, this has not been used consistently.

4.16 The ANAO examined documentation from a sample of 10 inspections undertaken since January 2010 with poor compliance levels. A review panel was convened for seven of the 10 inspections. Of the other three, two were not referred following a discretionary decision made by the inspector and IGM

and in the remaining case, the application was withdrawn by the manufacturer prior to close-out.

4.17 For all but one of the seven inspections subject to the review panel, the panel was convened immediately prior to sending out the inspection report. In the remaining case the review panel was convened following the initial manufacturer's response. The ANAO observed that in most cases, the review panel's recommendations had been followed. These recommendations related to changes in the lead inspector's assessment of deficiencies, cancelling clearances, and monitoring through a close-out inspection and/or frequent follow-up inspections. Six of the seven sites in the sample were subject to subsequent inspections; of these two had improved their compliance ratings, while four remained at 'basic' compliance.

4.18 The review panel is an important means for lead inspectors to have their assessments peer reviewed, and to assist in determining a compliance approach when there are adverse inspection findings. While the ANAO's analysis on a limited sample indicated that the review panel recommendations had mostly been followed, it was not sufficient to determine the extent to which the panels had contributed to addressing deficiencies in compliance. The ANAO suggests that the OMQ follow up the outcomes of review panels as a basis for assessing whether actions recommended were effective in improving compliance.

Implementing and managing enforcement actions

4.19 Consistent with best practice, the TGA's regulatory compliance framework reflects a graduated approach to compliance.[80] Responses range from encouragement and guidance through to cancellation and prosecution under provisions of the Act and associated regulations. Supporting this overall framework, the TGA established the Regulatory Compliance Committee (RCC) in 2012 which reports to the TGA Executive Committee. In February 2013, the RCC considered and accepted a draft TGA Regulatory Compliance Strategy. This strategy reinforced the TGA's graduated approach and identified an intention to include detailed compliance plans for each office in the TGA. While the OMQ started working on its compliance plan in February 2013, it remains under development.

80 TGA, *Regulatory Compliance Framework,* TGA, Canberra, 2013, p.7.

4.20 The TGA's general approach is to use lower level responses to address identified deficiencies and reserve enforcement measures for serious non-compliance. For most inspections, the OMQ accepts the manufacturers' corrective actions proposed in response to the inspection report. The OMQ's lowest level response is to review corrective actions at the next inspection, but for more high risk compliance deficiencies, the OMQ has the option to require progress reports. The OMQ advised the ANAO that it does not use this option because the time to close-out an inspection with a relatively large number of major deficiencies is often close to the time required for a re-inspection.

4.21 In a minority of cases, when there is an actual or suspected breach of a requirement of the Act or regulations, or where a manufacturer has not adequately addressed major deficiencies, the TGA engages in graduated responses to enforce compliance. For domestic manufacturers, these include:

- advisory correspondence, providing the manufacturer with notice of the TGA's intention to initiate further escalation of enforcement action. In line with due process and procedural fairness principles, the manufacturer is given an opportunity to respond to the notice;
- special inspections, providing the TGA with an opportunity to verify the implementation of corrective actions in cases of adverse findings;
- variation of the scope of a licence by a TGA delegate, or imposing or varying conditions;[81]
- suspension or revocation of a licence; or
- as a last resort, civil or criminal sanctions brought against the manufacturer. The TGA may use this option when the regulator's enforcement actions have been breached or ignored, or where the actions of a manufacturer have led to actual harm.

4.22 In the event of non-compliance by an overseas manufacturer, section 25 of the Act allows the TGA to undertake all of the above administrative measures, with the exception of legal proceedings. Legal action is excluded as these manufacturers are generally not under Australian Government jurisdiction. The OMQ advised that information on the above actions (with the exception of legal proceedings undertaken centrally by the TGA) is not

81 Under the Act, the TGA can impose conditions such as restricting the products manufactured or requiring particular steps in the manufacturing process.

collated. The TGA was therefore not able to determine the number of times that administrative measures have been used to address poor compliance in sites manufacturing registered medicines, and the outcomes of such measures.

4.23 The TGA advised that in the five years to 30 June 2013, it had not brought legal proceedings against any manufacturer of prescription medicine regarding non-compliance with the Code of GMP. In particular, no issues were considered of sufficient risk to refer to the Commonwealth Director of Public Prosecutions and were instead handled by the OMQ using administrative measures. Further, the TGA advised that it rarely engaged in civil proceedings, and needed a high degree of certainty of winning the case and having costs awarded to the TGA. As a result, the TGA has only engaged in a total of three such actions since the civil penalty provisions were enacted in 2006, none of which involved prescription medicine manufacturers.

4.24 Currently, the OMQ does not centrally record its use of administrative measures to address deficiencies in compliance and so is not in a position to evaluate the effectiveness of each measure in returning the site to an acceptable level of compliance.

Recent initiatives to address significant deficiencies (including non-compliance)

4.25 In late 2012, the OMQ established a Compliance Unit reporting directly to the Office Head. In addition to developing the OMQ's compliance plan (see paragraph 4.19), the Unit's main responsibility is to ensure a rigorous and consistent approach to addressing manufacturers with a history of 'basic' compliance with the Code of GMP.

4.26 As discussed earlier, the TGA's approach has been generally effective in improving and/or maintaining manufacturers' compliance to a 'satisfactory' level. However, there is a small group of seven prescription medicine manufacturing sites with sequential 'basic' compliance ratings over three consecutive inspections (see paragraphs 3.10 to 3.13). Increased inspection frequency has only contributed to improved compliance in two of these seven sites, although not to the extent required to improve their ratings. Twelve months after it was established, the Unit remains in its developmental phase, and it is too early to assess its effectiveness. While the decision to establish the Unit indicated a concern about problematic sites, little progress has been made by the Unit to date.

Managing appeals and complaints by manufacturers

Formal review process

4.27 The Act makes provision for manufacturers to request that the responsible Minister review decisions regarding licence conditions, suspensions and revocations. Such reviews, known as section 60 reviews, are required to be conducted within 60 days of application. The Act identifies the Minister's decision as a reviewable decision under the *Administrative Appeals Tribunal Act 1975*, enabling what is known as an AAT review. Manufacturers are informed of the review process in the general guidance on inspections.[82] Information on the review process and how to apply is also available on the TGA website, including information on requesting an AAT review.[83] Manufacturers are formally notified of licence conditions, suspension or revocation in the close-out letter. This letter does not, however, refer in any way to the review processes as outlined above. The ANAO suggests, as a means to provide manufacturers with easy access to information on these processes, that formal communication on licence conditions, suspensions or revocations should include links to information on decision review processes.

4.28 Section 60 review processes are coordinated centrally within the TGA's Regulatory Integrity section. The TGA advised that no cases involving a registered medicine manufacturing site have sought section 60 reviews. Furthermore, no AAT reviews have been initiated by registered medicine manufacturers in the past five years. While the lack of section 60 and AAT reviews could indicate limited awareness by manufacturers of these formal reviews processes, the ANAO notes that over the past five years, only one domestic site manufacturing prescription medicine was rated with 'unacceptable' compliance.[84] As this was only a provisional rating, reclassified as 'basic' compliance following a close-out inspection, there have been no triggers to request a decision review.

82 TGA, *Guidance on licensing/certification inspections*, TGA, Canberra, 2013, p.10.

83 TGA, *TGA internal review guideline — The operation of TGA's internal review and how to apply* [Internet], TGA, Canberra, 2013, available from <http://www.tga.gov.au/about/tga-internal-review-guideline-04-att1.htm> [accessed 22 October 2013].

84 S60 and AAT reviews are not available to overseas manufacturing sites.

Complaints process

4.29 All agencies can expect complaints as a 'predictable and necessary part of program and service delivery'.[85] In providing a regulatory service to the therapeutic goods industry, the TGA should have an accessible, fair, responsive and efficient complaints system integrated into its core business.

4.30 As part of the SOP on conducting inspections, each OMQ inspector is required to explain the complaints and feedback process relating to the conduct of an inspector and the interpretation of findings at both the opening and closing meetings. The practice of explaining these processes and referring to the location of feedback forms on the TGA website was observed by the ANAO during an inspection. As with the appeals processes, manufacturers are also informed of the complaint process through the inspection guidance document[86] and on the TGA's website.[87]

4.31 In general, complaints are made to the Office Head of the OMQ. The Office Head advised the ANAO that a complaints register had not been kept until late 2012. In the period to September 2013 the OMQ had received five complaints from four manufacturers, only one of which was licensed to manufacture prescription medicine. The complaints from this manufacturer, who had been found to have several major deficiencies against the Code of GMP, related to the conduct of an inspector. At the time of writing, a preliminary response to this complainant indicated that the complaint was unsubstantiated. The Office Head also recalled a further complaint prior to establishing the complaints register that had been made by a testing laboratory involved in the prescription medicine manufacturing process; this complaint was proven correct. With so few complaints, the OMQ did not consider that they had sufficient data to analyse for trends in complaints.

4.32 A number of manufacturers advised the ANAO that they would be reluctant to use the TGA's complaints mechanisms, for fear of repercussions. One manufacturer reported that when they had made a complaint about the conduct of an inspector, it became apparent that the inspector was made aware

85 Commonwealth Ombudsman, *Better Practice Guide to Complaint Handling*, Commonwealth Ombudsman, Canberra, 2009, p 1.

86 TGA, *Guidance on licensing/certification inspections*, Canberra, 2013, p.10.

87 TGA, *Inspections and Inspectors: the Complaint Process*, [Internet], TGA, Canberra, 2013, available from <http://www.tga.gov.au/industry/manuf-complaint-process.htm> [accessed 9 August 2013].

of the complaint, when it was the manufacturer's understanding that it would remain confidential.

4.33 Complaints and feedback are an important means by which the OMQ can identify problems with processes and the skills and conduct of inspectors. Such information is also valuable for continuous improvement and identifying training requirements. The current availability of information arising from complaints and feedback is limited by fear of repercussions. The ANAO suggests that the OMQ could improve its access to such information by seeking feedback, including complaints, from manufacturers on the inspection process through an interactive survey form following inspection close-outs. Information obtained in this way could be analysed and used in a way that maintained the confidentiality of individual manufacturers.

Conclusion

4.34 Almost all inspections conducted on sites manufacturing prescription medicine identify at least one deficiency against the Code of GMP. To respond appropriately to the risks presented by compliance deficiencies, the TGA has developed graduated responses to support its risk-based compliance strategy.

4.35 The TGA's general approach is to use lower level responses to address most deficiencies and reserve enforcement measures for serious non-compliance or when lower level responses are failing to achieve the desired outcome. The TGA employs a risk-based strategy, known as inspection close-out, that allows most manufacturers to continue production while also correcting deficiencies. An inspection cannot be closed out until the lead inspector reviews and accepts information from a manufacturer on the corrective actions it proposes to address deficiencies. However, the timeliness of issuing inspection reports and closing out inspections is well below the TGA's targets. Further, while the TGA's approach has been generally effective and has helped avoid disruption to manufacturers' business operations, its approach to compliance has not led to improvements in the case of several domestic manufacturing sites with a history of 'basic' compliance, with one of these sites dropping from 'basic' compliance to a provisional rating of 'unacceptable' at one inspection.

4.36 Where required, review panels are convened following an inspection to provide an independent assessment and recommendation to the delegate on an approach to address 'unacceptable' compliance. In a minority of cases, the TGA does pursue stronger enforcement measures but advised the ANAO that,

with the exception of legal proceedings, it does not collect information on administrative compliance measures, including those recommended by review panels, centrally. Accordingly, the TGA is not well placed to evaluate the effectiveness of actions taken to address poor levels of compliance. A Compliance Unit established by the OMQ in late 2012 for the purpose of addressing such sites has made limited progress to date, and there would be benefit in TGA management revisiting this approach.

5. Supporting the Compliance Program

This chapter examines the TGA's cost recovery mechanisms, information management, risk management, performance measurement and reporting to assess the extent to which these support its program of compliance against the Code of GMP. Progress on reforms to the TGA, as they affect the compliance program, is also discussed.

Introduction

5.1 The TGA's regulation of the Code of GMP is supported by a range of structures and internal processes. In order to assess the extent to which these support the effective administration of the Code of GMP, and provide accountability and transparency of regulatory processes, the ANAO examined the following aspects:

- cost recovery arrangements;
- information management systems;
- overall management of risks to the compliance program; and
- performance measurement, monitoring and reporting.

Cost recovery

5.2 The Act includes provisions for the TGA to recover the full cost of its regulatory activities through fees and charges imposed on sponsors and manufacturers of therapeutic goods.[88] The TGA progressively increased its level of cost recovery in the years prior to 1998–99, when it moved to full cost recovery. The adoption of full cost recovery was part of a set of reforms within the TGA, aimed at increased flexibility, greater efficiencies and enhanced international competitiveness of Australian industry, including mutual recognition with the European Union.[89]

5.3 In examining the TGA's cost recovery arrangements, the audit focussed on: the basis for setting fees and the extent to which fees reflect the costs associated with administering the Code of GMP; and the extent to which the

88 The *Therapeutic Goods (Charges) Act 1989* requires that these fees and charges, as set out in the regulations, be imposed.

89 Australian Government, Budget Measures: Budget Paper No. 2: 1997–98, Commonwealth of Australia, Canberra, 1997.

fees for individual sites fairly reflect the effort required by the TGA to regulate compliance with the Code of GMP.

TGA fees and charges for regulating the manufacture of prescription medicines

5.4 On an annual basis, the TGA sets the fees and charges relating to its regulatory activities through annual amendments to the *Therapeutic Goods (Charges) Regulations 1990*. The TGA's main fees and charges for regulation of the Code of GMP for 2013–14 are set out in Table 5.1.[90]

Table 5.1: TGA fees and charges applicable to prescription medicine manufacturers 2013–14.

	Type of fee or charge	$
Australian manufacturers	Licence application fee (one-off)	920
	Annual licence charge for single step/single medicine/ingredients manufacturers (includes up to 16 inspection hours over 3 years)	5 760
	Annual licence charge for other types of prescription medicine manufacturers (includes up to 48 inspection hours over 3 years)	11 200
	GMP inspection fee (rate per site inspection hour)	600
Overseas manufacturers	GMP certification inspection fee (rate per site inspection hour)	1 220
	GMP certification inspection travel costs	At cost
	Clearances: assessment of GMP evidence (amount per manufacturer, per site and per sponsor)	350
	Clearances: obtaining evidence from overseas regulatory agency (amount per manufacturer, per site and per sponsor)	620
	Clearances: reinstatement of expired GMP clearance approval (amount per manufacturer, per site and per sponsor)	1 050
	Clearances: compliance verification assessment	1 870

Source: TGA (2013), *Summary of fees and charges: At 1 July 2013,* pp 22–23.

90 In addition to those set out in Table 5.1, there are a range of small fees related to issuing GMP compliance certificates.

Basis on which fees are set

5.5 The TGA uses activity based costing[91] (ABC) to determine fees, indexed annually. The index is based on 50 per cent of the Wage Price Index and 50 per cent of the Consumer Price Index for the financial year.[92] Table 5.2 shows the basis on which the hourly fees for 2010–11 were set.

Table 5.2: Basis for setting hourly inspection fees 2010–11

	Domestic ($)	Overseas ($)
Fully loaded staff costs[1] (a)	180 (EL1/APS 6 cost basis)	250 (EL 2 cost basis)
Percentage of inspection effort spent on-site (b)	34.5%	29.5%
Grossed up staff costs (that is, total inspection costs attributed to on-site fees) ((a)/(b)) (c)	522	847
Travel time costs (d)	n/a	167
Total estimate (c)+(d)	522	1014
Rate set for 2010–11	520	1015

Source: TGA.

Note 1: Fully loaded staff costs include direct staff costs, attributed corporate costs such as rent and use of information technology, and attributed support costs such as human resource management, finance, legal services and information technology support.

5.6 The TGA was not in a position to provide the ANAO with the following information, citing the extended length of time the assumptions had been in place:

- the reasons for using the EL1/APS 6 staffing costs for domestic inspections, when most inspectors are at the EL 2 level;
- the methodology used to determine the percentage of effort spent on-site during an inspection;
- the basis for estimating annual licence fees; and
- the basis for determining fees relating to clearances.

91 Activity based costing is 'an approach to the costing and monitoring of activities which involves tracking resource consumption and costing final outputs. Resources are assigned to activities, and activities to cost objects based on consumption estimates. The latter utilise cost drivers to attach activity costs to outputs.' Refer to: Chartered Institute of Management Accountants, *Activity Based Costing: Topic Gateway Series No. 1,* CIMA, UK, 2008, p. 3.

92 A further two per cent was added to the index in 2012–13 to cover the cost of scheduled TGA reforms.

5.7 During the course of the audit, the TGA initiated a project to revise its ABC model, expected to be operational for 2014–15. The TGA anticipates that this will alter the basis on which expenditure is attributed to the OMQ's regulatory functions and inform changes to the way fees are set.

The extent to which fees and charges reflect costs

5.8 On an annual basis, the TGA publishes its actual and forecast revenues and expenses for regulating compliance with the Code of GMP.[93] These revenues and expenses are outlined in Table 5.3.

Table 5.3: Revenue and expenditure for regulating compliance with the Code of GMP

Item		2010–11 Actual $m	2011–12 Actual $m	2012–13 Actual $m	2013–14 Forecast $m
Revenue					
Domestic	Licence application fees	0.0	0.0	0.0	0.0
	Annual licence charges	1.8	2.5	2.4	2.5
	GMP inspection fees	0.4	2.1	0.8	0.6
Overseas	GMP inspection fees[1]	6.7	6.6	5.5	5.9
	GMP clearance and certification fees	1.7	1.8	2.1	2.1
Total Revenue[2] (a)		**10.6**	**13.0**	**10.8**	**11.2**
Expenditure					
Operating expenditure including corporate and support costs (b)		**9.5**	**9.9**	**9.6**	**11.3**[3]
Surplus					
Surplus (a)-(b)		**1.1**	**3.1**	**1.2**	**-0.1**
Surplus as a percentage of revenue (%)		10.4	23.8	11.3	-0.7

Source: Therapeutic Goods Administration, *Cost Recovery Impact Statement — Good Manufacturing Practice*, 1 July 2012–30 June 2013; and TGA internal document.

Note 1: Includes recovery of overseas travel costs and interest.

Note 2: The sum of fees and charges may not equal the total revenue due to rounding.

Note 3: Forecast expenditure for 2013–14 was estimated using the TGA's newly developed ABC model (see paragraph 5.7).

93 TGA, *Cost recovery impact statement — Good manufacturing practice*. This is published on an annual basis, with the latest published in June 2013 for the period 1 July 2013–30 June 2014.

5.9 In the three financial years examined in Table 5.3, there was a surplus of revenue over costs of over $1 million. For example, in 2012–13, manufacturers and sponsors paid 11.3 per cent on average above the TGA's estimated cost to deliver the service. It is not clear whether these surpluses were the result of charging fees higher than required to recover costs, or due to poor attribution of costs to the OMQ's regulatory function. The ANAO noted that TGA revised its 2013–14 forecast expenditure from $10.2 million to $11.3 million once it had access to the revised ABC model.

5.10 In line with the guidance from the Department of Finance[94], the TGA prepares cost recovery impact statements (CRIS) for regulating the manufacture of therapeutic goods against the Code of GMP.[95] This was last prepared for the 2013–14 fees. Subsequent to approval by Government, the CRIS for regulating the manufacture of therapeutic goods is published on the TGA's website, also in line with guidance from the Department of Finance.

The extent to which there is fair distribution of costs across manufacturers

5.11 ANAO analysis indicates that in 2012–13, on average, it cost each Australian therapeutic goods manufacturing site $7 800 in fees and charges for the TGA to regulate compliance with the Code of GMP, and $13 900 for each overseas site to be certified by the TGA.[96]

5.12 Fees for the certification of overseas manufacturing sites are calculated on an hourly basis. This means that larger sites with 'basic' compliance pay more overall than smaller sites with 'good' compliance, as the latter require fewer inspection hours on an annualised basis.

5.13 Domestic manufacturing sites pay an annual licence fee that includes a specified number of inspection hours, with payments on an hourly basis once this allocation is exceeded. Based on a sample of 20 manufacturing sites, selected across size and scope of operation and varying compliance risks, the inspection cost on an hourly rate varied between $331 and $2004.[97]

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94 Department of Finance, *Australian Government Cost Recovery Guidelines*, Finance, Canberra, 2005.

95 TGA, *Cost recovery impact statement — Good manufacturing practice*. Under the current cost recovery guidelines, a CRIS is not required for indexation. In its review of cost recovery arrangements completed in May 2012, the TGA noted that the GMP CRIS had not been updated since 2005. An interim CRIS was prepared for 2012–13 and a subsequent CRIS was prepared for 2013–14.

96 This cost is based on fees and charges (excluding travel costs) recovered and the number of manufacturing sites licensed/certified at the time.

97 These are actual costs based on the ANAO's analysis of the sample.

Manufacturers with poor compliance ratings paid significantly lower hourly rates than those with higher compliance ratings.

5.14 There is a further characteristic that impacts on the distribution of fees between manufacturers, for both domestic and overseas sites. Fees are determined by the number of hours spent on-site during an inspection, adjusted to take account of the percentage of off-site inspection effort. As part of the TGA's ABC model, the percentage of total time spent on-site during an inspection is averaged at 34.5 per cent for domestic sites, and 29.5 per cent for overseas sites (see Table 5.2). This percentage does not change, irrespective of the effort required off-site.

5.15 As noted in paragraph 4.5, the OMQ requires as part of inspection close-out that all manufacturing sites respond to the inspection report, identifying the root cause of major and critical deficiencies and evidence of corrective action. Based on a sample of 30 inspections undertaken in the five years to 30 June 2013, the time from issuing an inspection report to close-out varied from 0 days to 587 days. The average close-out time for those with 'basic' or 'unacceptable' compliance ratings was 9.6 months, compared with 3.2 months for those with 'good' or 'satisfactory' compliance (see paragraph 4.11). Sites with a high number of major deficiencies are likely to require more off-site inspection effort, based on the further explanations requested on their remediation approach. Therefore, for sites with 'basic' or 'unacceptable' compliance, on-site hours are a smaller percentage of the total inspection effort than for sites with 'good' or 'satisfactory' compliance. Effectively, sites with higher compliance rates are paying more per hour of inspection effort and hence cross-subsidising the cost recovery of those with poor compliance. Further, the structure of fees and charges for domestic manufacturers does not provide incentives for sites with a history of 'basic' compliance to improve their level of compliance.

The TGA's plans relating to cost recovery for regulating compliance with the Code of GMP

5.16 In 2010, amendments were made to section 38 of the Act that linked licences to sites rather than to manufacturers. The intention of the amendment was to assign a unique licence to each manufacturing location able to be inspected during a single inspection. As a result, the number of Australian licences to manufacture therapeutic goods increased from 306 to 420.

5.17 The TGA recognised that an increase in the number of licences on issue provided potential for over-recovery of costs. In October 2010, the TGA

developed a cost recovery options paper for regulating compliance with the Code of GMP. In this paper, the TGA also recognised that its current cost recovery arrangements have the potential to be inequitable across Australian manufacturers. In particular, it stated that 'highly compliant Australian manufacturers often do not use the full (inspection) allowance included in a licence'.

5.18 The cost recovery options paper was prepared to elicit feedback from industry associations on the merits of three cost recovery options, with a view to developing a specific proposal for further consultation with industry, professional associations and consumer groups. This consultation did not go ahead at the time. Instead, the TGA decided in 2012 to undertake a review of its ABC model prior to revising its cost recovery approach and, in particular, review the effort required for the on-site and off-site component of inspections, as well as the corporate functions supporting the OMQ's compliance program.

5.19 The TGA foreshadowed changes to its GMP fees and charges at a bilateral meeting with industry in February 2014, advising its intention to progressively implement changes, beginning in 2014–15.

Stakeholders and cost recovery

5.20 Stakeholders presented a range of views to the ANAO regarding the TGA's cost recovery arrangements, mostly positive or neutral, but some expressed reservations about the difficulty it posed for small manufacturers in meeting the costs, particularly when entering the market, and about the transparency of how costs were attributed.

Information management

5.21 An effective information management system is an essential component of the OMQ's business operations. It must support the TGA's licensing, certification and ongoing compliance activities, as well as monitor staff adherence to the quality management system. To determine the effectiveness of the IT systems supporting the OMQ's regulatory workflow, the ANAO examined the extent to which:

- key information is captured in a way that assists in business management and enables reporting and analysis of regulatory processes and their outcomes;
- the data in the Manufacturers Information System (MIS) has integrity;

- confidentiality of data is maintained; and
- there is integration across the TGA's IT systems, particularly with the Australian Register of Therapeutic Goods (ARTG).

Capturing and recording key information

5.22 The OMQ's main IT system to support its compliance program is the MIS. This system is used to identify the sites due for re-inspection, and allows the OMQ to schedule dates on which to undertake these inspections. The inspection team is automatically assigned and confirmed through a scheduling process, before being re-entered into the system. At the end of each inspection, the MIS is populated with the actual dates of the inspection, its duration, and the actual effort required in person-hours. The actual effort is important, not only for re-inspection scheduling purposes, but importantly for invoicing. Overseas manufacturers are invoiced for the full cost of the inspection based on this information, and domestic manufacturers are invoiced for costs once they exceed the inspection hours included in their annual licence fee. The MIS also includes information on the site's compliance risk, the manufacturing and product risks, the number of critical, major and other deficiencies and the re-inspection frequency.

5.23 Currently, two main reports are drawn from the MIS:

- a listing of all inspections due to be undertaken in the forthcoming period, against which the scheduling of inspection teams is based; and
- biannual business reports that inform the Department of Health's Annual Report. The key information in these reports includes statistics for incoming licence, certification and clearance applications, and their outcomes.

5.24 Any further such reports are limited by the information currently stored in the MIS. As discussed in previous chapters, the MIS does not include information on the following:

- dates on which inspection reports were sent, manufacturers' replies were due and received, and inspections closed out. This information is necessary to track the timeliness of the inspection close-out process, including the timeliness of manufacturers to satisfactorily respond to the inspection report. Based on a download of MIS inspection data for prescription medicine manufacturers as at 30 June 2013, the ANAO identified that of the 32 inspections which had not been closed out,

18 (or 56 per cent) had not been finalised within six months following the end of the site inspection. This is further to the analysis in paragraph 5.15, which showed that the time from reporting to close-out took up to 587 days, well in excess of target timeframes;

- information on what quality reviews have been undertaken on the inspection process (for example, peer review of inspection reports, close-out and review panels). This information is necessary to monitor whether quality assurance processes have been undertaken; and
- details on the deficiencies themselves, important to identify systemic issues and determine the extent to which manufacturers address previously identified deficiencies.

5.25 Key information on timeliness, quality reviews and deficiencies are contained within the inspection record, as well as correspondence between the TGA and the manufacturer. Such records are stored in the TGA's records management system, known as TRIM, and the MIS records include hyperlinks to relevant TRIM records. Information on timeliness of inspection close-outs is recorded in spreadsheets maintained by each IGM. The information identified in paragraph 5.24 is retrievable insofar as it resides within the related electronic documents. However, the way in which records are stored limits the OMQ's ability to evaluate and report on its administrative performance and operational effectiveness.

5.26 The OMQ advised that it was developing an Inspection Intelligence Tool, designed to identify compliance trends and enhance the level of reporting on inspection records. Reports from these tools are expected to identify systemic deficiencies across manufacturing sites, determine whether there are recurring major deficiencies that a manufacturer has failed to address across inspections and, as discussed in paragraph 3.37, identify inconsistent application of the Code of GMP by inspectors. The Inspection Intelligence Tool was implemented in early 2014, a year later than scheduled. Advice from the OMQ indicated that a key difficulty in its implementation has been that inspectors do not consistently follow records management requirements, limiting the ability of the tool to extract accurate information.

5.27 In September 2009, the OMQ developed specifications for enhancing the MIS that would allow input into both the MIS and the inspection record on information such as timeliness and the quality review process. The TGA

advised that this enhancement was not progressed given competing IT priorities, including the Inspection Intelligence Tool.

Integrity of MIS data

5.28 Data integrity refers to accuracy, consistency and completeness in the way that business information is captured, processed and stored. The MIS ensures the continuity of business process workflows relating to licences, certifications and clearances by structuring each step to prevent users from skipping defined tasks. As each task is undertaken, the MIS automatically logs the user's identification, activity performed and its timestamp, providing an audit trail of the task. The data is automatically recorded in the MIS and must be reviewed by a supervisor before the process can be completed.

5.29 While partly automated, the MIS also relies on manual data entry, particularly for information recorded in inspection documents as this information is not linked electronically to the MIS record. This can lead to data errors in the MIS, which are not always detected through the supervisor's quality review. Alternatively, if they are detected and modified by the supervisor, information is not always updated in the MIS. Based on a download of MIS data for inspections of prescription medicine manufacturers conducted in the five years to 30 June 2013, the ANAO's analysis identified the following instances of incomplete and inaccurate data recordings:

- of the 367 inspections that had been completed, six records did not include any data on the number and type of deficiencies (critical, major or other), despite the inspections finding the manufacturer to have 'basic' compliance. While the number is not significant, incomplete data means that the OMQ is not readily able to assess the extent to which a manufacturing site is improving its compliance over time; and
- in comparing the actual effort recorded for a site inspection with the average effort determined by the ANAO[98], 21 per cent had a discrepancy of eight or more hours of effort, with eight per cent having a discrepancy of 20 or more hours. Actual effort is used to determine the effort required for subsequent inspections, and therefore poor

98 The ANAO based its estimates on information provided by the OMQ regarding the formula it used to determine effort. This used: the number of days spent on the inspection, 8 hours per day, and number of inspectors involved. The analysis involved 399 inspections undertaken over the five years to 30 June 2013, excluding those sites that required specialist involvement.

recording limits the accuracy for future scheduling. Further, the actual effort is used for invoicing purposes, and could lead to individual manufacturers being incorrectly charged for inspections.

5.30 Until recently, when information was entered incorrectly into the MIS by inspectors, the MIS IT administrators were responsible for correcting the data. The IT administrators had privileged access to the MIS and were able to change the data without any audit trail recorded. When the ANAO raised concerns about this practice and recommended that an audit trail be introduced, the TGA advised that the practice had stopped.

5.31 The IT administrators also have privileged access to update client information, such as contact details arising from a business acquisition, on the request of a sponsor or manufacturer. There is a lack of system functionality to otherwise make these changes. As such updates by IT administrators do not provide an audit trail, it adds to the risk that manufacturing site records could be inadvertently or inappropriately changed.

Maintaining confidentiality of manufacturers' and sponsors' data

5.32 Some information gathered through the OMQ's inspection and clearance processes is commercially sensitive and, if disclosed to unauthorised parties, could have an adverse effect on manufacturers' business activity and/or profitability.[99]

5.33 The OMQ provides external users access to its corporate data repository to upload compliance documents and to allow lodgement of applications and questionnaires for a licence, certification and clearance. The OMQ has not conducted any IT network security assessments specific to its data holdings. The OMQ did, however, participate in an external security threat and risk review for the whole of the TGA's IT environment in 2008. This review did not include a risk assessment of confidential information from a third party held by the TGA or network penetration testing. Penetration testing is used to test the strength of security measures aimed at preventing cyber intrusion; essentially, this testing involves attempts to hack into an IT system under tight controls. Understanding the strengths and weaknesses of its IT network security controls enables the TGA to defend against cyber intrusions

99 This information could include deficiencies identified in a manufacturer's operations, intellectual property related documentation or business intelligence obtained by TGA during its compliance activities.

and improves the security of information in its IT network, including commercially sensitive information.

Integration across the TGA's IT systems

5.34 The Australian Register of Therapeutic Goods (ARTG) is a public database maintained by the TGA listing all therapeutic goods approved for import, export or supply in Australia. At the time of the audit, the OMQ's IT system containing information on manufacturers' compliance was not aligned with the details published on the ARTG. As a result, products are included on the ARTG which are produced either wholly or partially by manufacturers who do not have a current GMP clearance.

5.35 In 2007, the TGA undertook an exercise to determine the currency of entries on the ARTG and found that a number of clearances had expired, with the potential that TGA held no evidence on their GMP compliance status. To assess the extent of this problem, the ANAO worked collaboratively with the TGA to identify the percentage of imported products on the ARTG that are not the subject of a current clearance, noting that the ANAO did not assess the extent to which these products were currently supplied in Australia. The ANAO first examined 1233 'injectable' medicines listed on the ARTG in June 2013. These prescription medicines were selected as they have the highest risk and therefore consumers expect that they will be carefully monitored by both the TGA and the Australian sponsor. However, of these 'injectable' medicines, approximately 30 per cent had their sponsors' clearances marked as 'expired'.

5.36 A second analysis was undertaken involving 13 164 registered medicines on the ARTG. Of these, 2011 products (or 15 per cent) were fully or partially manufactured by 297 overseas manufacturers whose GMP approval status was 'uncertain'. Approximately 44 per cent of the 2011 products were classified as sterile, a category reserved for prescription medicines. In this context 'uncertain' approval means that either:

- there is no current information held in the form of a clearance by the OMQ on the compliance of the manufacturing facility; or
- the site address of the overseas manufacturer does not match a known manufacturing site and there is sufficient uncertainty as to require clarification of the manufacturing site's compliance.

5.37 The TGA advised that the responsibility for ensuring that clearances are current lies with the sponsor, who can access this information

electronically. An application for renewal of a clearance will trigger an assessment of the status of all manufacturing sites involved in the product manufacture at the time and, if necessary, result in a TGA inspection of an overseas manufacturing site. The TGA identified a number of scenarios that may have contributed to the above results:

- sponsors may no longer supply the product in Australia, but have neglected to advise the TGA to remove the entry from the ARTG;
- the product may have a number of alternative manufacturers listed on the ARTG, some of which have expired certifications but are no longer supplied to the sponsor. Such a situation can be addressed through the sponsor applying for a variation to their clearance; or
- the product has one or more current manufacturers in the manufacturing process that have expired certifications, or certifications that have been obtained since the clearance was last assessed by the TGA, and have not as yet been approved by the TGA. In either case, the sponsor can address the situation by applying to the TGA for renewal of their clearance.

5.38 The process for gaining entry onto the ARTG involves approval of the manufacturer's risk management plan and manufacturer agreement to conditions, including that the manufacturer informs the TGA of any new information relating to the quality or safety of the product. To provide further assurance that all prescription medicines on the ARTG have been manufactured at sites compliant with the Code of GMP, the TGA should ensure that ARTG entries remain current and align with the compliance information held by the OMQ. The TGA advised the ANAO that it is considering a range of options to update current entries.

5.39 One project proposed was to identify ARTG products with expired clearances or those with anomalies regarding their manufacturing certification and either invite their sponsors to withdraw the product from the ARTG or apply for a clearance renewal. Given the potential size of this project and the need to balance resources for the project over the TGA's usual business needs, the TGA has signalled it would work through the ARTG product list, based on risk to the consumer. This would concentrate first on the highest risk, namely, sterile products, including vaccines. Further, the TGA advised the ANAO that its Office of Medicines Authorisation is conducting a business process review, with a view to identifying improvements in processes and information

management. Part of this review will explore options for preventing the lapse of GMP clearances, including providing sponsors with alerts and identifying high risk products with lapsed GMP clearance.

System maintenance and plans for replacement

5.40 The IT systems used by the OMQ for regulating compliance with the Code of GMP use legacy technology and the TGA has advised that it is increasingly challenging to enhance their functionality and capability to support the changing business environment. The ANAO was further advised that there have been a number of change requests for system enhancements to the MIS lodged over the past two years that have been approved but not yet implemented. They are unlikely to be addressed in the near future through the TGA's standard IT system maintenance process due to budget constraints.

5.41 In order to address this challenge, the TGA's IT branch has proposed a new business improvement project to update the current IT environment and build a new IT platform capable of supporting evolving business needs. As part of this project, the MIS is earmarked for replacement. The project was in its formative stage in early 2014.

Information management: conclusion

5.42 The use of legacy IT systems presents a challenge for the OMQ in maintaining and updating their systems, particularly in a resource constrained environment. As a result, the IT system supporting the OMQ's regulation of the Code of GMP does not fully meet business requirements and lacks the functionality to assess administrative performance and monitor staff adherence to SOPs. The ANAO identified data integrity issues relating to the completeness, accuracy and currency of the OMQ's data holdings. Further, the TGA has not assessed its IT network security controls relating to the OMQ's data holdings to ensure that commercially sensitive information is protected against cyber intrusion.

5.43 Some initial work has been undertaken on a new IT platform to supersede the current systems used by the OMQ. The design of this new system should have regard to the issues identified within this report, as they have implications for the OMQ's operational effectiveness. These issues relate to: the capture of key information against which to monitor administrative performance and staff adherence to SOPs; ensuring that all products on the ARTG are produced by manufacturers with current GMP certifications; and

ensuring a level of cyber security appropriate to the commercial sensitivity of the OMQ's data holdings.

Recommendation No.2

5.44 To improve the security and utility of the Office of Manufacturing Quality's (OMQ) information management arrangements, the ANAO recommends that the Department of Health enhance the OMQ's processes for:

- capturing management information, including key dates relating to the inspection process, and whether quality assurance reviews have been undertaken;
- aligning the manufacturing information held on the Australian Register of Therapeutic Goods with that held by the OMQ; and
- protecting commercially sensitive information held by the OMQ.

Department of Health's response:

5.45 *The department agrees with this recommendation.*

Overall management of risks to the compliance program

5.46 The OMQ is responsible for assessing the manufacturing compliance of Australian and overseas manufacturers of therapeutic goods. Appropriate identification, management and monitoring of related risks supports the OMQ in implementing a risk-based approach to provide assurance that therapeutic goods available in Australia (or produced in Australia for export) are manufactured in accordance with the Code of GMP.

Annual risk management plan

5.47 On an annual basis, the OMQ develops a risk management plan (RMP) to address the risks associated with its therapeutic goods compliance program. This plan identifies the risks, current/target consequence, likelihood and risk ratings, along with mitigation treatments to achieve the targets. Important risks identified relate to internal fraud, external fraud, and the manufacture of unsafe/substandard/counterfeit medicines. Table 5.4 shows the assessed consequence, likelihood and overall risk ratings for these risks in 2013–14.

Table 5.4: Assessment of key risks 2013–14

	Consequence	Likelihood	Rating
Internal Fraud: severe reputation damage amongst international regulatory agencies and Australian stakeholders	Severe	Unlikely	High
External Fraud: unjustified approval of a manufacturer in the supply chain on the basis of incorrect and/or misleading information provided during, after and between TGA inspections	Major	Possible	High
Manufacture of unsafe/substandard/counterfeit medicines: consumer harm resulting from such medicines, resulting in reduced confidence in TGA's ability to ensure quality therapeutic goods	Severe	Possible	Extreme

Source: OMQ Risk Management Plan 2013–14.

5.48 A 'high' risk is that of internal fraud, which could result from incentives provided by manufacturers to inspectors. The mitigation treatments related to this risk have the following limitations:

- rotation of lead inspectors. The ANAO's analysis found that subsequent inspections undertaken by the same lead inspector were less likely to result in a change to the compliance rating when compared with subsequent inspections where lead inspectors were rotated (see paragraphs 3.32 to 3.37);
- a quality review program for inspection reports (limitations are discussed in paragraph 5.49); and
- using more than one inspector in countries where corruption is a known/perceived issue. In the five years to 30 June 2013, 42 per cent of inspections on sites manufacturing prescription medicine in countries with a corruption perception index of less than 50, as determined by Transparency International,[100] were undertaken with only one inspector. While identified as a treatment in the 2012–13 RMP, it was not included in the 2013–14 RMP because departmental policy requires overseas travel to be justified on a case-by-case basis. The OMQ has replaced this treatment with a signals analysis to detect abrupt changes in manufacturers' compliance levels. The software for this task is

100 The Corruption Perception Index is prepared annually by Transparency International on 176 countries, with a range from 0 (highly corrupt) to 100 (very clean). Countries with scores below 50 are considered to have a serious corruption problem. See <www.transparency.org/cpi2012/results>.

currently being tested, with the TGA advising that it has not yet been successful because inspectors do not consistently follow requirements for recording deficiencies. Further, there will be a considerable time lag, in some cases over three years, before abrupt changes can be detected. Currently, the OMQ does not consider information on the corruption index status of the countries in which manufacturing sites are located. The ANAO suggests that corruption index information be assessed, among other relevant information, when determining the risk of sending a single inspector.

5.49 The 'high' risk of external fraud and the 'extreme' risk of the manufacture of unsafe/substandard/counterfeit medicines largely rely on an effective compliance monitoring program. The ANAO noted that the OMQ's assessment of these risks relates to all therapeutic goods rather than just prescription medicine manufacturers, which it considered to be amongst the more compliant manufacturers. Nonetheless, as discussed in the previous chapters, there is scope for improvement to the OMQ's compliance program, including:

- the quality review of inspection reports (paragraph 3.47);
- the quality review of clearance applications (paragraph 2.31); and
- timeliness in closing out an inspection (paragraphs 4.9 and 4.11).

5.50 To determine the extent to which the OMQ manages the risks identified in its RMP, the ANAO compared the current and target risks for the RMPs developed for 2012–13 and 2013–14. The overall rating of some risks as 'extreme' and 'high' underscores the importance of monitoring treatments for mitigation. The ANAO's review of the 2012–13 and 2013–14 RMPs indicated that none of the target risk ratings set in the 2012–13 RMP were achieved. Rather, the risk ratings remained the same, except for the risk of increased litigation and challenge against decisions and findings, which was identified as having a higher consequence than previously, leading to an increase in its rating to 'extreme'. The lack of movement in the risk ratings indicates either limitations in mitigation treatments or in the way that these risks have been assessed. Given the identification of a relatively substantial number of 'extreme' and 'high' risks and the experience of not reducing risks to the target level, there would be merit in TGA management more actively monitoring the OMQ's risk management activities.

Risks related to the manufacture of prescription medicines not managed by the OMQ

5.51 There are two risks related to the manufacture of prescription medicines that are currently not managed by the OMQ or TGA in general. These include risks to the safety, quality and efficacy of prescription medicines arising from:

- compounding prescription medicines in pharmacies; and
- the transport and storage of prescription medicines once they leave the manufacturing site and prior to receipt by dispensers.

Compounding medicines

5.52 Medicines may be compounded in pharmacies in order to: change the dosage form or concentration of a medication; prepare medicines that have been discontinued by the manufacturer; or enable medications to be administered via an alternative method.[101]

5.53 Of the 195 million prescriptions dispensed under the Pharmaceutical Benefits Scheme (PBS) in 2011–12, approximately 300 000 of these were compounded medicines. Compounded medicines can also be purchased outside the PBS. While this is a relatively small percentage of prescription medicines, a small number of compounding pharmacies supply medicines to other pharmacies and hospitals in quantities comparable with manufacturing sites, raising their risk profile. In the three years to March 2010, the former Pharmacy Board of New South Wales cited problems in compounding pharmacies relating to: scales and balances; lack of recorded expiry dates for ingredients; and lack of active ingredients in final preparations.[102]

5.54 Pharmacies compounding medicines are exempt from the requirement to hold a manufacturing licence under the Act[103], and are therefore not inspected for compliance with the Code of GMP. There are other, less direct requirements for assuring the quality of such medicines, including:

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101 M Feldschuh, 'Compounding in community pharmacy', *Australian Prescriber* April 2008, 31: 30–1.

102 TGA, *Consultation: Options for Reform of the Regulatory Framework for Pharmacy Compounding* [Internet], TGA, Canberra, 2013 pp 13–14, available from <http://www.tga.gov.au/newsroom/consult-medicines-130605.htm> [accessed 4 November 2013].

103 Schedule 5, Item 6 of the *Therapeutic Goods Regulations 1990* identifies that compounded medicines are exempt from listing on the ARTG, and therefore their manufacture is exempt from the Code of GMP.

- pharmacists to be registered to practice by the Pharmacy Board of Australia and to meet competency standards;
- approval of pharmacy premises by state and territory governments relating to the size, facilities, publications and equipment; and
- voluntary compliance with the Australian Quality Care Pharmacy Standard, requiring pharmacies to follow a system for compounding medicines.

5.55 In the second half of 2013, the TGA alerted the Minister for Health to the risks associated with compounding medicines, and proposed a legislative change, following industry consultation on options for regulating compounding pharmacies.[104]

Transport and storage of medicines on leaving manufacturing sites

5.56 The TGA's responsibility for monitoring compliance with the Code of GMP applies to the manufacture of therapeutic goods until they are finished products 'released for supply'.[105] 'Release for supply' of a finished product may be to a wholesaler, for example, who then stores and transports prescription medicines to pharmacists and hospitals. The Code of GMP covers the 'release for supply' of intermediate products between manufacturing sites.

Release for supply conducted in Australia

5.57 After 'release for supply' is conducted in Australia, the Australian Code of Good Wholesaling Practice[106] (Code of GWP), regulated by state/territory governments, applies. This Code of GWP covers, amongst other matters, the storage and transport of prescription medicines to prevent tampering, deterioration and other loss. The TGA and representatives from the prescription medicine manufacturing sector informed the ANAO of a number of concerns regarding the application of the Code of GWP, including a lack of compliance (for example, issues with product tracking through the wholesaling phase), and limited and inconsistent approaches to regulation by state and territory governments.

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104 TGA, *Consultation: Options for Reform of the Regulatory Framework for Pharmacy Compounding* [Internet].

105 Release for supply is defined in the Act as a step in medicines manufacture and is therefore covered by the Code of GMP.

106 National Coordinating Committee on Therapeutic Goods, *Australian Code of Good Wholesaling Practice for Medicines in Schedules 2, 3, 4 and 8*, NCCTG, Canberra, 2011, available from <http://www.tga.gov.au/pdf/manuf-medicines-cgwp-schedule2-3-4-8.pdf> [accessed 13 May 2013].

5.58 These issues were reiterated in meetings the ANAO held with state and territory governments, where representatives expressed concerns about controls across borders, particularly in more remote areas of Australia, many of which experience extreme weather conditions likely to compromise the quality of medicines in transit. Regular liaison between the TGA and state and territory governments regarding wholesaling practice occurred in the past, including through the National Coordination Committee on Therapeutic Goods. However, other liaison has ceased and this committee was disbanded in November 2012 following a decision by the Australian Health Ministers' Advisory Council (AHMAC). It was suggested to the ANAO by state and territory government representatives that it would be beneficial if this was reinstituted or an alternative forum provided to facilitate discussion between all levels of government on concerns around the wholesaling of drugs and poisons.

5.59 As part of the Fifth Community Pharmacy Agreement established between the Australian Government and the Pharmacy Guild of Australia, a Community Service Obligation (CSO) Funding Pool exists to ensure that arrangements are in place to provide all Australians with ongoing, timely access to all PBS medicines via their community pharmacy.[107] One of the criterion to access the funding pool is for wholesalers to meet the Code of GWP, with the role of monitoring compliance against all criteria outsourced by the Australian Government to a third party entity. While the CSO Funding Pool provides some assurance that the supply chain between manufacturers and the public maintains the quality of prescription medicines, it has limitations. These include:

- only covering PBS medicines. The Australian Institute of Health and Welfare estimated that, in 2010, only three-quarters of the 271 million prescriptions dispensed were subsidised under the PBS or the Repatriation Pharmaceutical Benefits Scheme; and
- only covering a limited number of wholesalers. Currently, there are three national wholesalers and two state-based wholesalers who have signed up to the CSO, meaning not all wholesalers of prescription

107 Community pharmacy agreements have been in place since 1 July 1990, aiming to give Australians equal access to affordable medicines and health services. The CSO Funding Pool was established in 2006 under the previous agreement. At 1 July 2006 the funding pool was set at $150 million and has since been subject to increases based on the Wage Cost Index.

medicines have signed up. The audit could not identify any readily available information on the percentage of prescription medicines distributed by non-CSO wholesalers.

Release for supply overseas

5.60 Following 'release for supply' of finished products by an overseas manufacturer, the supply chain is self-regulated until the product arrives in Australia, when the relevant state/territory government or CSO regulation against the Code of GWP applies. In particular, while the TGA provides sponsors of therapeutic goods manufactured overseas with market authorisation based on agreements between the Australian sponsor and overseas manufacturer, there is no regulation to ensure that these agreements are met. This introduces a number of risks to the quality, efficacy and safety of prescription medicines, including:

- deterioration in the quality of medicines from inappropriate storage during transportation, for example, from prolonged heat exposure in unrefrigerated shipping containers;
- substitution with counterfeit medicines; and
- the introduction of contaminants.

5.61 In 2009, the OMQ drafted an internal paper for management consideration to address these risks. In particular, it proposed that responsibility for 'release for supply' of a finished product rest with the Australian sponsor of a therapeutic good. Not only would the sponsor be responsible for each step in the manufacturing supply chain, including transportation to their Australian premises, it would also make it easier for Australian authorities to hold an individual within their jurisdiction accountable for the quality of the product. While the draft paper was considered by OMQ management, it has not been progressed or finalised.

Performance measurement, monitoring and reporting

5.62 Adequate performance information, particularly in relation to program effectiveness, allows management to review the appropriateness and success of programs, as well as identify areas for improvement. Further, the Parliament and the public's consideration of a program's performance relies heavily on the availability of reliable and appropriate performance information. To ensure this, the TGA's framework for reporting on performance must meet the needs

of internal management, as well as satisfy external accountability and reporting requirements.

Internal reporting

5.63 Using information compiled by the individual business units, the TGA prepares a half-yearly performance report containing statistical data on its regulatory workflows. This report is distributed to the TGA-Industry Consultative Committee, allowing industry an opportunity to provide direct feedback on the TGA's performance.

5.64 Relating to the OMQ's compliance program, this performance report includes information on licences, certifications and clearances across all therapeutic good manufacturing sites. The statistics included in this half-yearly report allow for the identification of trend information, such as compliance outcomes over time and numbers of new applications. However, there is no explanatory information indicating possible reasons contributing to the trends, or in deviations from those trends.

External reporting

5.65 The TGA reports publicly to Parliament as a division of the Department of Health, through the Portfolio Budget Statement and Annual Report processes. Therapeutic Goods is included as a sub-program (Sub-Program 1.4.2) of Outcome 1 (Population Health).[108]

Key performance indicators

5.66 The TGA identified three quantitative key performance indicators (KPIs) for the 2012–13 Portfolio Budget Statement, of which one (shown in Table 5.5) relates to the performance of the OMQ's manufacturing compliance program.

Table 5.5: KPI: Percentage of licensing and surveillance inspections completed within target timeframes

Inspections	2012–13 Target	2012–13 Actual	Result
Domestic	100%	73%	Not met
Overseas	90%	71%	Not met

Source: Department of Health and Ageing Annual Report 2012–13, p.43.

108 Department of Health, *Portfolio Budget Statements 2013–14*, May 2013, p 57–59.

5.67 The guidance issued by the Department of Finance, advising on Portfolio Budget Statement reporting requirements, states that a KPI is not a measure of input or output but rather the effectiveness of a program in achieving its objectives.[109]

5.68 The OMQ has reported internally that the KPI shown in Table 5.5 does not provide an appropriate measure of performance because it is primarily a measure of timeliness. Further, the transparency of the measure is limited as it does not include an explanation of 'target timeframes'. To supplement current public reporting, the TGA foreshadowed its intention to report online biannually from 30 June 2014 on a range of revised performance indicators. Measures relating to the OMQ's regulation of the Code of GMP for prescription medicines include: information on participation in international GMP harmonisation activities; and percentage of regulatory decisions subject to internal or legislative review processes. Neither provides a measure of the compliance program's effectiveness.

Proposed KPIs

5.69 As part of the TGA Blueprint Reforms, discussed at paragraph 5.70, the TGA committed to developing a new range of internal and external KPIs to provide quantitative and qualitative information on the TGA's organisational effectiveness and operational efficiency. The third and final phase of this Blueprint Reform commitment involves agreeing upon a new set of KPIs and beginning to report against them. This initiative is currently scheduled for implementation between July 2013 and December 2015, meaning that external reporting against these KPIs will not commence until the release of the 2015–16 Department of Health Annual Report.

The TGA reform program

5.70 The TGA is currently implementing two significant reforms: the Blueprint Reforms; and the development of the Australian and New Zealand Therapeutic Products Agency (ANZTPA).

109 Department of Finance, *Guidance for the Preparation of the 2013–14 Portfolio Budget Statements*, Finance, Canberra, 2013, p 30.

Blueprint Reform

5.71 The TGA has been subject to a number of reviews in recent years[110], particularly following the Pan Pharmaceuticals recall in 2003.[111] These reviews examined transparency, advertising of therapeutic goods, complementary medicines, the medical devices regulatory framework, and health technology.[112] In December 2011, following extensive consultation and collaboration with consumers, health care professionals and industry bodies, the Government released its response: *TGA Reforms: a Blueprint for the TGA's future*.[113] With the exception of the development of key performance indicators, none of the reforms directly involve the Code of GMP, although some relate to prescription medicines.

Australia and New Zealand Therapeutic Products Agency

5.72 The proposed ANZTPA will be a joint scheme for the regulation of all therapeutic goods, absorbing the current regulators the TGA and New Zealand's Medsafe. The establishment of ANZTPA is planned progressively over a period of five years and will be overseen by a Ministerial Council involving the Australian and New Zealand Health Ministers.[114] ANZTPA is expected to be operational by 2016.

5.73 One of the projects currently underway is for integrated GMP inspections. The TGA has identified some progress to date through the routine exchange of: inspection reports; information on inspection scheduling; quality system documentation (for example, SOPs); and training schedules. The TGA and Medsafe are currently working through legal, administrative and technical differences in order to develop a single pooled inspectorate.

110 These reviews have been conducted by the ANAO (2004 and 2011), the Australian Government (2004), the JCPAA (2005) and the TGA (2010 and 2011).

111 In 2003, the TGA recalled 219 products manufactured by the Australian company Pan Pharmaceuticals Limited and subsequently suspended their licence for a period of six months due to serious concerns about the quality and safety of products manufactured by the company.

112 Department of Health, *Department of Health and Ageing Annual Report 2011–12*, Health, Canberra, 2012, p 71.

113 TGA, *TGA reforms: A blueprint for TGA's future*, TGA, Canberra, 2011.

114 The Regulatory Policy and Governance Division of the Department of Health has carriage of the ANZTPA reforms.

Conclusion

5.74 The TGA undertakes regulation of the Code of GMP on a cost recovery basis. However, the TGA's current fee structure for regulating compliance with the Code of GMP is such that domestic manufacturers with 'good' compliance are cross-subsidising the effort spent by the TGA to regulate manufacturers with 'basic' compliance, as the licence fee is fixed and inspections identifying a high number of deficiencies require considerably more resources to finalise. The TGA has acknowledged there is scope for improvement and advised that it plans to revise fees and charges in 2014–15, pending the outcome of a structural review of fees, charges and activity based costing.

5.75 The OMQ's primary IT system supporting its compliance program, the MIS, was built on legacy platforms and has not been fully modified to meet business requirements. Consequently, it does not capture key management information required to monitor performance and adherence to SOPs, and the TGA should enhance the system to record the dates on which inspection reports are sent, manufacturers' responses are received and inspections are closed out. The TGA has not assessed its IT network security controls relating to OMQ's data holdings to ensure that commercially sensitive information is protected against cyber intrusion, and should review relevant system controls. Further, the compliance information contained in the MIS is not aligned with information held on the ARTG to ensure that publicly accessible information on prescription medicines is current and reliable.

5.76 The TGA reports on its regulatory performance through the Department of Health's Portfolio Budget Statement. The TGA identified three quantitative KPIs for 2013–14, one of which relates to the timeliness of inspections. The TGA has acknowledged the limitations of its current KPIs and has advised that it plans to develop revised performance measures by December 2015.

Ian McPhee
Auditor-General

Canberra ACT
7 May 2014

Appendices

Appendix 1: Agency's Response

22 APR 2014
10.30

Australian Government
Department of Health

SECRETARY

Dr Tom Ioannou 22/4
Group Executive Director
Performance Audit Services Group
Australian National Audit Office
GPO Box 707
CANBERRA ACT 2601

Dear Dr Ioannou

PROPOSED AUDIT REPORT – ADMINISTERING THE CODE OF GOOD MANUFACTURING PRACTICE FOR PRESCRIPTION MEDICINES

I refer to your letter of 26 March 2014 and the enclosed proposed report for the ANAO performance audit of Administering the Code of Good Manufacturing Practice for Prescription Medicines.

I note the report and the suggestions made in the report. The findings of the report have informed a review of the systems and processes that underpin the TGA's manufacturing quality inspections programme. The recommendations of this review will be implemented in accordance with the therapeutic goods legislation.

The Department's formal comments on the audit report and recommendations are attached. The Department's response for noting in the report summary is:

The Department of Health notes the audit report and agrees with the recommendations.

Attached are some additional commentary and matters of a minor editorial nature.

If you have any further questions about the Department's response, please contact Mr Colin Cronin, Assistant Secretary Audit and Fraud Control on (02) 6289 7877 in the first instance.

Yours sincerely

Jane Halton PSM
Secretary

4 April 2014

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Appendix 2: Countries with which Australia has a Mutual Recognition Agreement and Other Countries with PIC/S Membership

Australian has MRA (or equivalent) agreements with the following countries to mutually recognise the GMP certifications undertaken on their therapeutic goods manufacturing sites:

Austria	France	Liechtenstein	Spain
Belgium	Germany	Luxembourg	Sweden
Canada	Greece	Malta	Switzerland
Cyprus	Hungary	Netherlands	United Kingdom
Czech Republic	Iceland	Norway	
Denmark	Ireland	Portugal	
Finland	Italy	Singapore	

The therapeutic goods manufacturer regulators from the following countries are members of PIC/S, but not subject to an MRA or other agreement with Australia:

Argentina	Latvia	Romania	Ukraine
Taiwan	Lithuania	Slovak Republic	
Estonia	Malaysia	Slovenia	
Indonesia	Poland	South Africa	

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The following Better Practice Guides are available on the ANAO website:

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