The Auditor-General
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Performance Audit

Regulation of Non-prescription Medicinal Products

Department of Health and Ageing
Therapeutic Goods Administration

Australian National Audit Office

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Australian National
Audit Office

Canberra ACT
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Dear Mr President
Dear Mr Speaker

The Australian National Audit Office has undertaken a performance audit in the Department of Health and Ageing 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 and the accompanying brochure. The report is titled *Regulation of Non-prescription Medicinal Products.*

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

Yours sincerely

P. J. Barrett
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. The ANAO assists the Auditor-General to carry out his duties under the *Auditor-General Act 1997* to undertake performance audits and financial statement audits of Commonwealth public sector bodies and to provide independent reports and advice for the Parliament, the Government and the community. The aim is to improve Commonwealth public sector administration and accountability.

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Abbreviations

ANAO	Australian National Audit Office
API	Active pharmaceutical ingredient
ARTG	Australian Register of Therapeutic Goods
ELF	Electronic Listing Facility
EU	European Union
GMP	Good Manufacturing Practice
Health	Department of Health and Ageing
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
OTC	Over-the-counter (medicine)
PIC	Pharmaceutical Inspection Convention
PIC Scheme	Pharmaceutical Inspection Cooperation Scheme
SARS	Severe Acute Respiratory Syndrome
SOPs	Standard operating procedures
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
TICC	TGA–Industry Consultative Committee
URPTG	Uniform Recall Procedures for Therapeutic Goods

Glossary

ARTG	A register showing therapeutic goods approved by the TGA for supply to the Australian and export markets.
Announced audit	An audit where the manufacturer receives advance notification of the audit's date. Notification is usually within one week of the commencement of the audit.
Certification	The approval that an overseas manufacturer is compliant with Australian or equivalent manufacturing standards.
Close out	The last phase of an audit when a manufacturer addresses deficiencies and a final decision is taken by the TGA on the manufacturer's level of compliance with mandated requirements.
Code of GMP (the Code)	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.
Complementary medicines	Complementary medicines include vitamin and mineral supplements, and herbal and homoeopathic preparations.
Deficiency	A deficiency occurs when a manufacturer's actual performance is assessed as not complying with the mandated requirements.
Deficiency Report	A report detailing the nature and classification of deficiencies identified during the on-site inspection phase of an audit.
ELF	Electronic facility through which sponsors apply to list a product on the ARTG. The current version (ELF3) checks the information provided in the application, and when appropriate, approves the listing.
GMP	See Code of GMP.
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.

Licensing (or certification) audit	Initial audit conducted by the TGA to confirm a manufacturer complies with mandated requirements.
Listed medicines	Medicinal products included in the Part of the ARTG known as 'listed goods'.
Non-prescription medicinal products	Collective term used to refer to OTC and complementary medicines.
OTC medicines	Medicines that do not fit into the prescription or complementary medicines groups.
PIC	The Pharmaceutical Inspection Convention (PIC) is a formal treaty between countries. PIC members are legally bound to recognise the manufacturer inspections of PIC members. Australia joined the convention in 1993.
PIC Scheme	An informal cooperative arrangement between national health authorities, having no legal status. Its purpose is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of auditors. Australia has participated in this scheme since its inception in 1995.
Post-market	All aspects of contact with a product, product sponsor and/or manufacturer *after* the TGA's approval of the product/manufacturer.
Pre-market	All aspects of contact with a product, product sponsor and/or manufacturer *before and during* the TGA's approval of the product/manufacturer.
Prescription medicines	Registered medicines that have high-risk active ingredients listed on the *Standard for the Uniform Scheduling for Drugs and Poisons*.
Recall (product recall)	Removal of a therapeutic good from supply or use, for reasons relating to deficiencies in the quality, safety or efficacy of the good.
Registered medicine	A medicinal product included in the Part of the ARTG known as 'registered goods'.
Review Panel	A TGA panel (usually auditors) convened to review the findings of an audit.

Routine audit	A periodic audit conducted by the TGA to confirm a manufacturer continues to comply with mandated requirements.
Special audit	An audit conducted by the TGA in response to special circumstances that warrant a focused investigation.
Sponsor (product 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.
Standards	Standards for therapeutic goods established pursuant to s.10 of the *Therapeutic Goods Act 1989*. Standards may be specified in relation to, *inter alia*, therapeutic goods and procedures to be carried out in the manufacture of therapeutic goods.
Therapeutic goods	Medicinal products, blood and tissue products, or therapeutic devices that are used to diagnose and treat diseases, ailments, defects or injuries in people and/or improve well being.

Summary and Recommendations

Summary

Background

1. The Therapeutic Goods Administration (TGA) is responsible for the regulation of the manufacture and supply of medicines, including complementary and over-the-counter medicines, in Australia, to protect public health and safety. The *Therapeutic Goods Act 1989* gives effect to the regulatory powers required to fulfil this role. The TGA is a division of the Commonwealth Department of Health and Ageing (Health).

2. Manufacturers of non-prescription medicinal products must be licensed or certified to manufacture. Approval by the TGA is only granted if the proposed manufacturing premises are compliant with the Australian Code of Good Manufacturing Practice for Medicinal Products (Code of GMP). Products supplied to the public must also be approved by the TGA.

3. Compliance with regulatory requirements is monitored by the TGA. Where a manufacturer or a product is not compliant with regulatory requirements, the TGA has a range of actions available to reduce possible risks to public health and safety.

This audit

4. The objective of this audit was to assess the TGA's regulation of non-prescription medicinal products. In particular, it addressed the systems, procedures and resource management processes used to:

- confirm new manufacturers comply with requirements for the manufacture of non-prescription medicinal products;
- monitor manufacturers and medicines to ensure requirements continue to be met; and
- manage non-compliance.

5. The progress and timeliness of this audit was adversely affected by limitations in the TGA's information and records management. Where necessary, the Australian National Audit Office (ANAO) has made estimates in key areas, for the purpose of this report.

Key findings

Licensing and certification of manufacturers (Chapter 2)

6. About 40 per cent of manufacturers of non-prescription medicinal products supplying the Australian market are directly approved by the TGA. Some 25 per cent of the manufacturers are located in Australia and 15 per cent overseas.

7. Before TGA approval to manufacture is granted, it undertakes an audit so that compliance with the Code of GMP can be assessed. The TGA does not

measure, or have a standard or target for, the timeliness of the approval process. This limits the TGA's ability to manage and monitor this aspect of its regulatory process.

8. The remaining approximately 60 per cent of manufacturers supplying the Australian market are located overseas, and are certified by an overseas regulator. These regulators are in countries with which Australia has either a Mutual Recognition Agreement (MRA) or Memorandum of Understanding (MOU)/cooperative arrangements.

9. The TGA carries out a formal assessment to establish regulatory equivalence to Australian manufacturing standards for MRA signatories. However, this is not common practice for MOUs/cooperative arrangements. The TGA advised that this is because there was already a mutual understanding of each other's regulatory practices.

10. Regular reassessment of regulatory equivalence is undertaken through an international inspection cooperation scheme for most countries that are signatories to the agreements. However, for some countries, reassessments have been done on an informal basis only. The ANAO also found that one MOU established in 1993 had not been formally reassessed to ensure standards had remained appropriate.

11. The TGA plans to implement new, and maintain existing, agreements. However, this is not supported by a strategic plan and appropriately allocated funding. The ANAO considers that a strategic plan to manage, fund and maintain these agreements would increase assurance that overseas standards continue to be equivalent to those in Australia, for the benefit of all stakeholders.

Preparing and executing the audit program (Chapter 3)

12. Manufacturers approved by the TGA are subject to regular audit. An audit frequency matrix determines the time to next audit. This is based upon two risk parameters: the products manufactured; and compliance with the Code of GMP from the previous audit. However, the rationale for assigning audit frequencies for these risk parameters has not been documented, nor supported by a systematic risk analysis.

13. The audit frequency may be varied from that indicated by the risk parameters. However, the reasons for the variation are often not documented, reducing transparency and accountability for these discretionary judgments.

14. The ANAO also found that the level of compliance with the Code is not recorded on the TGA's management information systems. Other information on these systems was incorrect or out of date. As well, more reliable records are necessary to support an automated audit scheduling tool, which is shortly to be implemented.

15. Monitoring arrangements limit the TGA's ability to assess, and be accountable for, performance in the execution of the audit program.

16. Overall, the TGA's audit program is behind schedule and the majority of audits are conducted after the due date. For a sample of audits conducted in recent years, Australian audits had, on average, a due date of 16 months after the previous audit, but were conducted after 22 months. For overseas audits, the comparable figures were 21 and 30 months respectively.

17. Many audits that have not been conducted by their due date are not considered overdue by the TGA. In part, this is because the TGA does not consider audits overdue if they are less than six months past their due date. The ANAO also found that the TGA has accepted audit assessments by regulators in countries with which Australia has no GMP agreement. In other cases, the TGA advised that it has rescheduled audits to later than the due date, because of adverse international circumstances.

18. The TGA advised that the risk of unsafe products does not increase because a manufacturer has not been audited according to the TGA's defined risk treatments. It considers that there are other safeguards, such as adverse reaction reporting, which would assist in identifying whether an audit should be conducted as a matter of priority.

19. The TGA's view that some manufacturers have acceptable compliance, on grounds other than a TGA audit, is not supported by systematic risk-based processes. Further, the TGA does not have documented contingency plans to support its regulatory obligations when international events prevent it from executing the overseas audit program.

20. The TGA is planning to increase the number of its auditors. However, it has not conducted a strategic assessment of the impact of the increase on the backlog of audits for non-prescription medicine manufacturers.

Conducting manufacturer audits (Chapter 4)

21. There was a marked increase in effort on non-prescription medicine manufacturer audits in 2003. The TGA advised that the increase was risk-based, following the Pan Pharmaceuticals Limited enforcement action. Non-prescription medicine manufacturers were targeted, the length of audits increased, and more unannounced audits used.

22. The TGA did not undertake a structured risk assessment to guide these changes. Nor has it assessed the broader lessons for the future of the targeting of non-prescription medicine manufacturers.

23. Checklists and/or proformas are not used to plan and collect audit evidence, although auditors are encouraged to develop personal aide memoires. This practice limits transparency to stakeholders, and provision of

management assurance regarding consistency in the conduct and reporting of audits.

24. The Code of GMP defines outcomes rather than processes. Consequently, there is a risk that auditors will identify deficiencies inconsistently, unless clear guidance and adequate definitions are provided. The TGA has instituted several systems to improve consistency, but progress on some initiatives has not matched expectations or has been only partial.

25. Audit consistency continues to be a concern of the industry. Instances were cited where manufacturers perceived auditors to assess a practice as deficient, when it had previously been accepted.

26. The ANAO considers that the TGA could increase the transparency and accountability of its audit processes. For example, more robust and transparent procedures for the handling and resolution of complaints, appeals and disputes would greatly assist in addressing manufacturer concerns.

Addressing manufacturer non-compliance (Chapter 5)

27. Almost all TGA audits of non-prescription medicine manufacturers identify deficiencies against standards. The TGA uses a risk-based approach to allow most of these manufacturers to continue to manufacture, while deficiencies are addressed (known as audit close out).

28. Evidence of corrective action taken or proposed by manufacturers is required before close out. However, guidance to auditors on what is acceptable evidence is limited. The ANAO found that some corrective action reported by manufacturers was subsequently found to have been inadequate.

29. For an estimated 20 per cent of audits, the TGA assessed the level of a manufacturer's compliance as a potential risk to public health and safety. These audits are reviewed to determine appropriate action to be taken.

30. There is a range of enforcement action available. Some action, such as requiring regular reporting by manufacturers, and the placing of restrictions on overseas manufacturers, is not supported by documented operational procedures.

31. There was a marked increase in enforcement action against non-prescription medicine manufacturers in 2003. It is not clear, given the limitations of the TGA's management information, whether the increase reflected a serious decline in manufacturer compliance, or was the result of changes to the TGA's approach to compliance auditing and enforcement.

32. In general, enforcement action is timely. However, the TGA does not have timeliness or performance standards to assist in the management of enforcement action.

33. A significant enforcement action in 2003 took 12 weeks from initial audit action to the suspension of the manufacturer's licence. In this case, the TGA did not have contingency plans in place in the event of access to the manufacturer's premises becoming difficult, as occurred. The TGA advised that a vast amount of work was undertaken during the 12 week period. A thorough and independent review of key enforcement actions, such as this case, would assist the TGA to assess its regulatory performance and identify lessons for future regulatory action.

34. The TGA does not have systematic monitoring arrangements to ensure that the action it proposes to manage non-compliance is undertaken. Also, approaches used to address non-compliance vary for similar cases and may not be in accord with operational procedures. While there is a degree of judgment involved, the limited nature of the TGA's records makes it difficult for management to assess whether variations are supported, at least for some audits.

35. The ANAO found that documentation of decisions regarding enforcement action was often incomplete or inadequate.

Monitoring compliance of approved products (Chapter 6)

36. There is a targeted monitoring system to address the potential risks to safety, quality and efficacy of non-prescription medicinal products. Several enhancements have been made to the elements of the system to increase their reliability and efficiency. For example, automation of the approval process for listing of medicines (mostly complementary medicines) has increased the reliability and efficiency of this process.

37. Laboratory testing is part of the TGA's strategy to identify unsafe non-prescription medicinal products. The TGA expends as much on testing as it does on audits of manufacturers of these products. Nevertheless, only one to two per cent of the 21 000 non-prescription medicinal products are subject to laboratory testing each year. The TGA advised that this is commensurate with the inherent risk of these medicines. Also, it is confident that the safety and quality of these products can be assured through other monitoring elements, such as adverse reaction reports.

38. The TGA does not have a systematic and structured approach to the use of priority testing when there is an increased risk exposure arising from limitations in manufacturer audits.

39. In addition, while the TGA's laboratories aim to undertake tests within specified time periods, these are not recognised as formal performance standards. They are often not met, particularly for prioritised testing.

Addressing product non-compliance (Chapter 7)

40. The TGA has several administrative measures available to respond to products that do not comply with conditions of listing or registration. Recent amendments to the Act have strengthened the TGA's ability to cancel and recall products.

41. Warning letters are the most frequently used means of addressing product non-compliance. However, TGA's management information systems do not capture information on the number, reasons or impact of warning letters issued.

42. In 2003, the TGA recalled 1 805 medicines due to deficiencies in their safety, quality or efficacy. The ANAO found that, generally, the TGA had an effective approach to planning and conducting these recalls. However, until recently, risk analyses undertaken to determine the danger and consequences presented by the defective product had not been documented.

43. Many recalls stem from manufacturing deficiencies. Corrective action undertaken by manufacturers is reviewed in the next GMP audit. However, formal feedback to the Product Regulator only occurs where the audit identifies unsatisfactory corrective action.

44. Limitations in the TGA's information systems restrict its ability to conduct trend analyses of recalls. The TGA is developing a new recalls system that will improve data capture for such analysis.

Management framework (Chapter 8)

45. The TGA operates on a full cost-recovery basis. However, fees and charges do not align with the costs. Hence non-prescription medicine manufacturers and sponsors do not have assurance that their payments are not, at least in part, cross subsidising other TGA activities.

46. Approximately 11 per cent of resources budgeted for the regulation of non-prescription medicines are expended on the licensing and compliance auditing of manufacturers. The other 89 per cent is expended on product regulation. Strategic plans and risk assessments do not provide documented details to support this distribution of regulatory effort.

47. The Act sets an overall strategic framework for the management of risk posed by therapeutic goods. The TGA has recently implemented a risk management policy. However, there are a number of ways in which more structured and consistent risk management would substantially enhance regulation of non-prescription medicines. These include: addressing differences in risk treatments between Australian and overseas manufacturers; improved monitoring of risk treatments; and assessing the impact of slippage on planned risk treatments.

48. Management information is often not captured in management information systems, or is not reliable or complete. In addition, the systems are not well integrated, limiting the TGA's ability to share information. The TGA is implementing a new audit management information system. However, current weaknesses in information need to be fully addressed to obtain the benefits from the new system.

49. There are also weaknesses in documentation. Some key regulatory decisions have not been supported by formal documentation, including reasons and supporting evidence. As well, files have not been well maintained.

50. There is inadequate information to support good performance management. The published effectiveness indicator provides only limited insight into the TGA's effectiveness in achieving its regulatory objective. A strengthened performance management system that includes statements of outcomes, key performance indicators and targets would better inform planning and management. It would also provide for better accountability to stakeholders.

Overall audit conclusion

51. The TGA has a structured framework for the regulation of risk presented by non-prescription medicinal products. This has regard to the risk presented by the type of product, and by the adequacy of manufacturing operations. However, more rigour around systems, procedures and resource management within the framework is required to provide assurance that non-prescription medicines are appropriately and cost-effectively regulated.

52. Aspects of risk management for non-prescription medicines require better articulation and structure, to support targeting and monitoring of risk treatments. This is the case both for manufacturers audited by the TGA, and for the almost 60 per cent of manufacturers audited by overseas regulators. Risk management would also be better informed by greater utilisation of information available.

53. The TGA's regulatory framework is supported by a substantial number of standard operating procedures. However, greater clarity and guidance is required for some key aspects of the TGA's regulatory functions. There are also some gaps in documented procedures.

54. Maintaining the quality, consistency and reliability of manufacturer audits, and of any enforcement actions, continues to be an area that requires management attention, as is recognised by the TGA and industry stakeholders. Initiatives recently implemented have the potential to improve the integrity of these processes, but require management focus, better information support, and monitoring of effectiveness for the assurance of all stakeholders.

55. Decision-making, including reasons for particular action and enforcement, requires more structured documentation, especially when discretionary judgments have been made.

56. Key information obtained through the TGA's regulatory functions is often not captured, or not utilised for the purposes of monitoring and analysis of trends. Information that is recorded is often unreliable, limiting its value for management purposes. Better management of information is required to inform the TGA in its regulation of non-prescription medicines.

57. Performance management arrangements are insufficient to support sound management of regulation, and accountability to stakeholders. Performance indicators provide limited insight into the effectiveness of the regulation of non-prescription medicines, and of manufacturer compliance.

58. Transparency to manufacturers and sponsors can be enhanced, both to facilitate manufacturers' ability to comply with regulatory requirements, and to improve the TGA's accountability for its actions.

Recommendations and the Department of Health and Ageing's response

59. The ANAO made 26 recommendations aimed at strengthening the regulation of non-prescription medicinal products.

60. The Department of Health and Ageing's full response to this audit can be found at Appendix 15. The Department also provided the following summary:

> The Department acknowledges the work of the ANAO in conducting this audit, and the contribution such audits make to continuous improvement in the public sector.
>
> The Department notes that the TGA:
>
> - has a legislative framework and documented procedures;
> - is subject to international and peer review;
> - has governance structures appropriate to its position within a department of state;
> - has a structured framework for the regulation of the risk presented by non-prescription medicinal products; and
> - a program of continuous management improvement.
>
> The Department notes that the audit commenced in October 2003, and many of the issues raised have already been addressed over the period of the audit as part of the TGA's continuous improvement program.
>
> The Department agrees with all recommendations set out in the ANAO report.

Recommendations

Recommendation No.1 Paragraph 2.25

The ANAO recommends that the Department of Health and Ageing develop, and publish, suitable performance indicators and targets for the processes associated with the licensing and certification of non-prescription medicine manufacturers. The targets should be reflected in the TGA's customer service charter, and in decision-making and audit processes.

Departmental response: Agreed.

Recommendation No.2 Paragraph 2.43

The ANAO recommends that the Department of Health and Ageing, taking into account any international agreements, develop a strategic management plan to monitor the regulatory equivalence of countries with which it has GMP agreements, including:

- standards and procedures to be monitored;
- performance measures and targets to be monitored;
- the currency of the agreements;
- resources required to monitor equivalence, including management arrangements; and
- reporting arrangements.

Departmental response: Agreed.

Recommendation No.3 Paragraph 3.22

The ANAO recommends that the Department of Health and Ageing strengthen the management of, and accountability for, the process for assigning GMP audit frequency by:

- articulating the rationale for audit frequencies, based upon systematic risk analysis, and undertaking regular evaluation of their appropriateness;
- ensuring that reasons for use of discretion in setting audit frequency are documented;
- maintaining reliable records of risk ratings, and supporting information; and
- recording the degree of acceptable compliance.

Departmental response: Agreed.

Recommendation No.4 Paragraph 3.41

The ANAO recommends that the Department of Health and Ageing:

- establish systems for the collection of management and performance information to enable it to assess performance in the execution of the GMP audit program; and
- assess the impact on TGA's regulation of manufacturers, including the risk of undetected non-compliance, from failure to achieve a GMP audit program consistent with risk profiling.

Departmental response: Agreed.

Recommendation No.5 Paragraph 3.71

The ANAO recommends that the Department of Health and Ageing establish contingency plans, consistent with the TGA's regulatory responsibilities, to address the risk of delays in the execution of the overseas GMP audit program.

Departmental response: Agreed.

Recommendation No.6 Paragraph 4.23

The ANAO recommends that the Department of Health and Ageing assess the cost-benefit of unannounced GMP audits, and their role and contribution in the regulatory oversight strategy. The assessment could also address the broader lessons for the future from the targeting of non-prescription medicine manufacturers in 2003.

Departmental response: Agreed.

Recommendation No.7 Paragraph 4.40

The ANAO recommends that the Department of Health and Ageing establish greater structure around administrative procedures, and develop support tools around planning of GMP audits and collection of evidence to facilitate consistency and adequacy of coverage in the conduct and reporting of audits of non-prescription medicine manufacturers.

Departmental response: Agreed.

Recommendation No.8 Paragraph 4.59

The ANAO recommends that the Department of Health and Ageing provide guidance to auditors and manufacturers on the deficiencies considered critical for OTC medicine manufacturers and for complementary medicine manufacturers. The department should also monitor the consistent application of such guidance by GMP auditors and Review Panels.

Departmental response: Agreed.

Recommendation No.9 Paragraph 4.75

The ANAO recommends that, to improve transparency and to assist its clients in their compliance, the Department of Health and Ageing:

- improve the information available to non-prescription medicine manufacturers and sponsors on the GMP audit process; and
- develop, and make transparent to its clients, procedures for the handling and resolution of complaints, appeals and disputes regarding audit findings.

Departmental response: Agreed.

Recommendation No.10 Paragraph 5.23

The ANAO recommends that the Department of Health and Ageing strengthen GMP audit close out procedures by:

- establishing clear guidance, including examples and standards, on the assessment and acceptance of evidence of corrective action by manufacturers;
- subjecting close out to appropriate review; and
- maintaining relevant and reliable management information to facilitate monitoring of close out, and allocation of audit resources.

Departmental response: Agreed.

Recommendation No.11 Paragraph 5.32

The ANAO recommends that the Department of Health and Ageing:

- establish a suitable range of expertise on TGA Review Panels to address regulatory issues, consistent with procedural requirements; and
- ensure that Review Panels are constituted in accordance with SOPs.

Departmental response: Agreed.

Recommendation No.12 Paragraph 5.54

The ANAO recommends that the Department of Health and Ageing establish, and promulgate, TGA procedures for the:

- imposition and management of short term reporting enforcement action;
- consistent application of licence restrictions; and
- imposition of restrictions on overseas manufacturers audited and certified by the TGA. Relevant matters include the roles and responsibilities of officials, key steps, complaints mechanism and time-lines.

Departmental response: Agreed.

Recommendation No.13 Paragraph 5.70

The ANAO recommends that the Department of Health and Ageing arrange independent assessment of recent key enforcement actions, to draw lessons for the future when making decisions potentially affecting public health and safety.

Departmental response: Agreed.

Recommendation No.14 Paragraph 5.76

The ANAO recommends that the Department of Health and Ageing establish procedures to guide and prepare staff and management should there be difficulty in gaining access to premises to conduct a GMP audit.

Departmental response: Agreed.

Recommendation No.15 Paragraph 5.81

The ANAO recommends that the Department of Health and Ageing strengthen the TGA's management and monitoring of enforcement action by establishing:

- timeliness standards for key decision steps in the enforcement process, and monitoring performance against the standards; and
- monitoring and reporting procedures for the implementation of Review Panel recommendations and other enforcement action.

Departmental response: Agreed.

Recommendation No.16 Paragraph 5.99

The ANAO recommends that the Department of Health and Ageing enhance management procedures for GMP compliance ratings to enable review and analysis over time, and to identify issues needing correction, by:

- assessing and recording initial compliance ratings; and
- documenting reasons for ratings and subjecting them to appropriate review.

Departmental response: Agreed.

Recommendation No.17 Paragraph 5.104

The ANAO recommends that the Department of Health and Ageing inform manufacturers of their compliance rating, to assist manufacturers in improving quality management, and to reinforce findings presented in Deficiency Reports.

Departmental response: Agreed.

Recommendation No.18 Paragraph 6.46

The ANAO recommends that the Department of Health and Ageing increase testing when there is increased risk exposure arising from limitations in the manufacturer audit program and where there is a reasonable expectation it will assist in monitoring compliance. The overall strategy for priority testing should reflect this increased use, as well as the requirement for the Manufacturer Regulator to advise the laboratory when limitations arise.

Departmental response: Agreed.

Recommendation No.19 Paragraph 6.57

The ANAO recommends that the Department of Health and Ageing develop performance indicators and targets for the timeliness of TGA laboratory testing.

Departmental response: Agreed.

Recommendation No.20 Paragraph 7.35

The ANAO recommends that reports be provided to the TGA's Product Regulator on the effectiveness of recall-related corrective actions implemented by manufacturers.

Departmental response: Agreed.

Recommendation No.21 Paragraph 7.43

The ANAO recommends that the Department of Health and Ageing conduct, and disseminate to relevant stakeholders, regular trend analysis of recalls information, in order to assist in identifying systematic issues.

Departmental response: Agreed.

Recommendation No.22 Paragraph 8.19

The ANAO recommends that the Department of Health and Ageing review and enhance the TGA's risk management framework for non-prescription medicinal products. The revised framework should, *inter alia,*:

- be systematic, structured and integrated with the TGA's overall risk management strategies;
- allocate resources to various risk treatments;
- identify any necessary differences in risk treatments between Australian and overseas manufacturers, and their impact;
- provide information necessary to support effective management of risk and monitoring of treatments;
- ensure new or targeted strategies are based upon structured risk assessments, and evaluate their outcomes for lessons learned for future management of compliance; and
- identify the impact of slippage on planned risk treatments.

Departmental response: Agreed.

Recommendation No.23 Paragraph 8.27

The ANAO recommends that the Department of Health and Ageing strengthen the capture, recording, management and use of information to support regulation of non-prescription medicines by:

- holding key information collected from its regulatory processes on management information systems;
- maintaining the reliability and completeness of data holdings; and
- enabling better integration and sharing of information between the different areas of the TGA involved in regulatory functions.

Departmental response: Agreed.

Recommendation No.24 Paragraph 8.33

The ANAO recommends that the Department of Health and Ageing strengthen its documentation procedures to ensure key regulatory decisions taken by the TGA are fully documented, and that files are appropriately maintained.

Departmental response: Agreed.

Recommendation No.25 Paragraph 8.38

The ANAO recommends that the Department of Health and Ageing review and improve the TGA's quality assurance program to improve the quality, consistency and reliability of its GMP audits.

Departmental response: Agreed.

Recommendation No.26 Paragraph 8.47

The ANAO recommends that the Department of Health and Ageing implement a performance management system that defines key outcomes, key performance indicators and targets for the regulation of non-prescription medicinal products.

Departmental response: Agreed.

Audit Findings and Conclusions

1. Introduction

This chapter describes the background to, and purpose of, this audit.

Types of therapeutic goods

1.1 Therapeutic goods comprise medicines, medical devices, and blood and tissue products. The Therapeutic Goods Administration (TGA) classifies medicines according to their active ingredient,[1] and how they can be sold, as indicated in Figure 1.1.

Figure 1.1

Medicine types

Medicine type	Ingredients	Availability
Prescription	Have high-risk active ingredients listed on the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).[2]	A patient requires a prescription from a medical practitioner.
Complementary	Mostly have TGA-approved active ingredients[3] with a traditional or prescribed use. Therapeutic claims for these medicines are generally that their use provides: health maintenance, including nutritional support; vitamin and mineral support; or relief of symptoms.[4] Complementary medicines include vitamin and mineral supplements, and herbal preparations.	Available through health food shops and supermarkets.
Over-the-counter (OTC)	Medicines that do not fit into the prescription or complementary groups. Most OTC medicines have active ingredients listed on the SUSDP. However, the approved pack size and intended use represent a lower risk than prescription medicines.	Generally sold in pharmacies, although some are available in supermarkets.

Source: TGA

1.2 The term **non-prescription medicinal product** covers both OTC and complementary medicines. These products represent an increasing proportion of the Australian therapeutic goods market.

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1 The active ingredient is the component in a medicine's final formulation that is responsible for its physiological or pharmacological action.

2 The SUSDP comprises schedules that identify and restrict access to high-risk poisons and medicines. The schedules are governed by the National Drugs and Poisons Schedule Committee, established under s.52B of the *Therapeutic Goods Act 1989*.

3 Listed in Schedule 14 of the *Therapeutic Goods Regulations 1990*.

4 *Guidelines for Levels and Kinds of Evidence to Support Indications and Claims—For Non-Registrable Medicines, including Complementary Medicine, and other Listable Medicines*, TGA, October 2001, p.4.

1.3 Approximately $800 million of complementary medicines were sold in Australia in 2002–03, with a further $200 million exported.[5] Australian pharmacy sales of OTC medicines totalled approximately $2 billion in 2003.[6]

Policy and legislative context

1.4 The National Medicines Policy 2000 sets out Australian Government policy for the health industry. It aims for a cohesive focus between the medical industry, government and consumers. The Policy has four central objectives:

- timely access to the medicines that Australians need, at a cost individuals and the community can afford;
- medicines meeting appropriate standards of quality, safety and efficacy;
- quality use of medicines; and
- maintaining a responsible and viable medicines industry.[7]

1.5 The *Therapeutic Goods Act 1989* (the Act) gives effect to elements of the National Medicines Policy. It establishes a system of national controls over all goods making therapeutic claims. Accordingly, its provisions apply to non-prescription medicines.[8]

1.6 The major parts of the Act cover:

- the determination of standards for therapeutic goods;
- establishment of the Australian Register of Therapeutic Goods (ARTG) showing therapeutic goods that are approved for supply to the Australian market and export; and
- licensing of Australian manufacturers of therapeutic goods.[9]

1.7 A range of subordinate legislation supports the Act. **Therapeutic Goods Regulations** are disallowable instruments[10] that assist regulation of

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5 Expert Committee on Complementary Medicines in the Health System, *Complementary Medicines in the Australian Health System: Report to the Parliamentary Secretary to the Minister for Health and Ageing*, Commonwealth of Australia, September 2003, p.37.

6 AZTEC Information Systems, *Pharmacy National [Sales]*, Australian Self-Medication Industry, available from <http://www.asmi.com.au/industry.htm> [accessed 1 September 2004].

7 Available at <http://www.nmp.health.gov.au/objectives/policy.htm> [accessed 1 September 2004].

8 There is a global move towards regulating complementary medicines as therapeutic goods, rather than as dietary supplements or foods.

9 Explanatory Memorandum, Therapeutic Goods Bill 1989, p.2.

10 Disallowable instruments include determinations, regulations and rulings. These are tabled in both the Senate and the House of Representatives and may be subject to disallowance by both.

therapeutic goods. For example, Regulations have been enacted to regulate: advertising; the registration or listing of therapeutic goods; and the licensing of manufacturers.[11] Regulations also provide for the formation and operation of several expert advisory committees.

1.8 **Therapeutic Goods Orders** (TGOs) provide additional standards for therapeutic goods. For example, TGO56 specifies standards that apply to tablets, pills and capsules, and the test methods to be used when assessing compliance with these standards.

1.9 The Act defines a range of offences, including:

- importing, exporting, manufacturing or supplying therapeutic goods not included on the ARTG;
- a false registration or listing number on packaging; and
- the manufacture of therapeutic goods without a licence.

1.10 Penalties were strengthened in the *Therapeutic Goods Amendment Act (No.1) 2003*. Maximum monetary penalties for a range of offences were increased to 1000 penalty units.[12] In addition, prison terms were introduced for certain breaches of the Act.[13]

The Therapeutic Goods Administration

1.11 The TGA is a division of the Commonwealth Department of Health and Ageing (Health). Its role under the Act is to enhance public health and safety by regulating the production and supply of therapeutic goods in Australia.

1.12 The TGA's average staffing level for the year 2003–04 was 424 (full time equivalents). During the same period, its total operating revenue was $66.7 million, compared with operating expenses of $62.4 million.

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

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11 *Therapeutic Goods Regulations 1990*, Parts 2, 3 and 4 respectively.

12 Section 4AA of the *Crimes Act 1914* (Cwlth) sets out the current value of a penalty unit as $110.

13 The standard term of imprisonment is 12 months. However, counterfeiting therapeutic goods; causing serious risk to public health; and damaging required documentation attract a prison term of five years.

Regulation of non-prescription medicinal products

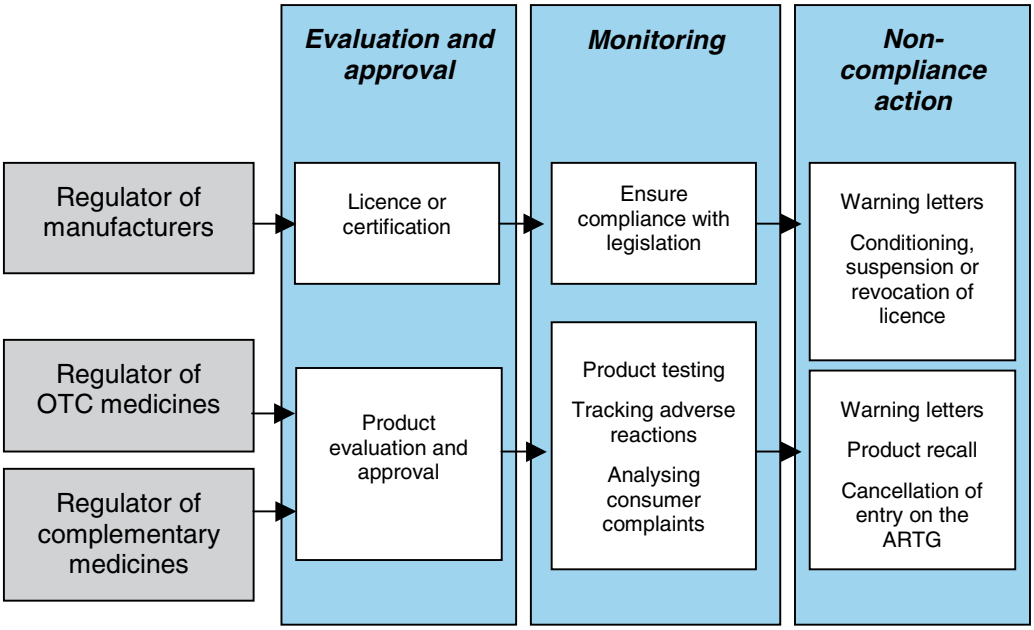
Role of regulators

1.14 Regulators play a key role in the TGA's regulatory framework. There are separate regulators for manufacturers of therapeutic goods; OTC medicines; and complementary medicines. External committees with relevant expertise provide advice to the regulators.

1.15 The roles of the regulators are summarised in Figure 1.2.

Figure 1.2

Key regulator roles



Source: ANAO analysis of TGA information.

Approval of manufacturers

1.16 Australian manufacturers of non-prescription medicinal products require a **licence** from the TGA before they can legally manufacture products approved for supply in Australia or for export. The licence states that they are compliant with the requirements of the Australian Code of Good Manufacturing Practice for Medicinal Products (Code of GMP).[14]

[14] This requirement has its legal foundation in section 36 of the Act, which grants the Minister power to 'determine written principles to be observed in the manufacture of therapeutic goods for use in humans'.

1.17 Overseas manufacturers producing non-prescription medicinal products for supply to the Australian market require **certification** stating that they are compliant with the Code of GMP.[15] However, overseas manufacturers do not require certification if they only produce active ingredients for OTC and complementary medicines supplied to the Australian market.

Monitoring manufacturers

1.18 Manufacturers licensed and certified by the TGA are subject to audit by the TGA to ensure that they continue to be compliant with the requirements of the Code of GMP.

1.19 The TGA has a range of action for dealing with manufacturers that do not meet acceptable manufacturing standards. This includes conditioning the licence to restrict the types of products that may be manufactured, suspending the licence or revoking the licence.

Approval of products

1.20 A non-prescription medicinal product has to be 'sponsored' by an Australian importer, exporter and/or supplier of that product. The sponsor is required to be a resident of Australia, or registered as a business in Australia.

1.21 Prior to supply, the sponsor must have the product evaluated and approved by the TGA. The product will be either registered or listed on the ARTG, depending on, *inter alia*, its ingredients and the therapeutic claim(s) made.[16]

1.22 The therapeutic claim is classified into three categories—high, medium or general (see Appendix 1). For example, 'a treatment for depression' is a high therapeutic claim; whereas 'an aid for digestion' is a general therapeutic claim. Figure 1.3 summarises the process.

1.23 A non-prescription medicinal product will be **registered** if it contains ingredients from the SUSDP or the sponsor wishes to make high-level therapeutic claims. A sponsor is required to submit the application and supporting evidence for evaluation by the TGA.

1.24 Most OTC medicines, and a small number of complementary medicines, are registered. A product will be **listed** if it contains TGA-approved active ingredients and does not make high-level claims. Applications are subject to an automated eligibility check before approval is granted. The

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[15] The TGA advised that certification is given by the TGA following a TGA audit confirming GMP compliance or following TGA's assessment of an acceptable certificate issued by an overseas regulator with which Australia has an agreement. See Chapter 2.

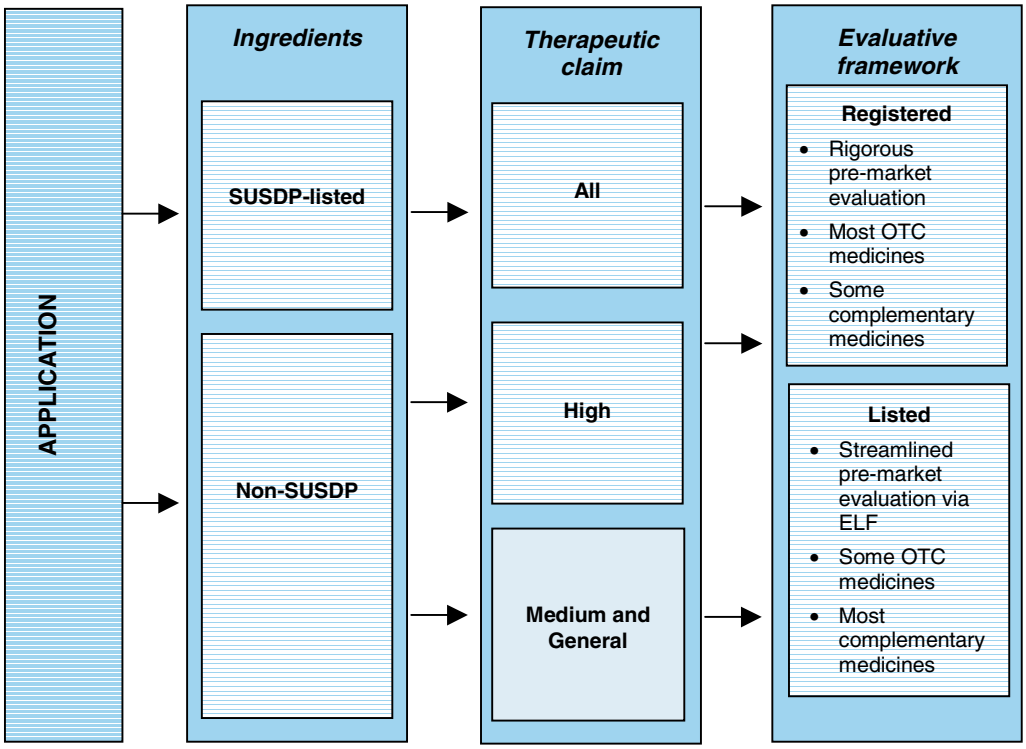
[16] Product packaging identifies an approved registered product by an AUST R number. Listed products are identified by an AUST L number.

product's sponsor must certify that appropriate supporting evidence is held. However, this evidence is not confirmed by the TGA prior to approval.

1.25 Most complementary medicines, and some OTC medicines, are listed.

Figure 1.3

Evaluation of non-prescription medicinal products



Source: ANAO analysis of TGA information.

Monitoring of products

1.26 After the TGA has registered or listed a non-prescription medicinal product, it may be manufactured and sold. The TGA undertakes monitoring to ensure that the product supplied to the market complies with its conditions of listing or registration. This monitoring includes, *inter alia*, investigating reports of unusual or unexpected reactions to the product, as well as conducting laboratory testing to give assurance on the product's quality.

1.27 If a product does not comply with the conditions of its listing or registration, the TGA can enforce a product recall and/or cancel the product's listing or registration.

This audit

Audit objective and scope

1.28 The audit's objective was to assess the TGA's regulation of non-prescription medicines, particularly the systems, procedures and resource management processes used to:

- confirm new manufacturers comply with requirements for the manufacture of non-prescription medicines;
- monitor manufacturers and medicines to ensure requirements continue to be met; and
- manage non-compliance.

1.29 The audit did not examine the regulation of prescription medicines, devices, or other therapeutic goods. It did not examine the TGA's pre-market evaluation of medicines; this was examined in part in a previous ANAO audit (see paragraph 1.39).

Audit methodology

1.30 The ANAO undertook fieldwork at the TGA's national office in Canberra. This involved: interviews; reviews of manufacturer files and related documentation; and examination of other paper and electronic documentation, data and systems. The ANAO also held consultations with external stakeholders, including industry associations, committees advising the TGA, and manufacturers regulated by the TGA.

1.31 The ANAO reviewed files relevant to the regulation of several non-prescription medicine manufacturers. These included large contract Australian manufacturers, small specialist manufacturers and overseas manufacturers. The ANAO observed several TGA audits of non-prescription medicine manufacturers.

1.32 The analysis of manufacturers for the audit addressed manufacturers of non-prescription medicinal products, except for a small number where these types of products are only a very small proportion of production.[17]

Data quality

1.33 The progress of this report, and its cost, have been adversely affected by limitations in the TGA's information and records management, and the reliability of information supplied.

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[17] For example, a manufacturer approved to produce around 350 prescription medicines, but only one OTC product, was excluded.

1.34 There have been many amendments and corrections to data supplied, some significant. In some instances, information required was only available on paper records, or electronic records were inconsistent with paper records. Amendments to information supplied continued to occur throughout the audit.

1.35 Some key decisions had not been documented, requiring searches of electronic records, and informal paper records, such as diaries and notebooks.

1.36 Where necessary, the ANAO has made its own estimates in key areas, for the purpose of this report.

Audit conduct

1.37 The audit was conducted in accordance with the ANAO Auditing Standards. The audit commenced in October 2003. Total audit cost was $998 000.

Previous ANAO audits

1.38 ANAO Audit Report No.12, 1995–96, *Risk Management by Commonwealth Consumer Product Safety Regulators*, included a number of recommendations for the TGA. These addressed risk-based scheduling of manufacturer audits; re-auditing frequencies; and response to manufacturers with major deficiencies against the Code of GMP.

1.39 ANAO Audit Report No.8, 1996–97, *Drug Evaluation by the Therapeutic Goods Administration*, addressed evaluation and approval of prescription drugs. Recommendations addressed, *inter alia*, adverse drug reaction reporting and cost-recovery. A follow-up audit report found substantial progress in addressing the recommendations.[18]

1.40 Audit Report No.24, 1999–2000, *Commonwealth Management and Regulation of Plasma Fractionation*, considered issues arising from the privatisation of the Commonwealth Serum Laboratories Limited (CSL).[19]

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[18] ANAO Audit Report No.2 2000–01, *Drug Evaluation by the TGA—Follow-up Audit*, p.12.

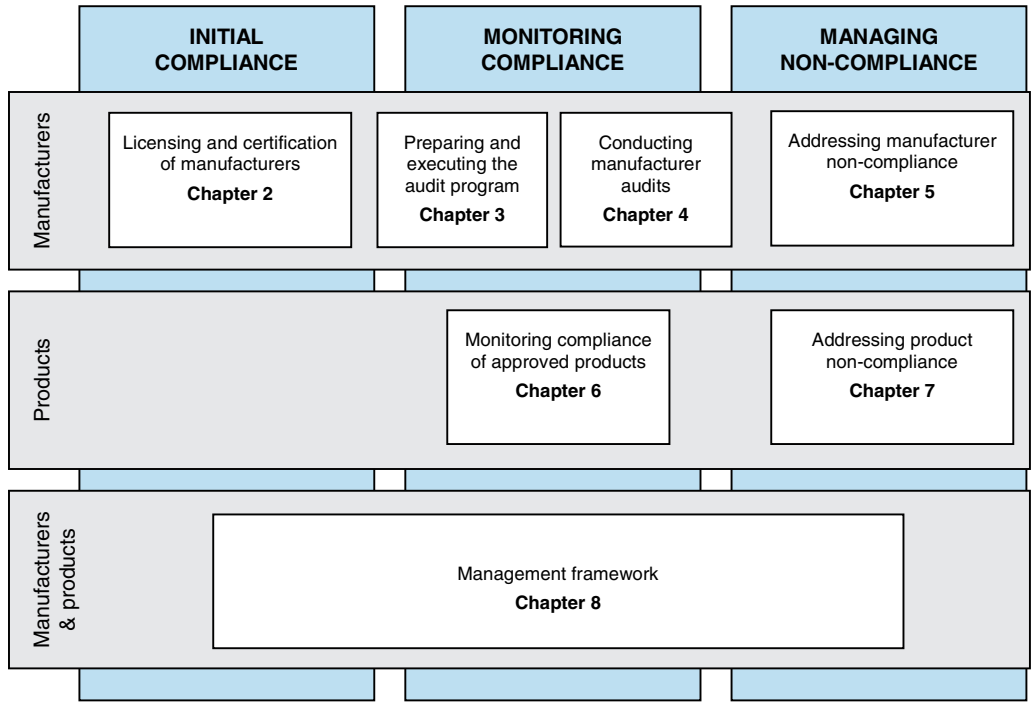
[19] The Commonwealth exercised an extension option to the Plasma Fractionation Agreement between itself and CSL Limited in June 2002. ANAO Audit Report No.4, 2003–04, *Management of the Extension Option Review—Plasma Fractionation Agreement*, examined the review process undertaken by the Department of Health and Ageing when formulating its advice to the Government on exercising this option.

Structure of this report

1.41 Figure 1.4 provides a diagrammatic summary of the report's structure.

Figure 1.4

Report structure



Source: ANAO

2. Licensing and Certification of Manufacturers

This chapter discusses the licensing of Australian manufacturers, and certification of overseas manufacturers, of non-prescription medicinal products.

Introduction

2.1 Manufacturer regulation is an essential element of the TGA's regulatory framework. The aim is that non-prescription medicinal products are produced with Good Manufacturing Practice (GMP) through all stages of manufacture and according to approved medicine formulations, to build quality into the medicines. This mitigates the need for an extensive post-market product testing program.[20]

2.2 The current Code of GMP was introduced on 16 August 2002.[21] It replaced a previous (1990) code. Manufacturers were granted a 12-month transition period to implement the new Code.

2.3 The Code is more outcomes based than its predecessor. That is, it describes the outcomes the manufacturing process should produce, rather than defining the process. It addresses: quality management; premises and equipment; personnel; documentation; production; quality control; contract manufacture and analysis; complaints and product recall; and self-inspection.

2.4 **Australian manufacturers** of non-prescription medicinal products are required to hold a manufacturing licence covering one or more sites where manufacture takes place.[22] TGA licences are perpetual. However, they are granted on the understanding that the TGA will undertake ongoing audits to confirm that the manufacturer remains compliant with the Code of GMP, and that the manufacturer pays the annual licence charge.

2.5 A manufacturer's licence lists the type(s) of products the entity is licensed to manufacture. It also identifies the manufacturer's quality assurance and production managers.

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[20] TGA, *Good Manufacturing Practice for Therapeutic Goods: What is Good Manufacturing Practice?* available from <http://www.tga.gov.au/docs/html/webgmp.htm#code> [accessed 7 September 2004].

[21] The Code is based entirely on the 2002 *Guide to Good Manufacturing Practice for Medicinal Products*, published by the PIC Scheme. This is the accepted international standard for the manufacture of medicinal products. It is applicable for all GMP agreements to which Australia is a signatory.

[22] A licence can cover multiple sites, provided they manufacture the same kind of product, and production and quality assurance at each site is controlled by the same persons nominated on the licence.

2.6 **Overseas manufacturers** supplying the Australian market are outside the jurisdiction of the Act. Instead, the Act requires the TGA to be satisfied that 'if a step in the manufacture of the goods has been carried out outside Australia…the manufacturing and quality control procedures used in the manufacture of the goods are acceptable.'[23]

2.7 Sponsors whose products are manufactured overseas must provide evidence that the products are manufactured to a standard of GMP equivalent to that expected of Australian manufacturers. A certificate of GMP compliance, issued by an overseas regulator with which Australia has a formal GMP agreement, is considered acceptable (see paragraph 2.27).[24]

2.8 If acceptable documentary GMP evidence cannot be provided, the TGA will itself undertake on-site audits, and certify the manufacturer if the audit finds compliance acceptable.

2.9 Figure 2.1 shows the ANAO's analysis of the number of non-prescription medicine manufacturing sites licensed or certified, as at 31 December 2003. Some 75 per cent are overseas manufacturers.

Figure 2.1

Licensed and certified non-prescription medicine manufacturing sites, 31 December 2003

Type	Number	Percentage
Australian sites licensed by the TGA	143	25
Overseas sites audited and certified by the TGA	95	16
Overseas sites certified by overseas regulators	345	59
Total	**583**	**100**

Source: ANAO analysis of TGA data.

Notes: The ANAO excluded a small number of manufacturers that produce predominantly prescription medicines.

The number of overseas sites certified by overseas regulators is a TGA estimate, as this information is not maintained on the TGA's management information systems.

Licensing of Australian manufacturers

Processing licence applications

2.10 Applicants for new licences for the manufacture of non-prescription medicinal products are audited to determine whether the applicant complies with the Code of GMP. The auditor has to be satisfied that the facilities, procedures and capabilities of staff are such that there is an assurance that,

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[23] *Therapeutic Goods Act 1989*, ss.25(1)(g), 25(2), 26(1) (g) and 26(2).

[24] The TGA may obtain the necessary confirmation directly from the overseas regulator.

once in production, the manufacturer will produce products that are safe, reliable and of consistent high quality.

2.11 The TGA carries out this audit according to its standard auditing procedures, which are discussed further in Chapter 4, along with interpretation and application of the Code of GMP.

2.12 After this audit, the TGA prepares a Deficiency Report. The manufacturer must provide evidence of acceptable corrective action for any deficiencies identified. The application is then subject to clearance by a TGA Review Panel.[25] Only then will the TGA issue a manufacturing licence.[26]

2.13 Figure 2.2 shows site licenses issued for the period 1999–2003.

Figure 2.2

Number of Australian sites licensed to manufacture non-prescription medicinal products, 1999–2003

Activity	Number of sites				
	1999	2000	2001	2002	2003
New sites licensed	15	9	7	11	6
Licence ceased	10	8	13	3	17
Sites licensed at 31 December each year	151	152	146	154	143

Source: ANAO analysis of TGA data.

Notes: In a small number of cases, a new site was added to an existing licence.

Licences cease because a manufacturer has moved to a new site; has stopped manufacturing; or has had its licence revoked by the TGA.

2.14 Over the five years 1999–2003, initial audits took, on average, one day to conduct. This is less time than for routine audits (see Figure 4.1) because the manufacturer was not yet producing medicines, so there is less for the auditor to examine.

2.15 Most applications for the manufacture of non-prescription medicinal products are accepted, although some manufacturers are subject to several TGA visits before the approval is granted. Four manufacturers had their licence applications disallowed between 2000 and 2003.

2.16 The practice of clearance by a Review Panel before a licence is issued provides an important assurance mechanism to address the risks presented by a new manufacturer. For example, one of the applications disallowed had provided an unsatisfactory response to deficiencies identified.

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[25] A Review Panel is a specially convened group, usually comprising three or more TGA auditors, including the Chief GMP Auditor. Review Panels are discussed further in Chapter 5.

[26] The TGA will also schedule a routine audit of the manufacturer between three and 12 months hence, to confirm compliance with the Code of GMP under production conditions. Routine audits are discussed further in Chapter 3.

Timeliness

2.17 The TGA's Standard Operating Procedures (SOPs) require new licence applicants to be scheduled for an audit as soon as possible.

2.18 The TGA does not have a standard or target for the time to conduct the audit and to issue a licence. As well, the TGA does not have performance indicators that measure the timeliness of these processes.

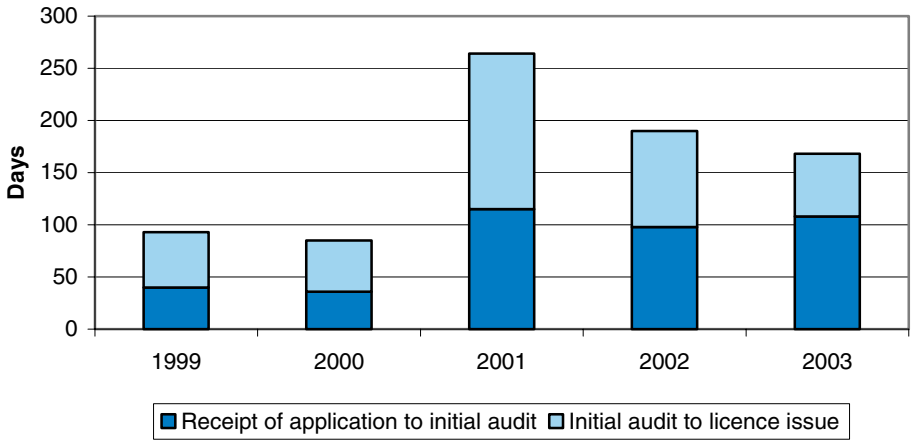
2.19 Figure 2.3 summarises actual times to issue a licence, separated into the period to undertake the audit, and the time to then issue the licence.

2.20 A number of factors, some beyond the TGA's control, affect the time taken to conduct licensing audits. For example, the TGA advised that, if a new manufacturer contacted them to discuss the application procedures, it would informally recommend application in advance of production readiness, so that it could schedule an audit for when the manufacturer would be ready. The TGA has now formalised this advice.[27]

2.21 Delays in the construction of a manufacturing plant may also delay audits. Data were not readily available to enable the ANAO to assess this.

Figure 2.3

Median number of days from application to issue of licence



Source: ANAO analysis of TGA data

2.22 After conducting the audit, the time taken to issue a licence may be affected by the need for the manufacturer to provide evidence of corrective action for deficiencies identified. An annual licence charge is also payable.

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[27] During this audit, the TGA changed the licence application form to advise manufacturers to submit applications four months in advance of when they expect to be ready for an audit. The four months advance notice allows the TGA to schedule the audit on its quarterly schedule in a timely manner.

2.23 The absence of reliable, and readily available, performance information on licensing processes limits the TGA's ability to manage and monitor this aspect of its regulatory process. Establishing performance indicators, targets and associated performance data would assist management to assess performance. Incorporating measures for those parts of the process under the TGA's control would enhance such information. They would also provide greater transparency to stakeholders, and an expectation of service standards.

2.24 The TGA advised that a new audit scheduling system will collect data on the time taken to issue a licence for Australian manufacturers, but not for certification of overseas manufacturers.[28]

Recommendation No.1

2.25 The ANAO recommends that the Department of Health and Ageing develop, and publish, suitable performance indicators and targets for the processes associated with the licensing and certification of non-prescription medicine manufacturers. The targets should be reflected in the TGA's customer service charter, and in decision-making and audit processes.

Departmental response

2.26 Agreed.

Certification by overseas regulators

2.27 There are approximately 345 overseas manufacturing sites whose certification by overseas regulators is accepted by the TGA under GMP agreements. These agreements cover manufacturers in 36 countries (see Appendix 2).

2.28 The TGA accepts certification by overseas regulators under two types of GMP agreement that have broadly similar effect, Mutual Recognition Agreements (MRAs) and Memorandum of Understanding (MOU)/cooperative arrangements. See Figure 2.4.

[28] The new audit scheduling system is discussed further in Chapter 3.

Figure 2.4

Two types of agreements between Australia and overseas countries

Agreement	Context
Mutual Recognition Agreement	Legally binding instruments between Australia and one or more countries. The countries have been assessed as having GMP standards equivalent to Australia. The agreements provide for the mutual recognition of manufacturer audits. That is, other signatories must accept determination of GMP compliance by one signatory. Australia is a signatory to five MRAs, covering 32 countries.
Memoranda of Understanding/ cooperative arrangements	Arrangements designed to facilitate exchange of information. GMP determinations are not binding on the signatories. The TGA will accept such determinations as proof of GMP compliance unless exceptional circumstances arise. Australia is a party to three arrangements. These are an MOU with Japan, and cooperative arrangements with the United States of America and as a member of the multilateral PIC Scheme.[29]

Source: TGA

2.29 Not all countries with which Australia has an MRA or an MOU/cooperative arrangement regulate complementary medicines to standards equivalent to Australia. For example, in the United Kingdom and New Zealand, most vitamin and mineral products are regulated as food. The TGA advised that, in Canada, the medicines regulator does not audit complementary medicines manufacturers, but has a system of self-certification of GMP compliance by those manufacturers. As this approach does not meet Australian standards, the TGA does not accept a Canadian certification of complementary medicine manufacturers. Consequently, the TGA will either request the regulator to conduct an audit, or conduct its own audit.

2.30 The TGA relies substantially upon GMP agreements. Establishing regulatory equivalence to Australian standards prior to entering into a GMP agreement, and reassessing ongoing equivalence, is therefore necessary. This provides assurance that certifications issued by regulators meet Australian requirements.

Assessment of equivalence prior to signing agreement

2.31 Prior to signing an MRA, each regulator carries out a systematic assessment of the other signatories. The aim is to confirm that standards and procedures are equivalent for mutual recognition.

2.32 However, this is not common practice prior to signing an MOU/cooperation arrangement. For example, for one country, the TGA advised that there was already a mutual understanding of each country's regulatory practices, based on several years of working together, hence a systematic assessment was not required.

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[29] There are 27 members of the PIC Scheme, including Australia. Of these, only Canada and Malaysia do not have an MRA with Australia. The MRAs prevail over the PIC Scheme agreement, to the extent that the MRAs allow for full mutual recognition of manufacturer audits.

Monitoring ongoing equivalence

2.33 Most countries with whom Australia has an MRA or MOU/cooperation arrangement are also members of the Pharmaceutical Inspection Cooperation Scheme (PIC Scheme). The PIC Scheme has recently initiated a formal program of peer reassessment and review. This provides the TGA with assurance that the majority of countries with which Australia has an agreement are maintaining their standards of GMP assessment.

2.34 However, the TGA does not have a formal mechanism for reassessing equivalence with countries that are not members of the PIC Scheme. The ANAO found that, while some monitoring of GMP agreements had been undertaken, reassessments have been done on an informal basis only. For example, one country recently sent two officers to Australia to meet with TGA officials and observe the conduct of a TGA audit. TGA auditors also meet with this country's officials, on an irregular basis, when in the country conducting audits.

2.35 Some MRAs and MOUs were established several years ago. The MOU with Japan was established in 1993, but has not been revised since. The number of products supplied from Japan has increased since 1993, but there have not been any reassessments to ensure that standards remain appropriate. The TGA has acknowledged the need to reconfirm equivalence and either reaffirm the MOU, or arrange an MRA.

Change to the EU MRA

2.36 On 1 May 2004, 10 countries joined the European Union (EU) (see Appendix 2), and became part of Australia's MRA with the EU. In July 2004, the TGA informed the EU that it will not accept certifications from the medicines regulators in the new EU member countries until it is satisfied that they regulate therapeutic goods manufacturers to a standard equivalent to Australia.[30]

2.37 This is possible because a provision in the EU MRA permits a member to refuse to accept a certificate from another member regulator, and to conduct its own compliance audit. The TGA advised that it has twice used this provision to conduct its own audits of prescription medicine manufacturers in European countries.

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[30] The TGA is planning to work with the Canadian medicines regulator to establish the regulatory equivalence of the 10 new EU member countries with standards applying in Australia and Canada.

Consultations and liaison

2.38 The majority of MRAs and MOUs/cooperative arrangements provide for regular meetings between signatories. The meetings aim to provide assurance that:

- GMP auditing standards are consistent across the signatories;
- training of GMP auditors is uniform and reflects best practices; and
- auditing guidelines and documents lead to consistent outcomes.

2.39 In addition, the members of the Pharmaceutical Inspection Convention (PIC) and the PIC Scheme conduct seminars and training sessions on issues related to the regulation of therapeutic goods. Officials meet on a regular basis. They exchange experiences on means and methods for achieving appropriate and effective audits of manufacturers; discuss the interpretation of current manufacturing standards; and hold training sessions.

2.40 TGA officers attend annual seminars, executive meetings and expert circles convened by the PIC Scheme. As Chair of the PIC Scheme during 2000 and 2001, the TGA attended several executive meetings, seminars and training programs. However, in general, attendance by TGA auditors at such meetings is dependent upon the ability of the TGA to align inspections of overseas manufacturers located in the same region as the meetings.

Funding MRA and MOU/cooperative agreement maintenance

2.41 The TGA's 2003–04 business plan included a target to implement and maintain agreements with respect to pharmaceutical GMP. However, this target is not supported by a strategic plan and appropriately allocated funding.

2.42 A strategic plan to manage, fund and maintain these agreements, including regular monitoring of the performance of overseas regulators, would increase assurance that overseas standards continue to be equivalent to those in Australia, for the benefit of all stakeholders.

Recommendation No.2

2.43 The ANAO recommends that the Department of Health and Ageing, taking into account any international agreements, develop a strategic management plan to monitor the regulatory equivalence of countries with which it has GMP agreements, including:

- standards and procedures to be monitored;
- performance measures and targets to be monitored;
- the currency of the agreements;
- resources required to monitor equivalence, including management arrangements; and
- reporting arrangements.

Departmental response

2.44 Agreed.

Certification of overseas manufacturers by the TGA

2.45 There are 95 overseas manufacturing sites audited and certified by the TGA.[31] Audits of these overseas sites are conducted by the TGA when:

- there is no GMP agreement with the country;
- there is a GMP agreement, but the overseas regulator does not regulate complementary medicines as therapeutic goods; or
- the TGA chooses not to accept the result of an audit conducted under an MOU/cooperative arrangement.

2.46 As with Australian manufacturers, most applications from overseas manufacturers are rated acceptable by the TGA. The TGA estimates that seven manufacturers of non-prescription medicinal products have had their applications refused since 1999. The majority of these were refused certification because non-conformities identified during the audit were not rectified to the satisfaction of the TGA's Review Panel.

2.47 As the TGA does not capture the required information, the ANAO was unable to analyse the time taken to conduct certification audits. However, the

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[31] 33 sites are in the USA; 25 in China; and 10 in India. The remaining sites are in 11 other countries, including Thailand, South Africa, Hong Kong, and the Philippines.

TGA advised that, as at April 2004, 21 overseas manufacturers of non-prescription medicinal products were awaiting GMP certification audits by the TGA. While the majority had been received in the second half of 2003, several were more than 12 months old.

2.48 The TGA attributes some of this backlog to factors limiting its ability to conduct audits overseas. These include the Iraq war and the Severe Acute Respiratory Syndrome (SARS) outbreaks in South-East Asia. The ANAO notes that some one-third of the backlog were Chinese manufacturers. However, SARS-related travel restrictions for China only applied for a four-month period in 2003.

2.49 The TGA has also accepted and processed applications for GMP certification from overseas manufacturers that do not have an Australian sponsor. In some instances, manufacturers have indicated that they have, at least in the short term, no intention of producing products for the Australian market.

2.50 The ANAO considers that accepting and processing such applications risks diverting scarce auditor resources from key regulatory work. This could result in the deferral of GMP audits of overseas manufacturers with a sponsor. Scheduling of audits is discussed in the next chapter.

3. Preparing and Executing the Audit Program

This chapter discusses how the TGA prepares and executes its audit program.

Introduction

3.1 There are three types of manufacturer audits conducted by the TGA:

- audits undertaken to licence or certify a manufacturer (see Chapter 2);
- routine audits. These aim to provide assurance that manufacturers continue to comply with mandated standards; and
- special audits. These result from tip-offs, complaints, product recalls and surveillance activities. They are accorded high priority, and usually address compliance with specific aspects of the Code of GMP.

3.2 The TGA does not record whether audits are licensing, routine or special audits. Recording this information would facilitate forward planning and scheduling of audits.

3.3 The ANAO made estimates of audit type, although there was insufficient information to separate routine and special audits. The estimates are shown in Figure 3.1 for the years 1999–2003.

Figure 3.1

Number of non-prescription medicine manufacturer audits, 1999–2003

	Type of audit	1999	2000	2001	2002	2003
Australian audits	Licence	19	14	14	13	7
	Routine/special	86	84	66	59	63
	Total Australian audits	**105**	**98**	**80**	**72**	**70**
Overseas audits	Certification	26	31	20	14	9
	Routine/special	9	24	27	37	14
	Total overseas audits	**35**	**55**	**47**	**51**	**23**
	Total	**140**	**153**	**127**	**123**	**93**

Source: ANAO analysis of TGA data.

Note: Includes audits not finalised as at 31 December 2003.

Determining due date for routine audits

Overall approach

3.4 At the conclusion of an audit, the TGA determines the date for a manufacturer's next routine audit. This is a risk-based process, intended to ensure the highest-risk manufacturers receive priority for an audit.

3.5 An audit frequency matrix[32] determines the time to next audit, based upon two risk parameters. The first is the manufacturer's risk rating, which is based upon the products it makes. The second is the GMP compliance rating, which is based on the findings of the current audit. This matrix applies for all types of medicine manufacturers. It is described in Figure 3.2.

Figure 3.2

Audit frequency matrix (months to next audit[33])

Manufacturer risk	GMP compliance rating			
	Acceptable			Unacceptable
	High	Satisfactory	Minimal	
High risk	24	18	12	Determined by Review Panel
Medium risk	30	20	12	Determined by Review Panel
Low risk	36	24	12	Determined by Review Panel

Source: TGA

3.6 The rationale for assigning the specific audit frequencies for given risk parameters has not been documented. That is, a systematic risk analysis has not been undertaken in support of the audit frequency matrix, nor has the matrix been evaluated since its introduction. The TGA's information systems do not contain some of the information necessary to do such analyses.

3.7 The ANAO considers it good management practice to support the identification and application of such risk parameters with appropriate data analysis.

3.8 Evaluation of audit frequencies would provide assurance that the months to next audit effectively controls identified risk.

Discretionary judgment

3.9 The TGA lead auditor has discretion to vary time to next audit from that in the risk matrix, having regard to factors other than those in the risk

[32] Introduced in July 2001.

[33] Excludes the first audit after licensing. This time is set at 12, six, or three months, depending on whether the licensing audit assessed GMP compliance as high, satisfactory or minimal respectively.

matrix. The reasons for the change must be documented on the Audit Log Sheet.[34]

3.10 The use of this discretionary judgment is relatively uncommon. It generally leads to shorter times to next audit. However, the ANAO found that the required documentation often did not occur. The ANAO considers that such documentation is required for sound management, including transparency and accountability.

3.11 The TGA advised during this audit that all manufacturer audits will in future be reviewed by senior audit management, prior to issuing a final audit report. The use of discretionary judgments will be included in these reviews. The ANAO considers that documentation of these judgments is a key aspect of any such review.

3.12 The ANAO also found that the TGA's SOPs provide conflicting advice on the frequency matrix and use of discretion. Clarification would enhance accountability and management effectiveness.

Manufacturer risk category

3.13 A manufacturer is categorised as high, medium or low risk, according to the type of product it produces. TGA SOPs outline the procedures. For example, herbal medicine manufacturers are medium risk, and mineral and vitamin products manufacturers are low risk. If a manufacturer produces two or more products, the highest-risk product determines the risk rating.

3.14 The manufacturer's risk is categorised at initial licensing and entered onto the TGA's electronic database. The rating is not reviewed unless the list of products approved for manufacture changes.

3.15 The ANAO reviewed risk ratings for a sample of overseas manufacturers for which audits had been conducted. More than half did not have the risk rating recorded on the TGA's database.

3.16 The ANAO examined Australian manufacturers for one type of product.[35] Some had the wrong risk rating on the database (although the time to next audit had been calculated accurately, as it was based upon paper files). One had the wrong rating on the paper file and the database. This led to a longer scheduled time to next audit than procedures require.

3.17 The TGA expects to introduce a new management information system to support the manufacturing audit function (see paragraphs 3.35–3.36). As

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[34] The Audit Log Sheet is used to record details of an audit. Part 1 is completed at the end of the on-site phase of an audit. Part 2 is completed after close out of the audit.

[35] Non-sterile herbal therapeutic goods for human use.

this system will automatically schedule audits according to the frequency matrix, the need for reliable records to support sound risk-based management of the audit process is reinforced. Current practices do not achieve this, and are inconsistent with defined procedures.

GMP compliance rating

3.18 A manufacturer's level of GMP compliance is assessed at the completion of an audit (see Figure 3.3).

Figure 3.3

Classification of GMP compliance

Compliance	Rating	Comment
High	A1	
Satisfactory	A2	TGA-defined classification.
Minimal	A3	Adopted July 2001.
Unacceptable	U	

Source: TGA

3.19 The classification categories have changed four times since 1992—see Appendix 3.

3.20 The degree of acceptable compliance (i.e. high; satisfactory; or minimal) is not recorded on the TGA's electronic database. This limits the usefulness of the information available to management to assist in assessing audit outcomes and compliance trends.

3.21 How compliance is assessed in audits is discussed in Chapters 4 and 5.

Recommendation No.3

3.22 The ANAO recommends that the Department of Health and Ageing strengthen the management of, and accountability for, the process for assigning GMP audit frequency by:

- articulating the rationale for audit frequencies, based upon systematic risk analysis, and undertaking regular evaluation of their appropriateness;
- ensuring that reasons for use of discretion in setting audit frequency are documented;
- maintaining reliable records of risk ratings, and supporting information; and
- recording the degree of acceptable compliance.

Departmental response

3.23 Agreed.

Scheduling audits

3.24 At the commencement of each calendar year, the Audit Scheduler[36] prints out a list of the manufacturers due for a routine audit during that year. This list forms the basis of the audit schedule for the first quarter. The annual list is not used thereafter, and is not retained. Thereafter, the quarterly schedules are drawn up at the start of each quarter.

3.25 The TGA advised that, as part of its quarterly scheduling process, it prioritises manufacturer audits in descending order as follows:[37]

- special audits;
- licensing audits;
- priority routine audits that are past their due date;
- priority routine audits becoming due;
- certification audits; and
- lower-priority routine audits.

3.26 All selected audits are consolidated onto a quarterly schedule. The audits are allocated to a lead auditor, who is responsible for determining the timing, planning and conduct of the audit. Some audits on the schedule are flagged as 'high priority' (or urgent), for completion during the quarter.

Selecting special audits

3.27 The need for a special audit can arise at any time. Tip-offs, product recalls or adverse reactions may require the TGA to conduct a limited, focused audit of a manufacturer as a matter of urgency.

3.28 The decision to undertake a special audit is the responsibility of the Chief GMP Auditor, who sets its priority and when it is to be scheduled. If auditor resources are fully committed, the scheduler is advised which programmed audit(s) to reschedule.

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[36] An auditor with responsibility for scheduling manufacturer audits for the TGA.

[37] Based on TGA advice. Prioritisation of types of audits is not documented in an SOP.

Selecting routine audits

3.29 The TGA assigns a priority to each routine audit, having regard to whether they are considered high-risk or not. There is a SOP that guides this process. Risk factors taken into account include: product recalls since last audit; product complaints since last audit; and results of product testing.

3.30 The TGA advised that the prioritisation process should involve a detailed review of manufacturers' records for each of the possible routine audits. In addition, there should be a review of information held in other areas of the TGA, such as recalls and complaints.

3.31 However, much of this information is held on paper files. Key data are not held electronically. For example, the detailed GMP compliance ratings assigned to each manufacturer are not on the electronic database. This is also the case for supplementary information regarding potential risk factors, such as any problems identified at the previous audit.

3.32 In addition, current information systems do not facilitate efficient and cost-effective risk assessments. For example, information collected by other parts of the TGA, such as the recalls section, the product regulators, and laboratories is held by the individual sections.

3.33 The TGA advised that other fields on the electronic database may be used for such information. However, the ANAO found that few audit records use this facility. Where it is used, the information held tends not to address the other risk factors required by the scheduler.

3.34 Accordingly, the assessments to support risk assessment and prioritisation for scheduling would require an extensive manual search process every quarter. Resources are not diverted to assist the scheduling auditor. There are, therefore, practical constraints on the effectiveness of the assessments made. Better capture and retrieval of information would improve the efficiency and consistency of the process.

3.35 The TGA has recognised the need to strengthen this aspect of scheduling. A computerised audit scheduling system is being developed to, among other things, automatically prioritise and schedule audits.

3.36 The TGA has advised that the new system is likely to be introduced before the end of 2004.[38] However, it was originally scoped in May 2002. Prompt introduction of the system, allied to arrangements to ensure reliability and completeness of data, would provide a more accessible, robust and reliable basis for prioritisation and scheduling of audits.

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[38] The TGA further advised that it will be the first international regulator to introduce such a system.

Monitoring the audit program

3.37 Sound arrangements for monitoring work programs seek to establish outcomes against schedule, and the impact of any shortfall. However, the ANAO found that the initial quarterly audit schedules are not retained by the TGA for such analysis.

3.38 The schedules are modified on an ongoing basis during the quarter, for example to add some unscheduled audits to be conducted as a priority. However, this does not happen consistently. The TGA advised this was because it was concerned that this information may be unintentionally leaked to manufacturers. The ANAO considers that strengthening security in this area would enable the TGA to improve its record-keeping.

3.39 Scheduled audits deferred because of the addition of unscheduled audits remain on the quarterly schedule.

3.40 The ANAO considers that these practices limit the TGA's ability to assess, and be accountable for, its performance in the execution of audit scheduling.

Recommendation No.4

3.41 The ANAO recommends that the Department of Health and Ageing:

- establish systems for the collection of management and performance information to enable it to assess performance in the execution of the GMP audit program; and
- assess the impact on TGA's regulation of manufacturers, including the risk of undetected non-compliance, from failure to achieve a GMP audit program consistent with risk profiling.

Departmental response

3.42 Agreed.

Executing the audit program—Australian manufacturers

Out-turn against schedule

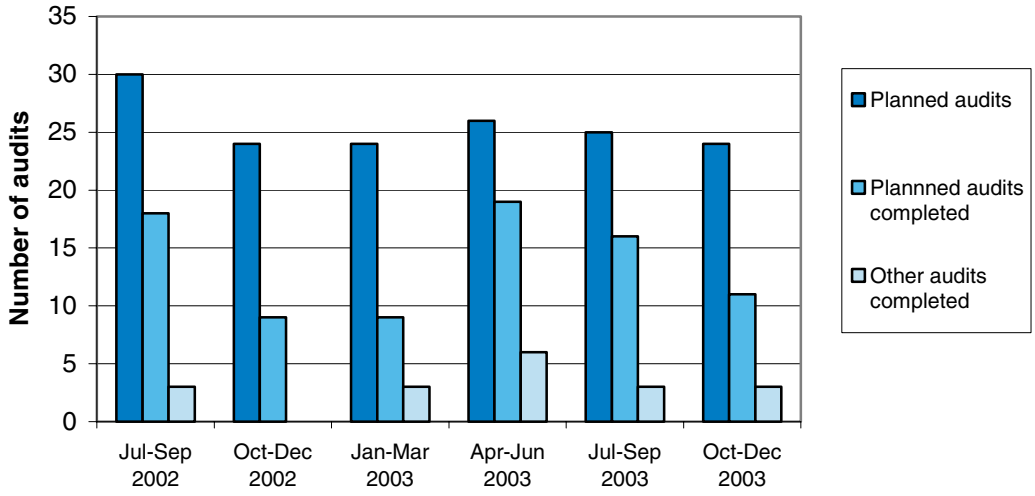
3.43 The number of audits undertaken in each quarter has been below the level planned by the TGA,[39] as illustrated in Figure 3.4. Over the 18 months to December 2003, 82 audits on the quarterly schedule were undertaken. That is,

[39] The ANAO estimated planned initial TGA audit schedules for six quarters from TGA data. Because of data limitations, this involved some approximations. The TGA does not retain schedules, even in adjusted form, for more than six quarters.

on average, just over half of each quarter's schedule was completed. The remaining audits were either held over to the next quarter, or deferred.

Figure 3.4

Scheduled and completed audits: Australian non-prescription medicine manufacturers, July 2002–December 2003



Source: ANAO analysis of TGA data.

3.44 An additional 18 unscheduled audits were undertaken, resulting in a total of 100 audits for the period.

3.45 Planned audits in Figure 3.4 include those rolled over from earlier quarters' plans. Accordingly, Figure 3.5 shows audits scheduled and conducted during 2003. It indicates that 31 per cent were not conducted in the quarter first scheduled. In addition, 19 audits scheduled for 2003 were not completed in that year. Some had been rolled over for several quarters.

3.46 The TGA advised that the total number of audits conducted over 2003 was consistent with its overall target.

Figure 3.5

Australian non-prescription medicine manufacturer audits conducted in 2003

	Number of quarters audit scheduled before being completed			
	One	Two	Three	Four
Number of audits	38	8	5	4
Per cent of audits	69	15	9	7

Source: ANAO analysis of TGA data.

3.47 The ANAO found that three high priority audits were added to the audit schedule, but were not completed in the quarter programmed. The TGA advised that these were deferred to undertake urgent audits of manufacturers of higher risk products. However, the ANAO found that other non-priority audits of low or medium-risk manufacturers were conducted, rather than being deferred. The TGA advised that it is sometimes appropriate and efficient to conduct low priority audits, particularly where travel to a specific location is involved.

3.48 One of these priority audits was added to the schedule in May 2003. It was not conducted until early 2004.

Impact on audit frequency

3.49 Failure to complete audits in accordance with the schedules increases the risk that audits are not conducted by their due dates. The ANAO compared planned and actual audit dates for recent routine/special audits. The analysis used available data for Australian manufacturers only.[40]

3.50 On average, the non-prescription medicine manufacturer audits examined had a due date of 16 months after the previous audit. The actual time taken to conduct the audits averaged 22 months—that is, six months later.

3.51 Some 80 per cent of the audits were conducted later than their due dates. Some were conducted much later than their due dates. The TGA advised that, because of changing priorities, the timing of when an audit is conducted can vary from its scheduled date.

Audits due, but not conducted

3.52 At 31 December 2003, some 40 per cent of Australian non-prescription medicine manufacturers were due for a routine audit, but the audit had not been conducted (see Figure 3.6).

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[40] Based on the most recent audit undertaken for each manufacturer for the five years 1999–2003, using available TGA data.

Figure 3.6

Routine audits of Australian non-prescription medicine manufacturers due, but not conducted, as at 31 December 2003

Audits due but not conducted	Months past due date					Total audits past due date	Per cent of manufacturers
	1-3	4-6	7-12	13-18	19-24		
On the schedule	1	1	1	1	1	5	3
Not scheduled	10	10	13	13	8	54	38
Total	**11**	**11**	**14**	**14**	**9**	**59**	**41**

Source: ANAO analysis of TGA data

Note: The TGA advised that three of these audits were conducted in December 2003, but were not on electronic audit records supplied to the ANAO.

3.53 The TGA advised that it aims to complete audits between three months before, and six months after, the due date. It does not consider an audit 'overdue' until it is six months past its due date.[41] Its performance target is that all audits are conducted within six months of the due date.

3.54 However, the TGA did not meet this target. 26 per cent of non-prescription medicine manufacturers were due for audits, but had not been audited by six months after the due date.

3.55 However, as noted in paragraph 3.20, the detailed compliance ratings are not held on the TGA's electronic systems. Accordingly, the risk consequences of rescheduling audits are not readily assessable, for action by management, and accountability to stakeholders.

3.56 Systematic delay in conducting audits creates the risk that regulatory risk treatments are not well aligned with risk profiles. When this occurs, sound information on the potential impacts is necessary, to assist the regulator to make the necessary risk-based judgments.

Executing the audit program—overseas manufacturers

Out-turn against schedule

3.57 For three of the six quarters examined in this audit, the TGA did not prepare specific audit schedules for overseas manufacturers.[42] Instead, the TGA identified the number of days each auditor was to spend in each overseas country, not the audits to be conducted. The ANAO considers that this practice further limits the TGA's ability to target, manage, and monitor its audit program against risk profiles.

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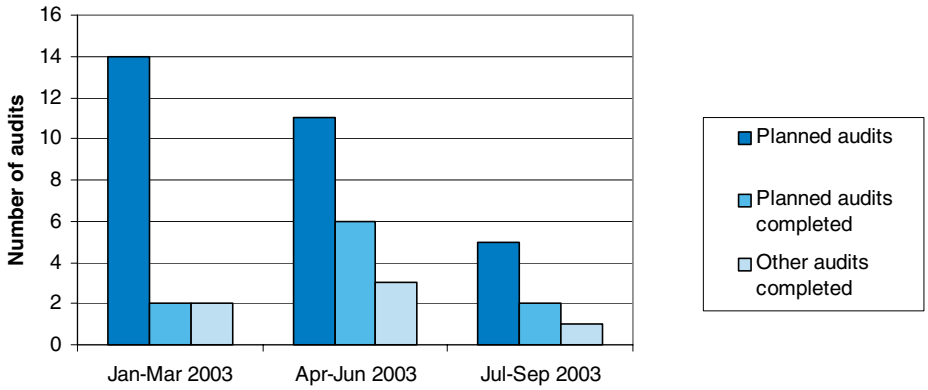
41 This practice is considered by the TGA to be consistent with international best practice. It had not been formalised, but TGA SOPs were updated during this audit to reflect the practice.

42 July to September 2002, October to December 2002, and October to December 2003.

3.58 Figure 3.7 summarises out-turn against the ANAO's estimated schedule for the remaining three quarters. On average, one third of each quarter's schedule was completed. The remaining audits were either held over to the next quarter, or deferred. Six unscheduled audits were conducted.

Figure 3.7

Scheduled and completed audits: overseas non-prescription medicine manufacturers, January–September 2003



Source: ANAO analysis of TGA data.

Impact on audit frequency

3.59 The ANAO examined the time between audits of overseas non-prescription medicine manufacturers.[43] On average, the audits examined had a due date of 21 months after the previous audit. The actual time taken to conduct the audits averaged 30 months—that is, nine months later. These planned and actual times to next audit are substantially greater than for Australian manufacturers (paragraph 3.50).

3.60 Some 70 per cent of the audits examined were conducted later than their due dates. There were a number of audits where the delays were substantial.

3.61 The TGA advised that the complexities of travel restrictions in relation to SARS,[44] civil unrest and war have impeded its ability to execute its overseas audit program, particularly in the Asian region.

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[43] Analysis undertaken on same basis as for Australian audits (see paragraph 3.49).

[44] SARS travel advisories warned against non-essential travel to China and nearby countries for the period 26 March–25 June 2003.

Audits due, but not conducted

3.62 At 31 December 2003, some 40 per cent of overseas non-prescription medicine manufacturers were due for a routine audit that had not been conducted by the due date. Over half of these were more than six months past their due date—the TGA's performance target. See Figure 3.8.

Figure 3.8

Routine audits of overseas non-prescription medicine manufacturers due, but not conducted, as at 31 December 2003

Months past due date								Total no. of audits past due date	Per cent of manufacturers
1-3	4-6	7-12	13-18	19-24	25-36	37-48	49-60		
12	5	6	9	2	3	2	1	40	42

Source: ANAO analysis of TGA data.

Notes: The ANAO was unable to estimate how many audits had been scheduled, but not conducted.

There were a further nine audits more than six months past their due date. However, the TGA advised that it had confirmed their GMP compliance through audits conducted by overseas regulators subject to MOU/cooperative arrangements with Australia. Most of the manufacturers were located in the USA. The TGA advised that this was a temporary measure and intends to conduct its own audits of these manufacturers in the future.

3.63 The TGA advised that it considers that very few of the audits in Figure 3.8 are overdue. This is, in part, because it does not consider audits overdue until they are more than six months past their due date.

3.64 However, the TGA has also been prepared to accept manufacturers as GMP compliant on the basis of assessments by regulators in countries where Australia has no MRA, MOU or other cooperative arrangements. Figure 3.9 provides an example. In another example, there was a seven-year gap between TGA audits for a Taiwanese manufacturer.[45]

Figure 3.9

A herbal and homoeopathic medicine manufacturer in the People's Republic of China was last audited by the TGA in 1998. The next audit was scheduled for 2000. The TGA advised that it attempted to schedule audits but two were postponed because of SARS. The TGA advised that Chinese authorities have regularly inspected the manufacturer. The TGA scheduled the next audit of this manufacturer for mid-late 2004, six years after the last TGA audit.

Source: ANAO analysis of TGA data.

3.65 The ANAO notes that the TGA conducts audits of overseas manufacturers when it is not satisfied that the level of regulatory oversight in a country is equivalent to Australia's standards. The practice of accepting an assessment from a country without a cooperative agreement reduces regulatory assurance that overseas manufactured products are compliant with Australian standards.

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[45] Taiwanese authorities undertook one audit during this period, at the request of the TGA.

3.66 The TGA also advised that it has rescheduled the due date for some of the overdue audits because of adverse international circumstances. Figure 3.10 provides an example. The ANAO notes that similar practices are not acceptable for Australian manufacturers.

Figure 3.10

An Indonesian manufacturing site that produces non-sterile medicines (risk rating 'medium') was last audited by the TGA in May 2000. The next audit was set for November 2001. The TGA advised that scheduling was attempted several times, but ongoing travel advisories warned against travel to Indonesia. The TGA further advised that the manufacturing site had a good standard of GMP at the 2000 audit, and no problems had been reported since. The inspection date was reset to December 2003. As at August 2004, no audit had been conducted.

Source: ANAO analysis of TGA data.

3.67 In summary, audits of overseas manufacturers are planned to be conducted at longer frequencies than for Australian manufacturers, and are subject to more slippage. The TGA does not have the management information to assess whether the longer planned frequency is consistent with risk profiles. Nor do information sources enable the TGA to assess the impact of slippage on management of risk, for both overseas and Australian manufacturers.

3.68 The TGA's decisions that some manufacturers have acceptable compliance on grounds other than a TGA audit is not supported by systematic risk-based processes. Nor are these decisions documented. Such regulatory discretion warrants more rigorous processes.

3.69 The ANAO also notes that several overseas manufacturers are located in countries that may continue to be subject to irregular and unpredictable circumstances. These have the potential to undermine the TGA's ability to conduct compliance audits according to its risk assessments and treatments.

3.70 The TGA has not prepared and documented contingency plans to confirm ongoing GMP compliance of overseas manufacturers. Such plans would provide assurance that, when international events prevent it from executing the audit program, it has appropriate strategies to address the risk of increased non-compliance.

Recommendation No.5

3.71 The ANAO recommends that the Department of Health and Ageing establish contingency plans, consistent with the TGA's regulatory responsibilities, to address the risk of delays in the execution of the overseas GMP audit program.

Departmental response

3.72 Agreed.

Addressing the audit backlog

3.73 The ANAO estimates that it would take over 2000 hours effort to complete routine non-prescription medicine manufacturer audits past their due date.[46] This represents a relatively substantial effort. It compares with some 1800 hours spent auditing non-prescription medicine manufacturers in 2003 (see Appendix 4).

3.74 The TGA is planning to increase the number of permanent GMP auditors from 15 to 20, and engage an additional 10 contract auditors. The auditors will be utilised across all therapeutic goods. However, in the absence of a strategic resourcing plan, allied to the audit program, it is not clear how this will impact on the backlog of audits for non-prescription medicine manufacturers.

3.75 The TGA advised that it does not consider that the risk of a non-prescription medicine manufacturer producing unsafe products increases because the manufacturer has not been audited according to the risk treatment defined in SOPs. It commented that there are other safeguards, such as adverse reaction reporting, that may identify whether an audit should be conducted as a matter of priority.

3.76 However, the SOPs reflect the intended assessment and treatment of risk of a manufacturer producing a harmful product. Divergence from these procedures, to the extent identified in this audit, undermines assurance that this risk is being managed appropriately.

3.77 This warrants a broader assessment of the implications for managing the risk of undetected non-compliance than has occurred.

[46] Based upon average 2003 audit effort.

4. Conducting Manufacturer Audits

This chapter discusses the TGA's manufacturer audit process.

Resourcing audits

4.1 The average auditor effort for on-site inspections of non-prescription medicine manufacturers is shown in Figure 4.1.[47] There was a marked increase in 2003.

Figure 4.1

Average on-site hours recorded on the conduct of non-prescription medicine manufacturer audits, 1999–2003

Audits	1999	2000	2001	2002	2003
Australian manufacturers	11	10	11	12	25
Overseas manufacturers	13	13	12	12	17

Source: ANAO analysis of TGA data.

Notes: Excludes licence and certification audits. These averaged some 7 hours and 13 hours respectively, with no increase in effort in 2003.

The 2003 average for Australian manufacturers was 21 hours excluding audits relating to Pan Pharmaceuticals Limited.

4.2 Over the period 1999–2002, the on-site inspection phase of some two-thirds of Australian audits was completed in one day or less—see Figure 4.2 . For overseas manufacturers, the comparable figure was 30 per cent.

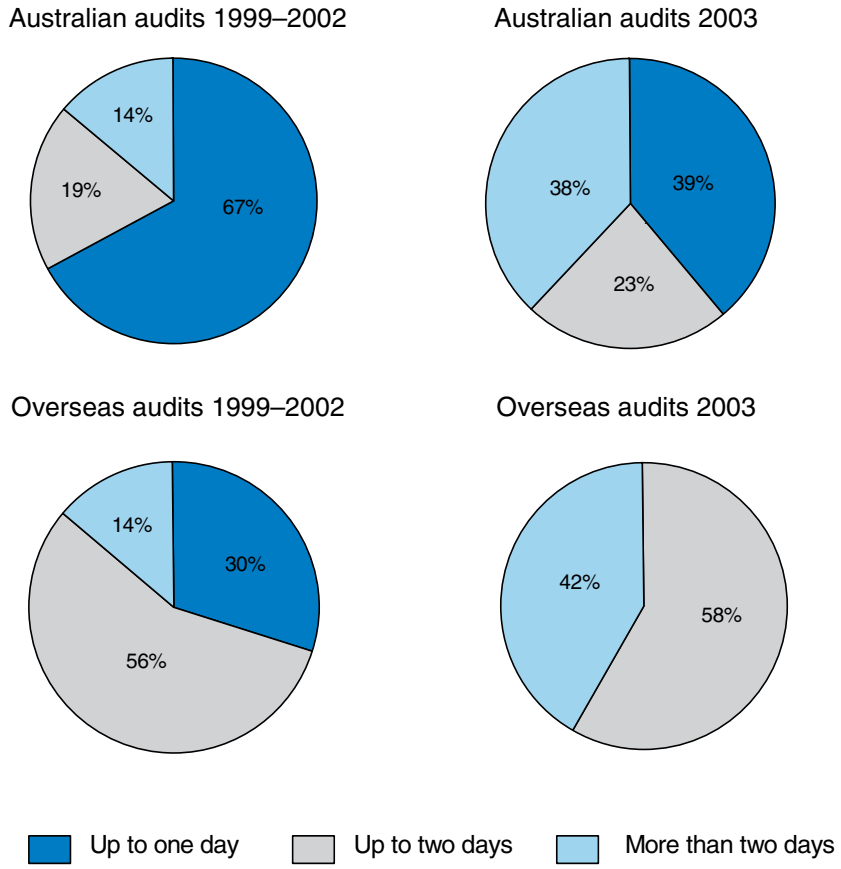
4.3 The limited extent of on-site inspection would have constrained the degree to which a manufacturer's compliance with the full Code of GMP could be assessed. That is, a limited range of standards would have been assessed.

4.4 The TGA advised that the increase in 2003 was a risk-based decision following the Pan Pharmaceuticals Limited action. Non-prescription medicine manufacturers were targeted in the audit program. The TGA increased the length of audits; the number of officials involved; and the use of unannounced audits (see paragraph 4.9). The TGA also advised that the changes were consistent with best practice—bigger teams are better able to assess compliance with a broader range of the standards.

[47] The TGA only records effort conducting the on-site phase of an audit. Preparation and close out effort are not recorded.

Figure 4.2

Effort on audits of non-prescription medicine manufacturers, 1999–2003



Source: ANAO analysis of TGA data.

Note: Excludes licence and certification audits.

4.5 Overall, the increased time spent on audits in 2003 increased the TGA's ability to collect evidence to assess compliance with the Code of GMP. However, the ANAO found that some of the changes to approach could also cause resourcing challenges. For example, the increased use of unscheduled high priority special audits can result in technical experts not always being available at short notice. Figure 4.3 provides an illustration.

4.6 Further consideration of how to align required skills with audit need, particularly where audits are conducted at short notice, would be of value.

Figure 4.3

During the conduct of an audit of a non-prescription medicine manufacturer, it was established that the manufacturer was introducing new computerised systems to support its manufacturing process. The lead auditor recommended, *inter alia*, that the next audit team include a computer/IT specialist to assess the new systems, and that the audit be conducted within six months.

The next audit was not actually conducted until 17 months after the previous audit and was conducted as the result of a tip-off.[48] Because the audit was conducted urgently, an IT specialist was not available at short notice. Instead, the TGA relied on the lead auditor to assess the new computer system.

Source: ANAO analysis of TGA data.

Auditor rotation

4.7 The TGA has had a long-standing auditor rotation policy.[49] This requires that auditors should not audit the same manufacturer more than twice consecutively. This is an appropriate governance and control practice for a Regulator to manage the risks to independence of audit inquiry and analysis.

4.8 However, the ANAO found that the TGA has not always met this requirement. For example, for one major manufacturer, the same auditor was the lead auditor on three occasions and a member of the audit team on two other occasions over a six-year period. The ANAO notes that changes in auditors have, on occasions, coincided with different compliance assessments.

Notifying manufacturers

4.9 The TGA's procedures require it to give advance notice to Australian manufacturers of an audit, in normal circumstances. However, the Chief GMP Auditor may approve an unannounced audit, if there is evidence that forewarning will limit the TGA's ability to assess compliance. An unannounced audit may also be undertaken as a result of a tip-off.

4.10 All audits of overseas manufacturers conducted by the TGA are announced. The TGA only undertakes an overseas audit after the product sponsor has paid the costs of the audit. Further, practical considerations, such as visa entry procedures, limit the opportunity to conduct unannounced audits overseas.

4.11 The TGA advised that the focus of unannounced audits has been on manufacturers of higher-risk prescription medicines, blood and tissues products and medical devices. It also advised that around five per cent of audits of these manufacturers are unannounced. However, the TGA's

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[48] Tip-offs are generally anonymous complaints that a manufacturer is not adhering to the Code of GMP.

[49] The policy was not formally documented in TGA SOPs until September 2003.

management information system indicates that the actual level in recent years has been just over one per cent, with most being for blood-related product.

4.12 Accordingly, the extent of unannounced auditing of Australian non-prescription medicine manufacturers has been low, until a sharp increase in 2003. See Figure 4.4.

Figure 4.4

Number of announced and unannounced audits of Australian non-prescription medicine manufacturers, 1999–2003

Audits	1999	2000	2001	2002	2003
Announced	83	84	65	59	45
Unannounced	3	0	1	0	18
Total	**86**	**84**	**66**	**59**	**63**

Source: ANAO analysis of TGA data.

Notes: Excludes licensing audits, which are announced.
The three unannounced audits in 1999 were of one manufacturer.

4.13 The increase in unannounced audits in 2003 was largely a result of the increased targeting of non-prescription medicine manufacturers for that year (paragraph 4.4). The TGA advised that these were a temporary measure to address quality risks from manufacturers increasing production after the suspension of Pan Pharmaceutical Limited's licence. There were also some tip-offs.

4.14 Notwithstanding the sudden increase in 2003, the TGA advised that it does not favour the routine use of unannounced audits. It seeks a 'collaborative, constructive, collegiate and communicative approach to auditing and has attempted to avoid an adversarial, directive or legalistic approach'.

4.15 The ANAO recognises that there are advantages in announcing audits. These include efficiency of the on-site component of the audit, as arrangements can be made by the manufacturer to facilitate preparation for the audit.

4.16 However, there are also advantages from conducting unannounced audits. For example, the incentive for manufacturers to maintain acceptable compliance rather than focussing effort when an audit is announced.

4.17 The ANAO notes that some regulatory bodies conduct unannounced audits as a normal part of their regulatory oversight strategy.

4.18 Some medicine manufacturers have advised that unannounced audits are manageable for them, provided they are conducted in an equitable and accountable manner. The ANAO was also advised that unannounced audits are common in the industry; product sponsors often undertake unannounced audits of their contract manufacturers.

4.19 The TGA did not undertake a structured risk assessment to guide its unannounced audit initiative in 2003. Further, it has not assessed and documented the ongoing role of unannounced audits, and their costs and benefits, as part of an overall risk management strategy.

4.20 Such an assessment would enable it to consider options in the use of unannounced audits. For example, use of short unannounced audits to increase knowledge of higher risk aspects of manufacturer operations.

4.21 The ANAO also found that the targeting of non-prescription medicine manufacturers in 2003 coincided with a marked increase in enforcement action (discussed further at paragraph 5.56). The extent of the change suggests that a more in-depth assessment of the costs and benefits of the changed approach in 2003 is warranted, to assist planning and management of the audit program in the future.

4.22 The TGA advised that the 2003 strategy was a response to a unique event, and that it does not need evaluation, as the situation was managed effectively. It noted that it has not continued with this approach.

Recommendation No.6

4.23 The ANAO recommends that the Department of Health and Ageing assess the cost-benefit of unannounced GMP audits, and their role and contribution in the regulatory oversight strategy. The assessment could also address the broader lessons for the future from the targeting of non-prescription medicine manufacturers in 2003.

Departmental response

4.24 Agreed.

Audit preparation

4.25 The TGA's SOPs require auditors to review relevant manufacturer information to prepare for an audit.[50] The lead auditor is then required to prepare an audit plan.

4.26 The plan should identify the manufacturing standards and other matters to be given priority in the audit. It should allocate sufficient time to critical GMP activities, such as validation, change control and testing.

4.27 However, auditors are not required to adopt a particular structure to the plan. Nor is there a systematic approach that enables the findings from the

[50] This includes: reviewing the manufacturer's site master file; at least the two previous audits reports and associated correspondence; any outstanding complaints; and recalls.

review of files and databases to be consolidated in a structured way to identify the priorities for the audit.

4.28 The ANAO found that audit plans varied considerably in detail and nature. This variation was often related to the auditor engaged, rather than the nature of the audit. For example, some auditors produced a general list of areas to address, with little supporting research, detail, and timings. Others prepared more structured plans and methodologies to support the conduct of the audit.

4.29 The ANAO also found that the quality of documented audit planning varied. Some plans did not identify priority areas that appeared pertinent from examination of files and other information. For example, plans for audits of a manufacturer did not target product testing, despite a history of poor laboratory work and testing.

4.30 These limitations reduce assurance for management and stakeholders that audit preparation has: adequately assessed priority areas for audit examination; allocated appropriate resources to priority areas; and that audit implementation is consistent with priorities and risk assessment.[51]

4.31 The ANAO notes that a planning proforma is utilised for audits of medical devices manufacturers. This approach could usefully be extended to non-prescription medicine manufacturer audits.

Collecting evidence

4.32 During an audit, evidence is collected to assess whether a manufacturer is compliant with the Code of GMP. Auditors make handwritten notes on their observations.

4.33 TGA SOPs require only deficiencies against the Code to be recorded in the Deficiency Report. Auditors are not required, for example on checklists, to note details of areas examined that are satisfactory. The ANAO also found that filed handwritten notes varied in detail, especially in the area of satisfactory compliance.

4.34 The TGA advised that the use of checklists is not considered international best practice, as they may make auditors reliant on a 'tick-in-the-box' approach.[52] Instead, it encourages auditors to develop personal aide memoires, particularly new auditors. However, the ANAO considers that the use of such personal aids will inevitably vary in quality and effectiveness.

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[51] The ANAO notes that the use of such proformas by manufacturers can be a test criteria when the TGA is assessing a manufacturer's quality control and assurance system.

[52] The TGA advised that GMP inspectorates in Europe, the USA or Canada do not use checklists.

4.35 These practices limit management assurance regarding quality of evidence gathering. For the same reason, the ANAO was unable to assess whether appropriate evidence was consistently collected during TGA audits.

4.36 The introduction of greater structure in evidence collection, through the use of tools such as a proforma or a checklist, would assist the TGA to assess whether appropriate evidence has been collected consistently. This would assist in a more structured approach to collection and analysis of evidence and to the assessment of deficiencies. It could also assist in analysing the findings from previous audits and identifying trends in compliance.

4.37 A structured approach is good regulatory practice. It would increase transparency to stakeholders that audits are appropriately comprehensive and consistent. Also, it would help address the perception by some manufacturers that some auditors pursue particular lines of inquiry, notwithstanding findings, rather than a balanced assessment of GMP practice.

4.38 There would also be other benefits for the manufacturer. It could assist their understanding of the priority that the TGA places on each element of the Code, thereby facilitating their own checking of on-going compliance with standards.

4.39 The risk of overly simple checklists could be addressed by developing appropriate tools for different types of manufacturer.

Recommendation No.7

4.40 The ANAO recommends that the Department of Health and Ageing establish greater structure around administrative procedures, and develop support tools around planning of GMP audits and collection of evidence to facilitate consistency and adequacy of coverage in the conduct and reporting of audits of non-prescription medicine manufacturers.

Departmental response

4.41 Agreed.

Assessing manufacturer deficiencies

4.42 The audit team compares the practices being applied by a manufacturer with GMP standards. A deficiency is recorded if the auditor considers the practice does not produce the outcome stipulated in the Code. The deficiency is classified as:

- *critical*—it has produced, or may result in a significant risk of producing, a product that is harmful to the user. Examples are lack of sterilisation, and evidence of gross pest infestation; or

- *major*—non-critical, but of sufficient seriousness to be listed in a Deficiency Report. An example is damage to walls/ceiling in manufacturing areas where product is exposed; or
- *other*—neither critical or major, but a departure from good manufacturing practice.[53]

4.43 The deficiencies are rated and consolidated into a Deficiency Report. The Report is discussed with the manufacturer at an exit meeting.

4.44 The assessment and classification of deficiencies are key elements in the conduct of an audit. The extent and nature of the deficiencies determine the overall extent of non-compliance and any subsequent enforcement action (enforcement action is discussed further in Chapter 5).

4.45 The TGA does not record the number and nature of deficiencies in its management information systems. Consequently, key information that would facilitate monitoring and analysis of trends in manufacturer compliance is unavailable.

Identifying and classifying deficiencies consistently

4.46 The Code of GMP is not prescriptive. It defines the outcome the manufacturing should produce, rather than the process. Consequently, there is a risk that auditors will identify deficiencies inconsistently, unless clear guidance is provided.

4.47 The TGA advised that it recognises that consistency is a key requirement of a quality audit and licensing system. It also advised that maintaining audit consistency is a challenge for any regulator.

4.48 Audit consistency was also identified in a TGA-commissioned review in 2002—the Corcoran review[54]—as a weakness that was detracting from the performance of the GMP audit and licensing function.

4.49 The TGA has instituted several systems to better manage consistency of auditing. These include:

- training of, and discussions amongst, TGA auditors;
- standard operating procedures for the conduct of audits;
- promulgation of interpretive guidelines; and
- a quality system documented in a Quality Manual, and supported by a Quality Manager.

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[53] The classification has changed five times over the last 10 years. See Appendix 5.

[54] Brian Corcoran, *Review of TGA Audit and Licensing of Good Manufacturing Practice*, Canberra, March 2002. The TGA advised that the report was not 'finalised' until August 2002.

4.50 However, progress on some quality management initiatives has not matched expectations or has been partial. For example, the TGA has not conducted regular audits of auditors, a requirement of the Quality Manual.[55]

4.51 Some other quality management changes were implemented during this audit, and their impact is yet to be assessed. For example, the TGA advised that it has implemented review of audit documentation by senior audit management for all audits from 2004.

4.52 The ANAO found that audit inconsistency and the lack of appropriate application of GMP continue to be a concern of industry. For example, instances were cited of auditors assessing a practice as deficient that had previously been accepted by another auditor.

4.53 In one instance, a manufacturer acknowledged that part of the manufacturing process identified as deficient by the TGA was not meeting industry best practice. However, the manufacturer observed that the same system had previously been assessed as compliant. Further, the TGA's suggestion to address the deficiency was not considered by the manufacturer to be consistent with practice elsewhere. The TGA advised the ANAO that the auditor considered that the relevant equipment had deteriorated since the previous audit. However, the manufacturer advised that they considered that this was not the case; rather, the relevant equipment was being upgraded at the time of the audit.

4.54 However, the current approach to structure and documentation of the TGA's audit planning and collection of evidence limits the ANAO's ability to assess the extent to which systems and processes have been checked previously and found to be satisfactory. That is, whether such examples reflect undocumented technical changes or different auditor opinions. This reinforces the value of improvements in this area (paragraph 4.40), to better support quality management systems.

4.55 Overall management of quality control and assurance are discussed further in Chapter 8.

4.56 The ANAO also found that guidance provided to auditors on the classification of deficiencies could be enhanced. SOPs provide examples of what might constitute a critical, major or other deficiency. However, they do not give clear guidance on classifying deficiencies for the various types of manufacturer.

4.57 For example, a deficiency that is critical for an OTC medicine manufacturer may not be critical for a complementary medicine manufacturer.

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[55] The Quality Manual requires each auditor to be subjected to an internal audit at least every two years.

This judgment is left to the auditor to make. Industry also advised the ANAO that greater clarity in this area would be desirable.

4.58 The ANAO also noted that, in responding to audit reports, two Review Panels categorised the same deficiency differently. One categorised it as a critical deficiency, the other as a major deficiency.[56]

Recommendation No.8

4.59 The ANAO recommends that the Department of Health and Ageing provide guidance to auditors and manufacturers on the deficiencies considered critical for OTC medicine manufacturers and for complementary medicine manufacturers. The department should also monitor the consistent application of such guidance by GMP auditors and Review Panels.

Departmental response

4.60 Agreed.

Interpretation of standards

4.61 Clarity, and a shared understanding, of requirements in manufacturing standards assist the Regulator to fulfil his/her functions. It facilitates compliance by manufacturers through increased ability to design, with confidence, manufacturing practices to meet the Code. It also reduces the risk that, for similar circumstances, auditors will interpret, and assess, compliance differently.

4.62 The TGA advised that it recognises that manufacturers do not always understand aspects of standards, particularly for complementary medicines. The Corcoran review identified the need to enhance industry education and information on GMP, to assist the TGA achieve its goals.

4.63 The TGA's response to the Corcoran review has included the development of web pages and the promulgation of interpretative guidelines. Three guidelines were added to the TGA website late 2003/early 2004.[57]

4.64 The TGA also presented short sessions at industry-run seminars in capital cities during the transition period to the new Code. The TGA collected questions from participants during the sessions, which formed the basis of a new 'Question and Answer' page on its website.[58]

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[56] Notwithstanding the different categorisations, the Panels in this case recommended the same licence restriction action.

[57] The guidelines addressed: overseas manufacturing; analysing complementary medicines using quantified by input techniques; and interpretation of the Code for complementary medicine manufacturers.

[58] For example, *Question and answer for the identification of herbal materials and extracts*, May 2004, <http://www.tga.gov.au/cm/idherbal.htm> [accessed 6 September 2004].

4.65 This audit reinforced the extent to which there has been confusion, and differing interpretations, by industry of the requirements of the Code of GMP. This was especially the case for testing of products and ingredients, including stability testing, uniformity of content testing (especially for microdose mineral products), and testing of starting materials.

4.66 Overall, the TGA has sought to improve the interpretation and application of the Code for non-prescription medicine manufacturers. However, ANAO observations, and advice from manufacturers during this audit, suggest that ongoing consultation with industry and the promulgation of interpretative material are areas that warrant continued attention.

Transparency of the audit process

4.67 The Corcoran report considered that:

> The Standard Operating Procedure on the audit process and, especially on the complaints process, be placed in the public domain...the review sees no net benefit in such a lack of transparency, and significant upside gain in signalling a more open process and in making it clear for those to be audited what to expect by way of both their responsibilities and rights.[59]

4.68 The TGA placed only summaries of the SOPs on its website.[60] It considered that it was inappropriate to provide detailed internal documents.

4.69 The ANAO found the published summaries outline steps in the scheduling and conduct of audits. However, important details of the TGA's procedures are not described. Examples include how the TGA determines the time to next audit, and the role and functioning of Review Panels.

4.70 The TGA advised that publishing SOPs would inhibit the conduct of an audit, as manufacturers may review the TGA's adherence to SOPs, rather than address the auditor's advice and judgment. However, some manufacturers advised the ANAO that the limited information on audit procedures reduced their confidence that auditors adhere to procedures. This hampered their ability to establish a constructive relationship with the TGA.

4.71 The ANAO considers that publishing procedures more fully would increase the transparency and accountability of the TGA's processes.[61] In addition, it would increase audit efficiency as manufacturers could be better prepared for audits.

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[59] Brian Corcoran, *Review of TGA Audit and Licensing of Good Manufacturing Practice*, Canberra, March 2002, p.27.

[60] TGA, *Audit of medicine manufacturers*, <http://www.tga.gov.au/docs/html/auditmed.htm> [accessed 17 September 2004].

[61] The ANAO notes that the Australian Pesticides and Veterinary Medicines Authority publishes its procedural documentation, including its GMP Audit Procedure and GMP Audit Checklist. See APVMA, *APVMA forms*, <www.apvma.gov.au/forms/subpage_forms.shtml> [accessed 17 September 2004].

4.72 The ANAO also found that the complaints process is described only very briefly on the website, and refers complaints to the Chief GMP Auditor.[62]

4.73 Some manufacturers expressed considerable concern that there was limited ability to complain or dispute audit findings, and that the process was not independent. The ANAO was advised that, on occasions, manufacturers may consider they have no option but to implement the changes required by the TGA, even though the change may be considered unjustified by the manufacturer in the context of the Code of GMP.

4.74 More robust and transparent procedures for the handling and resolution of complaints, appeals and disputes regarding audit findings would assist in addressing such concerns.

Recommendation No.9

4.75 The ANAO recommends that, to improve transparency and to assist its clients in their compliance, the Department of Health and Ageing:

- improve the information available to non-prescription medicine manufacturers and sponsors on the GMP audit process; and
- develop, and make transparent to its clients, procedures for the handling and resolution of complaints, appeals and disputes regarding audit findings.

Departmental response

4.76 Agreed.

Informing the manufacturer of the consequences of unacceptable compliance

4.77 The TGA requires auditors to include an explicit warning in the audit Deficiency Report if compliance is considered unacceptable.

4.78 To address this, a proforma Deficiency Report was introduced in October 2002. It includes the text of a specific warning and the circumstances when it is to be used. The ANAO found that this requirement had not been consistently applied. Several Deficiency Reports examined by the ANAO used a different warning to the standard text.

4.79 This warrants attention for regulatory purposes and for transparency to stakeholders.[63]

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[62] It states; 'Complaints about auditing or against an auditor should be referred to the Chief GMP Auditor for appropriate action.'

[63] If the implications of non-compliance are not clear, the manufacturer may assume that the standard four week response deadline mentioned in the Deficiency Report applies. This is not the case.

5. Addressing Manufacturer Non-compliance

This chapter describes how the TGA responds to identified manufacturer deficiencies.

Introduction

5.1 Most audits reveal a number of manufacturing practices that do not comply with standards. Deficiencies are recorded in the Deficiency Report, issued to the manufacturer at the conclusion of the on-site phase of the audit.

5.2 Where the extent of non-compliance is considered unlikely to pose a risk to public health and safety, the manufacturer continues to manufacture. However, the manufacturer must report to the TGA lead auditor on plans and actions to address the deficiencies.

5.3 The ANAO estimates that some 80 per cent of audits are managed in this way.[64]

5.4 Where the lead auditor considers there may be a potential risk to public health and safety, the audit is to be referred to senior audit management. Non-compliance must be assessed as unacceptable if there is:

- at least one critical deficiency (see paragraph 4.42); or
- so many major or other deficiencies that overall compliance with GMP is considered unacceptable.

5.5 Audits are 'closed out' when deficiencies have been addressed, or enforcement action is complete. Appendix 6 describes the key steps used by the TGA to close out manufacturer audits.

Managing audit close out

5.6 Broadly, the required processes to close out an audit are summarised below, although there may be variations for higher risk non-compliance, as discussed later in this chapter:

- the manufacturer has four weeks after receipt of the Deficiency Report to report on the steps taken to rectify the deficiencies;
- the TGA should respond to this report within four weeks; and

[64] This is an ANAO estimate, as TGA information systems do not record this information.

- dialogue may continue until corrective action is considered satisfactory, or is assessed as ineffective.[65]

Obtaining assurance about corrective action

5.7 The ANAO found that manufacturers generally responded to Deficiency Reports within the required four weeks. The TGA was also prompt in reviewing manufacturer submissions, and seeking further information if considered necessary.

5.8 The TGA's SOPs require the lead auditor to obtain objective evidence of corrective action taken, or proposed, before the audit can be closed out. The SOPs note that this might include copies of procedures, photographs or purchase orders. No further guidance is given.

5.9 Also, the SOPs indicate that it may be necessary to conduct a follow-up inspection to obtain objective evidence of appropriate corrective action. However, they do not provide specific guidance when this is appropriate.

5.10 The ANAO found that on-site follow-up inspections are relatively uncommon, occurring in less than 15 per cent of audits reviewed. As well, the ANAO found that recommendations for follow-up inspections may not have been implemented by the TGA.

5.11 The TGA advised that the SOPs in place are appropriate and provide sufficient guidance for assessing a manufacturer's corrective actions. It also advised that this is consistent with its principle of working cooperatively with industry and minimising regulatory burden.

5.12 However, these arrangements do not always provide appropriate assurance that corrective actions have satisfactorily addressed the deficiencies. For example, in one case, a Review Panel noted that 'following the last audit, the company had committed to corrective actions, yet this latest audit revealed that actual implementation was poor.' In this case, the subsequent audit, which was unannounced, found 50 major and other deficiencies (not all linked to the previous deficiencies).

5.13 The ANAO considers that establishing clearer guidance on the sufficiency of evidence for audit close out would aid management of the process. They would enhance assurance that the risks of continued manufacture, whilst non-compliant, are managed appropriately, for both low and high risk non-compliance.

5.14 The ANAO also notes that close out of audits, and associated documentary evidence, has not been subject to routine review by management.

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[65] If the audit is not closed out after three months, the lead auditor must report the reasons for delay to senior audit management. This time limit was increased from six weeks in September 2003.

The TGA advised, during the conduct of this audit, that such review is now a requirement and is reflected in SOPs.

Time to close out audits

5.15 Expeditiously closing out an audit, and having reliable management information in this area, is an important aspect of the TGA's regulatory framework. It allows the TGA to make timely decisions regarding necessary action, and provides information to plan the next audit.

5.16 The TGA's management information system indicates that, as at 31 December 2003, 31 audits of non-prescription medicine manufacturers had not been closed out within three months of the on-site phase of the audit. (By way of comparison, there were less than 100 audits undertaken in 2003). More than half of the identified audits had not been closed out for ten months or more.

5.17 However, the ANAO found that many had actually been closed out by the auditor. The management information system had not been updated; or details had been entered incorrectly.

5.18 Failure to complete administrative procedures to formally close out an audit reduces the TGA's ability to schedule audits appropriately. This is because important data required for scheduling are not on the management information system.

5.19 It also limits management's ability to monitor the status of audit close-outs, and to assess the risk of any delays.

5.20 As well, non-closed out audits are recorded as 'interim', and considered to be acceptable. Consequently, the TGA may issue a certificate of GMP compliance to a manufacturer.

5.21 Apart from the data errors, some audits do actually take substantially longer than three months to close out. Some examples are discussed later in this chapter.

5.22 The ANAO considers that closer adherence to standard procedures, and prompter recording of close out details, are necessary to meet the levels of assurance for non-compliant manufacturers envisaged in the TGA's SOPs.

Recommendation No.10

5.23 The ANAO recommends that the Department of Health and Ageing strengthen GMP audit close out procedures by:

- establishing clear guidance, including examples and standards, on the assessment and acceptance of evidence of corrective action by manufacturers;
- subjecting close out to appropriate review; and
- maintaining relevant and reliable management information to facilitate monitoring of close out, and allocation of audit resources.

Departmental response

5.24 Agreed.

Procedures for higher-risk non-compliance

Referral to a Review Panel

5.25 Around 20 per cent of audits[66] are referred to a Review Panel because the lead auditor assessed there may be a potential risk to public health or safety. However, the ANAO found that there has been confusion in procedural guidance on whether audits should be referred to a Review Panel.

5.26 Some audits that had assessed the manufacturer as having critical or major deficiencies were not referred to a Review Panel. The TGA advised that this was for a number of practical reasons. However, the ANAO found that the reason for this, and what management advice/decisions were, was often not well documented.

5.27 The TGA advised that it is now mandatory for all audits with unacceptable non-compliance to be referred to a Review Panel.

Role and membership of the Review Panel

5.28 Review Panels primarily provide expert advice to senior management, particularly manufacturer and product regulators, on the need for, and the nature of, enforcement action. They may also provide advice on a number of other matters, such as licence variations.

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[66] Excludes licence and certification audits.

5.29 TGA SOPs state that a Review Panel must be chaired either by the Chief GMP Auditor or the audit manager. The Chairperson plus two members represents a quorum.[67]

5.30 However, the ANAO found that some Panels comprised only the Chairperson and one other member. In addition, where Panels had a third member, one was often the lead auditor. While SOPs allow this, the ANAO considers this practice has the potential to limit the extent to which analysis is independent of the audit team.

5.31 The ANAO also noted that the Product Regulator was not usually represented on the Panel. The TGA has now made it a requirement that a representative from the relevant Product Regulator be invited if one or more critical deficiencies have been identified.

Recommendation No.11

5.32 The ANAO recommends that the Department of Health and Ageing:

- establish a suitable range of expertise on TGA Review Panels to address regulatory issues, consistent with procedural requirements; and
- ensure that Review Panels are constituted in accordance with SOPs.

Departmental response

5.33 Agreed.

Enforcement action procedures

5.34 The TGA has a range of enforcement action available to control the risks presented by a non-compliant manufacturer. There are two broad categories.

5.35 The lower-level response is utilised where non-compliance is considered unacceptable, but the risk to public health and safety is assessed as not serious or immediate. This action includes:

- issuing a warning letter to the manufacturer, which is likely to require it to submit regular reports on corrective action; and
- increasing audit frequency, or conducting special audits.

5.36 Alternatively, for risks assessed to be more serious, formal *restrictions* may be placed on the operations of the manufacturer. Such action may also be taken where lower-level action was not successful in achieving the required level of compliance.

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[67] SOPs also indicate that, if possible, the lead auditor from the most recent audit should be included.

Warning letter and short-term reporting

5.37 A warning letter informs the manufacturer that compliance has been assessed as unacceptable. The manufacturer is permitted to continue manufacturing. However, it is required to submit regular reports (short term reporting) outlining progress on corrective actions to address the deficiencies. The lead auditor or audit management manages the close out for short term reports.

5.38 The ANAO found that there are no documented procedures to manage short term reporting. Roles and responsibilities are not defined. Nor are there procedures for the on-going assessment and response to submitted reports. Time-lines to close out the procedure, and circumstances that warrant escalation of enforcement if responses are slow or unsatisfactory, are not defined.

5.39 Limitations in management guidance, and related information for manufacturers, risks confusion and inconsistency, especially when short term reporting extends for some time. For example, in one case, a manufacturer was required to submit reports every two months. When the TGA conducted a subsequent routine audit, both the TGA and the manufacturer were confused about whether, and how, the manufacturer should continue to submit the short term reports.

5.40 The TGA advised that it is willing to clarify any regulatory requirements imposed on manufacturers. However, it considers that it is reliant on manufacturers to raise their concerns with the TGA. Whilst appreciating that the TGA is a regulatory agency, it has some responsibility to seek client feedback, and ensure it has efficient processes that minimise industry costs.

5.41 Short term reporting seeks to raise a manufacturer's level of compliance from an unacceptable level, while allowing continued manufacture. This warrants a more structured approach to guidance and operational procedures than has been the case to date.

Increasing audit frequency, or conducting special audits

5.42 The TGA may use its audit program to monitor manufacturer non-compliance. For example, it may set a time to next audit that is less than required by its audit frequency matrix. Or it may conduct a special follow-up audit. Typically, three to six months is the time set to next audit in such circumstances.

5.43 However, the ANAO found that recommendations to shorten the time to next audit have not always been implemented. Chapter 3 addressed some of the delays that can occur in meeting audit scheduling.

Procedures for imposing licence restrictions

5.44 Restrictions on the operations of an Australian manufacturer require approval by the Manufacturer Regulator, under the powers of the Act.

5.45 This may involve: placing conditions on the licence regarding the manufacturer's operations; suspension of the licence for a specified period; or revocation of the licence.

5.46 The key steps in placing restrictions on a manufacturer's licence are defined in the Act. They cover, *inter alia*, the circumstances when restricting a licence is appropriate, when the restriction should be immediate, and the time that must be given to the manufacturer to respond to the TGA's intention to impose the restrictions. The Act also defines a formal appeals mechanism.

Conditioning licences

5.47 The Act stipulates that the date of effect of a licence *condition* shall be 28 days from the date of the issuance of a letter of intent. There is no requirement in the Act for a manufacturer to be provided with the opportunity to submit reasons why such action should not be taken. Nor is there any guidance in SOPs on when it is appropriate for the Manufacturer Regulator to give such an opportunity to a manufacturer.[68]

5.48 The ANAO found there were inconsistent approaches in this aspect of administration. In one case, the letter of intent explicitly provided the opportunity to make a submission regarding a decision to condition the licence. For another manufacturer, whose licence was to be conditioned in the same way, a similar, formally stated opportunity to respond was not stated in the letter.

5.49 The TGA advised that, notwithstanding the administrative inconsistency, the second manufacturer was aware of the opportunity to respond through other communications, and there is evidence that this was the case.

5.50 However, the ANAO considers that formal regulatory instruments, such as letters of intent, should be applied appropriately, consistently and equitably.

5.51 Clear protocols in this area would contribute to a consistent application of the regulatory framework.

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[68] These arrangements contrast with procedures for *suspension* or *revocation* of a licence. In these cases, the TGA must provide manufacturers with 'a reasonable time' to make a submission. The submission must be taken into account when the final decision is made on the action.

Restrictions on the operations of an overseas manufacturer

5.52 Restrictions on the operations of an overseas manufacturer are achieved through the certification arrangements. This may involve restricting the scope of the GMP certification (equivalent to conditioning), or withdrawal of the TGA's approval for the manufacturer.

5.53 There are no operational procedures for placing restrictions on overseas manufacturers. The ANAO considers that it would be appropriate regulatory practice to establish such procedures. This would increase transparency and accountability, for the benefit of stakeholders, and assist administrative effectiveness.

Recommendation No.12

5.54 The ANAO recommends that the Department of Health and Ageing establish, and promulgate, TGA procedures for the:

- imposition and management of short term reporting enforcement action;
- consistent application of licence restrictions; and
- imposition of restrictions on overseas manufacturers audited and certified by the TGA. Relevant matters include the roles and responsibilities of officials, key steps, complaints mechanism and time-lines.

Departmental response

5.55 Agreed.

Numbers of enforcement actions

5.56 The TGA does not capture management information on the various types of enforcement action taken. The information presented in Figure 5.1 was estimated by the TGA by reviewing its files.

5.57 In the four years 1999 to 2002, there were 35 instances of enforcement action. That is, approximately nine a year. This increased to 37 actions in 2003.

5.58 The marked increase in 2003 reflected the changed approach to auditing, discussed at paragraph 4.4, following the suspension of Pan Pharmaceuticals Limited's licence.

Figure 5.1

Number of enforcement actions: non-prescription medicine manufacturers, 1999-2003

Type of enforcement action		1999	2000	2001	2002	2003
Australian manufacturers	Short term reporting	0	1	2	2	6
	Licence restrictions	6	3	6	5	26
	Total - Australian	***6***	***4***	***8***	***7***	***32***
Overseas manufacturers	Short term reporting	1	1	2	2	4
	Certification restrictions	0	2	0	2	1
	Total - overseas	***1***	***3***	***2***	***4***	***5***

Source: TGA

Notes: Manufacturers may be subject to more than one enforcement action at the same time.
Most restrictions are licence revocations (Australia) or withdrawal of certification (overseas).

5.59 As part of this approach, the TGA targeted GMP audits at eight non-prescription medicine manufacturers that had GMP and/or marketing authorisation problems.

5.60 Figure 5.2 summarises the enforcement action imposed by the TGA for six of these manufacturers following the audits. Of the remaining two manufacturers, one was not audited until February 2004. The other requested that its licence be revoked after discussions with the TGA.

Figure 5.2

Enforcement action for six targeted audits, 2003

Manufacturer	Increased reporting	Conditioning of licence	Suspension of licence
1	Yes		
2	Yes	Yes	
3	Yes		Yes
4	Yes	Yes	
5	Yes		
6		Yes	

Source: ANAO analysis of TGA data.

5.61 It is not clear, on the evidence available, the extent to which the marked increase in enforcement action reflects a serious decline in compliance by

manufacturers, or is the impact of the changed approach to auditing and/or regulatory decision making. As recommended at paragraph 4.23, a more in-depth assessment of the results achieved would better inform the management and targeting of future potential non-compliance.

Timeliness of enforcement action

5.62 The ANAO found that, in general, Review Panels acted promptly in reviewing audit reports revealing unacceptable compliance. Typically, the Panels were convened within one week of the exit meeting for Australian audits.

5.63 Panel recommendations for enforcement action were addressed in a timely manner by the Manufacturer Regulator.[69]

5.64 However, there are no specific time–lines or standards to guide the imposition of enforcement action and the various processes involved. The TGA does not consider that setting timeframes would provide any benefit. It suggested that they might undermine the process, as many aspects must be dealt with on a case-by-case basis.

5.65 Nevertheless, the ANAO considers that explicit time-lines for completing key steps would provide greater transparency and accountability for enforcement action, and assist decision-making for exceptional cases.

5.66 In 2003, the TGA undertook the largest enforcement action in its history. Figure 5.3 summarises the time-lines.

Figure 5.3

The TGA conducted an unannounced audit of a large non-prescription medicine manufacturer, following serious adverse reactions to particular products. The audit found manipulation of records, but its scope was not extended to address other products. The audit resulted in the conditioning of the manufacturer's licence for the products concerned.

As the problems were seen to be widespread, a Review Panel recommended that a further audit be conducted within a week. The audit was actually conducted after three weeks. The reason for the delay was not documented. The TGA advised that it considers this a reasonable period, with considerable effort expended on preparation.

When the audit team arrived on site, the manufacturer objected to the audit, as the Quality Assurance Manager was on leave. The TGA negotiated two days access to documentation only, with agreement that they would audit the factory and operations at a later date. There is no formal record of this decision making process.

Five critical deficiencies were identified as a result of the audit. The TGA decided to complete the outstanding part of the audit. This was not conducted until six weeks after the first phase. The TGA advised that this was a period of intense activity related to the audit findings and preparation for the next phase.

Approximately 12 weeks after the first audit, the TGA suspended the manufacturer's licence, with immediate effect.

Source: TGA

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[69] The Regulator may not necessarily implement recommendations.

5.67 The TGA advised that it considered the 12-week gap between initial audit action and enforcement action in the above example to be appropriate. It considered that a vast amount of work was required to: identify the extent of the problems; assess them; collect the necessary information; identify the most appropriate enforcement action; and prepare for the subsequent product recall.

5.68 However, the TGA's views that all its decisions in this case were appropriate have not been supported by a thorough and independent assessment of whether these actions were optimal, or whether they hold lessons for the future. For example, in this case, an expert advisory group advised that there were imminent risks of death, serious illness, or serious injury. These would have been present during the 12-week period that the TGA was auditing and preparing for enforcement action.

5.69 Such an assessment would also enable the TGA to consider whether, should another risk of serious health consequences emerge in the future, the ongoing exposure of the public to potential risks is appropriately balanced with other considerations.

Recommendation No.13

5.70 The ANAO recommends that the Department of Health and Ageing arrange independent assessment of recent key enforcement actions, to draw lessons for the future when making decisions potentially affecting public health and safety.

Departmental response

5.71 Agreed.

Access to manufacturer premises

5.72 The TGA does not have explicit procedures that address circumstances where there is difficulty in obtaining access to a manufacturer's premises and/or information. Such circumstances might occur if a manufacturer refuses the TGA access to its premises, or when key manufacturer staff are absent from the work place.

5.73 The TGA advised that explicit guidelines are not necessary, as auditors will contact senior audit management if they are refused entry.

5.74 However, the ANAO considers that established procedures and contingency plans will facilitate consistency in officer behaviour; aid management decision making in the exercise of the TGA's powers; and contribute to equity for manufacturers subject to audit.

5.75 In the example in Figure 5.3, the TGA did not have contingency plans in the event of access becoming difficult. Decisions were made 'on the run',

including taking legal advice, before the reduced on-site audit was negotiated with the manufacturer. Such an approach risks limiting the TGA's capacity to conduct a thorough and timely risk assessment to support the execution of its regulatory powers.

Recommendation No.14

5.76 The ANAO recommends that the Department of Health and Ageing establish procedures to guide and prepare staff and management should there be difficulty in gaining access to premises to conduct a GMP audit.

Departmental response

5.77 Agreed.

Monitoring, and achieving consistency in, enforcement action

Monitoring actions to address non-compliance

5.78 The implementation of recommended enforcement action is a key component of the TGA's system to manage risks presented by a non-compliant manufacturer. However, the TGA does not have formal arrangements to systematically monitor the implementation of Review Panel recommendations to address non-compliance.

5.79 Accordingly, the ANAO was unable to assess statistically the extent to which proposed action was implemented. However, as noted a number of times in this report, recommended action may not be implemented in a timely or effective manner.

5.80 Such delays may arise from practical considerations, such as resource availability, or higher priority being given to other audits. Good management information would enable TGA management to be informed when this arises, and to make sound risk-based decisions to address the consequences.

Recommendation No.15

5.81 The ANAO recommends that the Department of Health and Ageing strengthen the TGA's management and monitoring of enforcement action by establishing:

- timeliness standards for key decision steps in the enforcement process, and monitoring performance against the standards; and
- monitoring and reporting procedures for the implementation of Review Panel recommendations and other enforcement action.

Departmental response

5.82 Agreed.

Failure to observe good manufacturing principles

5.83 The TGA's procedures require an auditor to assess the manufacturer's corrective action to address deficiencies. If the action is, ultimately, considered unsatisfactory, the manufacturer's compliance is to be rated unacceptable. If this is the case, the manufacturer is in breach of the conditions of its licence and not compliant with the requirements of the Act.[70]

5.84 However, the ANAO found that manufacturers with unacceptable compliance with the Code of GMP have been permitted to continue to manufacture, without restrictions. Appendix 7 provides an example. A manufacturer was found to have 10 critical, as well as other, deficiencies. Compliance was assessed as unacceptable.

5.85 The manufacturer was not assessed as acceptable until 14 months later, but continued to manufacture for most of this period.[71] During the period, corrective action was considered unsatisfactory, and a further two audits were undertaken. A notice of intent to suspend the licence was issued. However, the licence was not suspended, although the manufacturer's responses were again assessed as unsatisfactory.

5.86 The limited nature of the TGA's records makes it difficult to assess the basis of some of the decisions in this case, and whether they were fully supported by the evidence available.

5.87 The TGA advised that the manufacturer's non-compliance had not posed a risk to public health and safety sufficient to warrant imposing strong regulatory action.

5.88 Nevertheless, the TGA's procedures do not give clear support for the practices adopted in this case where there was ongoing unacceptable compliance. As noted at paragraph 5.38, guidance on managing audit close out is limited.

Adherence to SOPs

5.89 The TGA's SOPs indicate that it is highly likely that restrictions will be placed on a manufacturer's licence if one or more critical and/or several major

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[70] See ss.36 and 38 (1A) of the Act.

[71] The TGA placed a restriction on the licence to prevent the manufacturer of microdose products that required uniformity of content testing. Subsequently, it was established the manufacturer did not produce these products.

(significant) or other deficiencies are recorded at an audit. However, in practice, restrictions are not always imposed. (See Figure 5.4.)

Figure 5.4

An audit of a non-prescription medicine manufacturer identified two critical deficiencies and six other significant deficiencies.

Audit senior management and the Manufacturer Regulator considered that there was no immediate risk to public health and safety. They decided to closely monitor the company to ensure that it was taking appropriate corrective action.

The audit was referred to a Review Panel four months later, in the light of continuing concerns about progress on corrective actions. The Review Panel recommended a re-audit in the next quarter, because of problems and non-conformities. One week later, a limited scope unannounced audit was undertaken to address a specific matter that resulted from a tip-off.

The recommended full re-audit did not occur. The original audit was eventually closed out after 12 months.

Source: ANAO analysis of TGA data.

5.90 Management of the quality of audits and enforcement decision making is discussed further in Chapter 8.

Determining compliance rating at audit close out

5.91 When a manufacturer's corrective action for deficiencies identified in an audit is assessed as satisfactory, the lead auditor is required to rate the manufacturer's level of compliance. This rating is a factor in the time to the next audit (see paragraph 3.5).

5.92 The ANAO found that there was limited guidance on how to determine these ratings, and limited quality review of the ratings. For example, SOPs advise that, for an A2 rating, 'there may be a few major or other deficiencies…including relatively serious ones…and some of a relatively minor nature'.

5.93 The TGA advised that it is not feasible to be more prescriptive. It also advised that assessment of the impact of any deficiency must be considered on a case-by-case basis. This includes context, such as the risk category of the product, and overall compliance with the Code of GMP.

5.94 However, there is little guidance on how to assess such factors. For example, the quality of a manufacturer's response to identified audit deficiencies, and the reliability of supporting evidence, are pertinent factors in assessing overall risk to compliance.

5.95 The ANAO acknowledges the need for a degree of flexibility. However, arrangements leave scope for differing interpretations, which undermines the reliability of ratings, and subsequent risk treatments.

5.96 The ANAO also found that there was limited documentation on files of the reasons for ratings given. This reduces transparency of, and accountability for, an important regulatory decision.

5.97 The TGA advised that it is implementing greater review of auditor decisions, which may assist in assuring the quality of ratings.

5.98 In addition, the ANAO found that SOPs do not require an initial compliance rating to be captured and recorded at the conclusion of the on-site phase of the audit. Consequently, key information that would inform TGA management about the trends in compliance prior to manufacturers' corrective action, is unavailable.

Recommendation No.16

5.99 The ANAO recommends that the Department of Health and Ageing enhance management procedures for GMP compliance ratings to enable review and analysis over time, and to identify issues needing correction, by:

- assessing and recording initial compliance ratings; and
- documenting reasons for ratings and subjecting them to appropriate review.

Departmental response

5.100 Agreed.

Transparency and accountability

Transparency

5.101 Manufacturers are not informed of their rating. The TGA advised that it considers this of little value. It also considers that providing the rating would give the manufacturer prior notice of the likely timing of future audits. However, the ANAO notes that providing prior notice is normal practice for the TGA (paragraph 4.9).

5.102 The TGA further advised that manufacturers might use the information to promote the company.

5.103 However, the ANAO considers that informing manufacturers of their compliance rating has the potential to enhance compliance. Manufacturers would be better informed of the extent to which their manufacturing practices vary from the TGA's expectations, aiding the development of improvement strategies. The risk of manufacturer complacency could be addressed, for example, through risk-based use of unannounced audits.

Recommendation No.17

5.104 The ANAO recommends that the Department of Health and Ageing inform manufacturers of their compliance rating, to assist manufacturers in improving quality management, and to reinforce findings presented in Deficiency Reports.

Departmental response

5.105 Agreed.

Accountability

5.106 As noted in a number of examples above, the ANAO found that minutes of discussions held with, and decisions taken by, senior audit management regarding a manufacturer's non-compliance are not always formally recorded. This is so for both management information systems and paper files.

5.107 Records of these regulatory decisions are a key element of an audit quality control and assurance system for a regulator. Chapter 8 addresses the scope for strengthened documentary practices.

6. Monitoring Compliance of Approved Products

This chapter reviews the effectiveness of the planning and execution of the TGA's post-market monitoring of non-prescription medicinal products.

6.1 At 31 December 2003, there were 3 986 registered, and 17 013 listed non-prescription medicinal products approved and entered onto the Australian Register of Therapeutic Goods (ARTG).[72]

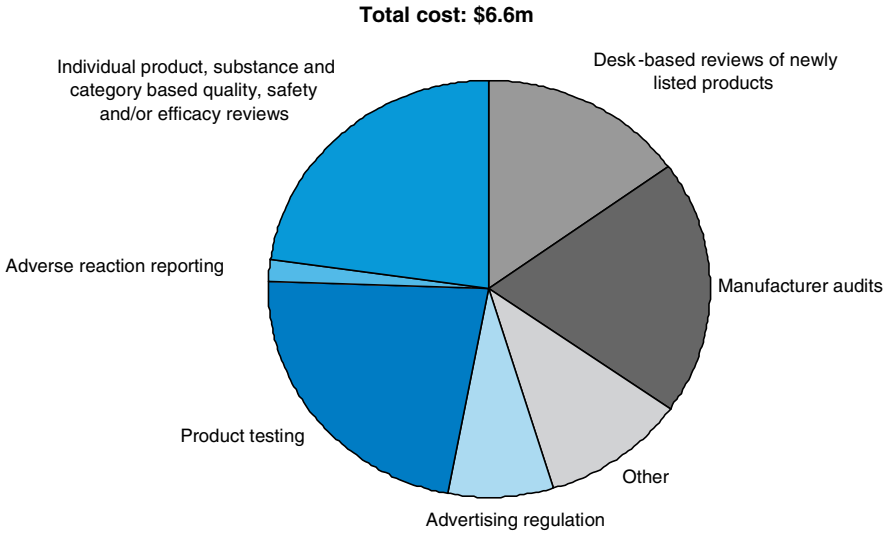
6.2 The TGA monitors approved products for potential risks to the product's safety, quality and efficacy. For example, if a product's conditions of approval are not met, there is a risk of the product being unsafe.

6.3 These arrangements are referred to as post-market monitoring.

6.4 In 2003–04, some $6.6 million was spent on its post-market monitoring program. The key elements, and their relative costs, are shown in Figure 6.1.[73]

Figure 6.1

Post-market monitoring of non-prescription medicinal products–relative costs



Source: TGA

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72 Therapeutic Goods Administration Quarterly Performance Report, October–December 2003.

73 TGA estimates, as non-prescription medicines costs are not separately identified. The cost of manufacturer audits is an ANAO estimate.

6.5 This chapter addresses risk-based targeting of post-market monitoring for non-prescription medicines, and the following aspects of monitoring:

- reviews of recently listed products. These seek to identify potential inaccuracies in information provided by the sponsor;
- laboratory testing of products and ingredients;
- reporting of consumers' adverse reactions to products; and
- safety and efficacy reviews. These re-assess the approval of products that may have safety or efficacy problems.[74]

Targeting of post-market monitoring

6.6 The risks to health and safety from non-prescription medicinal products are monitored within the context of the TGA's overall approach to all products. Substances and products are approved for listing or registration (see paragraphs 1.20—1.25). This categorisation determines the level of regulatory oversight applied, and the nature of post-market monitoring.

6.7 For example, registered products are subject to a full pre-market evaluation at which risks are identified, analysed and evaluated. Post-market monitoring for these products, therefore, focuses on checking that the requirements put in place at the approval phase are being met.

6.8 Listed medicines are not subject to the same level of pre-market evaluation because they have been determined to be low risk products. However, they are subject to additional post-market checks (see paragraph 6.15).

6.9 The strategies for post-market monitoring of non-prescription medicines are set out in manuals. However, the strategy for complementary medicines was less well articulated than for OTC medicines. This was being addressed by the TGA during the course of the audit, with a new draft Manual being developed.

6.10 The budget for the post-market monitoring system is largely based on a biennial activity based costing exercise. The TGA advised that resources are moved between elements to manage emerging risks. However, the TGA has not conducted a risk assessment to assess whether the distribution and balance of resources for its monitoring framework is appropriate. Nor is there a

[74] Manufacturer audits are discussed in Chapters 3–5. Advertising regulation alerts the regulator to misleading or incorrect advertising material or material that otherwise does not comply with the legislative provisions for advertising. This was not included in the scope of this audit. The approval of advertising is delegated to: the Australian Self Medication Industry for OTC products and the Consumer Healthcare Council for complementary medicines.

systematic assessment of the consequences when resources are diverted during the year.

Reviews of newly listed products

6.11 Products to be listed are lodged through an electronic system known as the Electronic Listing Facility (ELF). Sponsors certify that the product is eligible for listing,[75] and provide details such as ingredients, claims, and manufacturer(s).

6.12 If the ELF form has been completed, and the correct fees paid, the product is approved and entered onto the ARTG. The listed product may then be supplied for sale.

6.13 This lodgement process checks whether:

- ingredients are approved for use in listed medicines. That is, they are not included on the Standard for the Uniform Scheduling of Drugs and Poisons;
- claims made are general or medium level claims (see Appendix 1); and
- the product label has appropriate warnings.

6.14 The checks had been done by an inefficient manual process. This contributed to some three per cent of approvals being withdrawn from the ARTG shortly after approval. The process has now been automated through the use of a 'smart form' on the ELF. Resources saved are to be used in other areas of monitoring.

In-depth reviews

6.15 A proportion of newly listed products are subject to further in-depth review. Figure 6.2 shows the numbers undertaken recently. On average, 7.5 per cent of these reviews led to the cancellation of products from the ARTG.

6.16 The ANAO found that the TGA is strengthening the conduct of these reviews, following the improvements in the ELF. The number of in-depth reviews will increase to some 700 per year.

6.17 In addition, the method of selection has been improved. The TGA has implemented a statistically based sampling methodology for selecting

[75] For example, that: the medicine is not included in a Schedule of the SUSDP; it conforms to labelling regulations; and it is safe for the purposes for which it is to be used.

products for these reviews.[76] Until recently, selection had been, to some degree, ad-hoc and reactive.

Figure 6.2

Number of in-depth reviews conducted on the ELF system, 1999 to 2003

Activity	1999	2000	2001	2002	2003
Full reviews conducted	29	96	65	332	174
Cancelled listings	6	20	2	19	5

Source: TGA

Notes: After 2001, the reviews included labelling reviews. These checked product names, indications and the product label against requirements. The figures for 2003 represent nine months only, due to TGA system changes.

6.18 The checks undertaken on information supplied at the listing stage will also be enhanced in some cases. Further information will be sought from the sponsor. For example, the content of the product's advertising and promotional material will be reviewed to ensure that the consumer is not receiving misleading information.

6.19 The TGA advised that it intends to review the new approach six months after full implementation, to determine whether adjustments are required.

Laboratory tests

6.20 The TGA laboratory contributes to post-market monitoring through the testing and analysis of non-prescription medicinal products and ingredients. An internal agreement between the laboratory and the complementary and OTC medicines regulators governs these services.[77]

6.21 The laboratory may test whether there are substitute ingredients and whether products contain the correct quantities of active ingredients.

6.22 The number of samples and products tested for the period 2000–01 to 2002–03 are summarised in Figure 6.3. More than one sample may be tested for each product: for example, to test for variations in batches.

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[76] The ANAO found the sampling approach to be robust. It was developed by the Australian Bureau of Statistics, based on an expected 10 per cent proportion of applications with errors, a required precision of +/- four per cent, and a 95 per cent confidence interval.

[77] Each regulator has a separate MOU with the laboratory.

Figure 6.3

Number of non-prescription medicinal products tested, 2000–01 to 2002–03

Year	Samples tested	Approved products tested	Unapproved products tested	Products on the ARTG (to nearest '000)
2000–2001	628	255	47	23,000
2001–2002	311	212	24	24,000
2002–2003	369	192	40	21,000

Source: Department of Health and Ageing Annual Reports, and TGA data.

Notes: Approved products are those on the ARTG.

Unapproved products are not on the ARTG and include, for example, illegal imports seized by the Surveillance Section.

Routine and priority testing

6.23 Some two-thirds of laboratory tests are *routine* laboratory tests. These are undertaken as part of annual testing plans for products and ingredients, developed by the two regulators.

6.24 The other one-third of laboratory tests on non-prescription medicinal products or ingredients are *priority* tests, conducted on a needs basis. These are undertaken when urgent concerns arise about safety, quality or efficacy.

Level of testing

6.25 The ANAO found that only a small proportion of non-prescription medicinal products will be subject to laboratory testing. Some one to two per cent of approved non-prescription medicinal products are subject to laboratory testing each year.[78] The level of *routine* testing is estimated to be of the order of one per cent.

6.26 The TGA advised that this is commensurate with the inherent risk of listed medicines, and the degree of pre-market evaluation for most OTCs. It also considered that those products tested are done so for reasons set out in the annual testing plans. Furthermore, the TGA advised that it is confident that the safety and quality of low-risk products can be adequately assured through other aspects of monitoring elements, such as manufacturer audits and adverse reaction reports.

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[78] Figure 6.3 suggests less than one per cent. However, TGA advised numbers reported previously were inflated by products no longer being manufactured. For 2003-2004, the number of non-prescription medicinal products on the ARTG will be approximately 14 000.

6.27 However, laboratory testing also contributes to compliance through a deterrent effect. Such a low level of testing is likely to limit the deterrent effect for non-prescription medicinal products.

6.28 The ANAO considers that this reinforces the value, as suggested in paragraph 6.10, of structured consideration of the contribution, and costs, of the various elements of post-market monitoring.

Public reporting

6.29 As discussed in paragraph 6.22, more samples may be tested than products. Therefore, the ANAO notes that the Annual Report of the Department of Health and Ageing presents potentially misleading information on TGA laboratory output for all post-marketing monitoring. It reports the number of samples in a year against a target (800) of products.[79]

6.30 TGA information systems do not identify the number of products tested. The TGA advised that enhancements to its information systems will capture the relevant information in the future, allowing more accurate reporting.

Selection of samples for the annual testing plan (routine audits)

6.31 The Regulators nominate specific items, medicine groups or manufacturers for inclusion in the annual testing plans. These are placed on the annual plan, along with: the reasons why tests are required; identification of brands of products to test; and types of tests to conduct.

6.32 The Regulator considers advice from other internal and external experts before selecting items for the plan.

6.33 Selection is targeted according to the level of risk associated with the medicine. This includes risk relating to:

- intrinsic toxicity of the medicine;
- treatment failure if the medicine is ineffective; and
- medicine failure due to deficiencies in quality (for example, if the product is difficult to make, or are often made poorly).

6.34 Internal procedures require that risk analyses are conducted in support of this selection. Since mid 2004, the OTC Regulator has documented the risk analyses on each proposal for testing.

6.35 The Complementary Medicines Regulator has documented an overall matrix identifying the likelihood of inappropriate ingredients or constituents being present in a product. However, this matrix had limited information on

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[79] Department of Health and Ageing, *Annual Report, 2002–2003*, p.75.

the level and nature of risk associated with particular medicines and the associated consequences. The TGA advised that this information has not been documented because the estimated levels of risk are well recognised from experience. However, a template for conducting such risk assessments for products, or product categories, has recently been drafted in the new complementary medicines procedures manual (discussed in paragraph 6.9).

6.36 Overall, the ANAO considers that the process for developing testing plans is soundly based. However, improved documentation of the risk analyses for items selected for testing would provide greater assurance that the required risk analyses are appropriately undertaken, and that testing programs are appropriately targeted.

Selection of samples for priority testing

6.37 Priority tests are undertaken when there are urgent concerns about safety, quality or efficacy. This may arise from, *inter alia*, surveillance activity, reports of adverse consumer reactions (see paragraph 6.59), and quality problems identified in manufacturer audits.

6.38 The Regulators allow these samples to be given priority over routine testing.[80]

6.39 However, the ANAO found that limited use is made of priority product testing where exposure to risk may be emerging from limitations in the manufacturer audit program.

6.40 Chapter 4 notes that the TGA has had difficulty in undertaking audits of overseas manufacturers in some countries. While there has recently been an increase in testing of overseas products, the ANAO found that this was largely a result of safety reviews (described in paragraph 6.74) rather than as a response to outstanding GMP certification visits.[81]

6.41 The ANAO acknowledges the overseas sample results would have incidentally provided some indirect insight into the quality control of the overseas manufacturer. However, there is no evidence that audit management used the results of testing in planning how to address the backlog of audits.

6.42 As well, in the example at Figure 5.3, there was a growing likelihood during the course of auditing that unsafe products might be released into the supply chain. The TGA did not flag any of the manufacturer's products for

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[80] The circumstances under which the laboratory will conduct priority testing are outlined in the MOUs.

[81] For example, 11 samples of finished products from Asian suppliers were tested in 2000–01; 86 in 2001–02; and 110 in 2002–03. Samples were analysed for the purposes of detecting contamination with specific substances such as aristolochia acid, and podophyllatoxin. Only three samples were flagged for testing in relation to GMP issues.

priority testing during the three months before the manufacturer's licence was revoked.

6.43 The TGA advised, *inter alia*, that the widespread nature of the manufacturer deficiencies and the extent of the contamination that was possible in the manufacturer's products, meant that in this case, testing was not a practical option. The TGA further advised that laboratory resources were used to undertake detailed assessments of the manufacturer's records.

6.44 There is no documentation to support this decision. For example, detailing: the size of the sample that would be required to provide increased assurance; the number of tests necessary; and the information available from the initial audit that could assist in targeting testing.

6.45 Priority testing is part of the TGA's strategy to identify and address non-compliance. However, the TGA does not have a systematic and structured approach to the application of priority testing when post-market monitoring elements are not effective, or they are pointing towards an increasing risk.

Recommendation No.18

6.46 The ANAO recommends that the Department of Health and Ageing increase testing when there is increased risk exposure arising from limitations in the manufacturer audit program and where there is a reasonable expectation it will assist in monitoring compliance. The overall strategy for priority testing should reflect this increased use, as well as the requirement for the Manufacturer Regulator to advise the laboratory when limitations arise.

Departmental response

6.47 Agreed.

Timeliness of testing for non-prescription medicines

6.48 The laboratory is the sole service-provider of tests for the Regulator.[82] The MOU between the laboratory and each Regulator sets out standards for the length of time the laboratory has to complete tests.

6.49 The timeliness standards depend on the type of test to be conducted and sample priority. A priority sample will be allocated to a laboratory technician on the day it is received by the laboratory. A routine sample may be stored before being allocated to a laboratory technician. For example, for complementary medicines subjected to microbiological testing, the standard

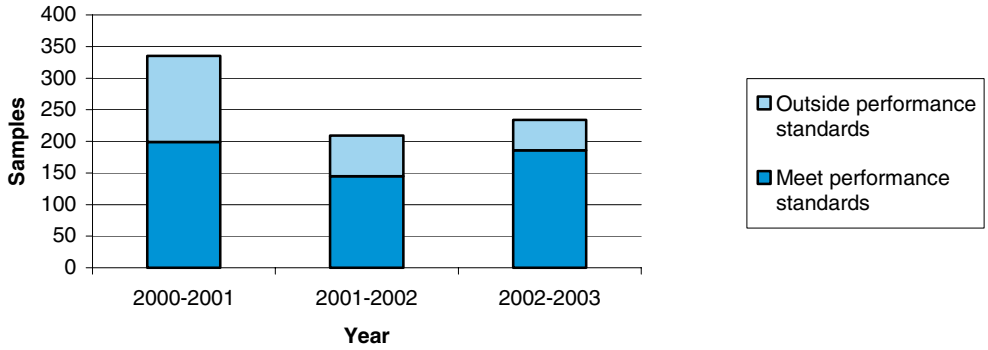
[82] However, the TGA laboratory does occasionally contract the services of an external laboratory when considered appropriate. For example, when the external laboratory specialises in a required test.

for both routine and priority testing is 40 working days once received by the laboratory technician.

6.50 Figures 6.4 and 6.5 summarise the performance of the laboratory for 2000–01 to 2002–03, compared with the timeliness standards for both routine and priority non-prescription medicines.

Figure 6.4

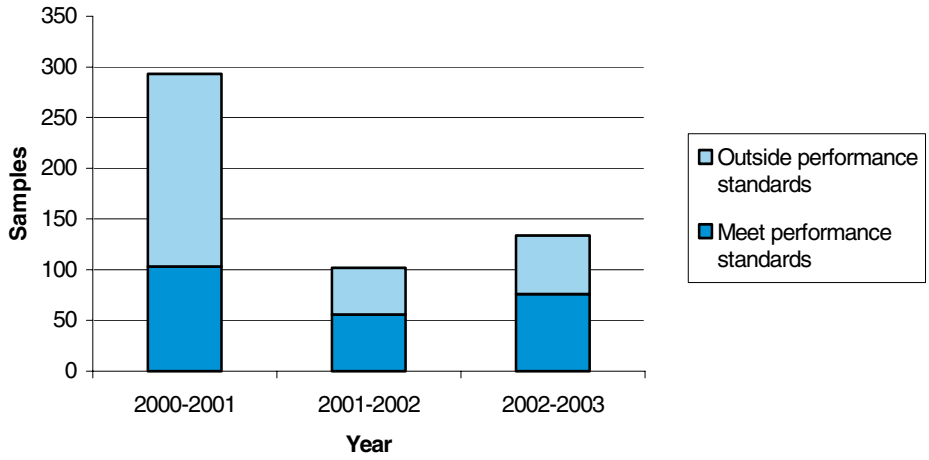
Timeliness of routine non-prescription medicine tests



Source: TGA

Figure 6.5

Timeliness of priority non-prescription medicine tests



Source: TGA

6.51 Over the three years, performance against the timeliness standards improved. It increased from 59 per cent in 2000–01, to 79 per cent in 2002–03 for routine non-prescription medicines; and from 35 per cent in 2000–01, to 56 per cent in 2002–03 for priority tests.

6.52 The ANAO notes that performance against standards, while improving, remains below the turnaround standard required by the MOU for many tests conducted. Further, performance for priority tests is below that of routine tests.

6.53 The TGA advised that the testing standards in the MOU are for indicative management purposes only. It has not set performance targets because it considers it more important to have the flexibility to direct resources to any priority issues arising.

6.54 However, the ANAO considers that performance targets and measurement against targets aids management in assessing performance and taking action as necessary. Priority tests are requested when there are urgent concerns about the medicine's safety, quality or efficacy. Performance against the standards suggests that resources are not directed sufficiently to priority testing to address urgent concerns in a timely manner.

6.55 The TGA advised that any deviations from the standard are usually discussed with the Regulators and are often noted in monthly reports. Further, a third category for sample testing, 'urgent', will be added to the testing regime during the latter half of 2004.

6.56 Improved use of performance indicators and targets would provide greater assurance of timely and adequate response to regulatory needs, and of appropriate consideration where performance is below standard.

Recommendation No.19

6.57 The ANAO recommends that the Department of Health and Ageing develop performance indicators and targets for the timeliness of TGA laboratory testing.

Departmental response

6.58 Agreed.

Adverse reactions reporting

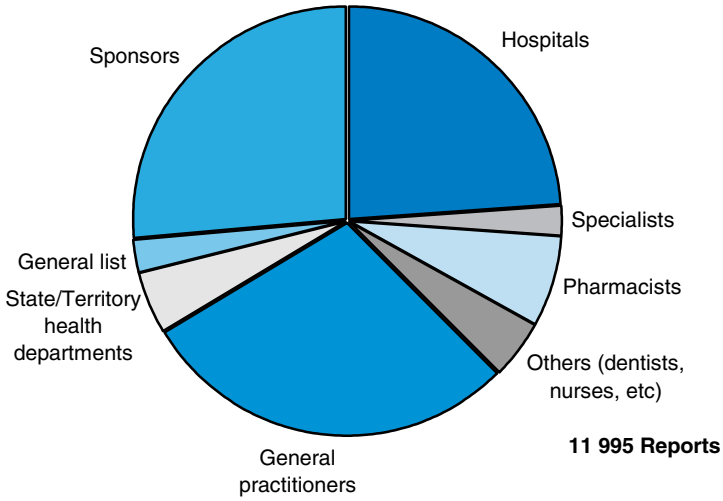
6.59 Reporting of adverse drug reactions is designed to alert the TGA to harmful, unexpected and unintended reactions to products. It is primarily aimed at monitoring reactions to properly manufactured products, but may also detect improperly manufactured products.

6.60 There were some 12 000 adverse reaction reports for all therapeutic goods in 2002–03. Figure 6.6 summarises the source of notification. It is

estimated that some six per cent of reactions are caused by non-prescription medicines.[83]

Figure 6.6

Adverse medicine reaction reports by source, 2002–03



Source: TGA Quarterly Performance Reports.

Note: Represents all medicines.

Under-reporting for non-prescription medicinal products

6.61 Sponsors of non-prescription medicinal products have formal obligations under the Act to report adverse drug reactions.[84] They may become aware of a reaction through, for example, a consumer complaint to a retailer.

6.62 The TGA considers that sponsors meet their responsibilities and report in a timely manner. However, it is recognised that there is limited reporting of adverse reactions to non-prescription medicinal products from other sources. This is especially so for complementary medicines.

6.63 The TGA advised that under-reporting occurs for the following groups, who have no legal requirement to report to the TGA:

- medical practitioners and pharmacists. For example, because a report form may not be readily available, or the event may not be recognised as an adverse drug reaction; and

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[83] Estimate from the Expert Committee on Complementary Medicines in the Health System, September 2003, page 102. The TGA is unable to identify the non-prescription medicines component.

[84] This is a condition of listing or registration. *Therapeutic Goods Act 1989*, Section 29A.

- retailers and consumers, who are unlikely to be aware of the importance of reporting adverse reactions to non-prescription medicinal products.

6.64 To address some of these concerns, the TGA has sought to make reporting easier. This includes enabling reports to be submitted: through the TGA website; an 1800 phone number; and by post. It has also sought to widen knowledge in the industry by publishing items relating to non-prescription medicines in the Australian Adverse Drug Reaction Bulletin.

6.65 In addition, the Australian Council for Safety and Quality in Health Care established an Adverse Medication Events Line in December 2003.[85] This is expected to improve consumer reporting of adverse drug events.[86]

6.66 The ANAO suggests that it may be timely to bring stakeholders together to review whether there are further opportunities to address under-reporting, especially for complementary medicines.

Assessment of adverse reaction reports

6.67 The TGA's Adverse Drug Reactions Unit (ADRU) receives and categorises adverse reaction reports as serious or non-serious, to reflect the severity of the reaction experienced (see Appendix 8).

6.68 To establish the probable cause of the reaction, the therapeutic goods used by the patient are evaluated. If the reaction suffered matches an expected or common reaction to those products, no further action is taken.

6.69 If the reaction is uncommon, or unexpected, the report is sent to the Adverse Drug Reactions Advisory Committee (ADRAC)[87] for review. However, the ADRAC reviews all reports of reactions to complementary medicines.[88]

6.70 The ANAO found that the assessment process for adverse reaction reports for non-prescription medicinal products is thorough. ADRAC may source reference material from other areas in the TGA, Australian and international medical professionals and overseas therapeutic goods regulators. Assessments by the ADRAC have led to:

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85 This service is operated by the Mater Misericordiae Health Services in Brisbane.

86 A pilot program for the service found that one in four consumer calls to the helpline resulted in an adverse drug reaction report to the Adverse Drug Reactions Advisory Committee.

87 The ADRAC is a sub-committee of the Australian Drug Evaluation Committee (ADEC). ADEC, empowered through the *Therapeutic Goods Regulations 1990*, is a committee consisting of 16–27 members with relevant expertise. ADRAC reviews about 65 per cent of reports received by the ADRU.

88 Completed assessments of adverse reactions to complementary medicines are referred to the Complementary Medicines Expert Committee for review (see Appendix 9).

- identification of patterns in reporting, such as problems with labelling or instructions for use;
- identification of specific batch problems;
- referral to other areas of the TGA for further investigation. For example, the manufacturer audit area or the laboratory; and
- a recommendation to the regulator to amend the medicine's product information, restrict availability, or remove from the market.

Monitoring and timeliness

6.71 Currently, the timeliness of actions that form the assessment process is not measured beyond initial data entry onto a TGA database. Assessment activities, such as corresponding with overseas regulation agencies and collecting product studies, are recorded manually on paper file and running sheets. The running sheets are reviewed and updated at each ADRAC meeting.

6.72 These methods do not facilitate efficient tracking of the timeliness of actions. In addition, the current system has limited capability to capture information on trends and patterns in reactions.

6.73 The TGA has investigated better means of tracking timeliness and managing information, but has yet to decide an appropriate solution.

Safety and efficacy reviews

6.74 Post-market safety and efficacy reviews are undertaken when concerns have been raised about the safety or efficacy of non-prescription medicinal products and ingredients. The reviews seek to ensure that:

- the conditions of listing or registration are still appropriate; and
- arrangements for supply of the medicine are appropriate. For example, whether a listed medicine should be upgraded to a registered medicine.

6.75 The reviews may be triggered by new information arising from:

- information in professional journals;
- actions undertaken by other regulators;
- reports in the scientific literature; or
- advice from medicine evaluators, expert committees, health professionals or the general public.

6.76 The Regulator considers the significance of the new information and the potential for risk to users, and then decides whether to conduct a review. Each review may potentially affect many hundreds of products. For example, some 300 products were potentially affected by reviews of the labelling of paracetamol and ibuprofen products in 2002.

6.77 The TGA has conducted an average of some 12 safety and efficacy reviews each year, for the years 1999–2003 (see Appendix 10). However, the TGA advised that it intends to increase the number to 40 a year–10 major safety reviews, 10 major efficacy reviews, and 20 minor reviews. Resources freed by the enhancements to the Electronic Lodgement Facility (see paragraph 6.14) will be used to meet new targets.

6.78 However, the ANAO notes that the changes have not been supported by a risk assessment. For example, to assess the consequences for compliance of limitations in the previous approach, and whether the changes will provide appropriate assurance about evidence of efficacy held by sponsors.

Conducting safety and efficacy reviews

6.79 The TGA does not have guidelines and SOPs for the conduct of safety or efficacy reviews. However, it advised that they follow a similar process to pre-market safety/efficacy assessment. It has therefore used guidelines for these processes when conducting a safety or efficacy review. The TGA advised that it is now preparing a SOP specifically for safety and efficacy reviews.

6.80 The ANAO found that the reviews range from a short survey-style review to a large in-depth review. An example of the former is a review resulting from concerns about the level of active ingredients in a medicine.

6.81 An example of the latter resulted from evidence of mis-identification of a key ingredient in a non-prescription medicine that was causing deaths in overseas countries. This review had several phases, as additional information became available during the course of review.

6.82 Appendix 10 provides examples of two reviews.

6.83 The ANAO found the review process to be effective. All the reviews examined by the ANAO met their objectives. They considered an extensive selection of literature, testing information and/or regulatory data.

6.84 The Regulator forwarded review findings, and proposals for action, to an appropriate expert committee. The Regulator made the final decision on action to be taken, following the committee's consideration. Action ranged from relatively straightforward changes to regulatory information, such as stakeholder advice, to more substantial changes to the conditions of listing or to product labelling and packet inserts.

6.85 In one review examined, a voluntary recall of products containing the ingredient of concern was one of the first actions taken. In another, changes to a condition of listing was monitored through the routine testing program, to confirm the new conditions were being met.

7. Addressing Product Non-compliance

This chapter addresses actions when the supply of non-prescription medicinal products does not comply with the Act.

7.1 Products are released to the public under a sponsor's name.[89] The sponsor is responsible for the product's safety, quality and efficacy. This applies irrespective of whether it has manufactured the product itself, or has contracted a manufacturer to produce the product.

7.2 Therefore, action by the Product Regulator is addressed to the sponsor. Administrative action available to the TGA include:

- issuing a warning letter to the sponsor;
- recall of a product from supply or use; and
- cancellation of a product from the ARTG.[90]

7.3 Section 30 of the Act establishes the TGA's ability to cancel or recall products. These provisions were strengthened in June 2003. Appendix 11 provides further information on the recall and cancellation options available to the TGA.

Warning letters

7.4 Warning letters are the most frequently used means by which the TGA addresses product non-compliance. They are used where the non-compliance is not considered to have serious consequences. That is, there are minor quality issues but no hazard to health.

7.5 The TGA's information systems do not capture information on the number, use and impact of warning letters issued. Accordingly, the TGA has been unable to advise or estimate how many warning letters have been issued. In addition, because of other data limitations, the TGA is unable to monitor its timeliness in responding to non-conformities using warning letters.

7.6 The TGA issues two types of warning letter. The first type requires the sponsor to correct an aspect of a product that the TGA considers is less than satisfactory. The sponsor is not required to cease supply. For example, the letter may require the correction of a minor labelling deficiency.

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89 Therapeutic Goods Order 69, *General requirements for labels for medicines*, requires the name and address of the sponsor or supplier of the goods to be included on the product label.

90 The Act also provides for criminal penalties (see paragraph 1.10).

7.7 The second type of warning letter advises that a defect has been identified and supply should cease until the defect is corrected. However, the sponsor is not required to recall the product. For example, sugar crystals in a liquid cough medicine may indicate a minor quality problem.

7.8 The ANAO found that, for the cases examined, the TGA had acted appropriately in addressing these kinds of non-conformity through warning letters. It had identified the reason for non-compliance, gathered sufficient evidence to assess the severity of the problem, and corresponded with the sponsor until the non-conformity had been resolved.

Managing recalls

7.9 A recall is undertaken to remove products from supply or use due to deficiencies in their safety, quality, or efficacy. In more serious cases of a threat to public health and safety, the recall may be undertaken in tandem with the cancellation of the product (see paragraph 7.45).

7.10 Recalls are generally conducted on a voluntary basis. That is, sponsors initiate the recall, for example, because sponsor testing has found a batch of tablets is not disintegrating as required. These procedures are underpinned by the Act, and the Trade Practices Act 1974.

7.11 Mandatory recalls are implemented when: the product is cancelled from the ARTG; the product is unlawfully supplied; or if the product fails to comply with a standard. In these cases, the Product Regulator initiates the recall action using the recall provisions of the Act.

7.12 The TGA's Uniform Recall Procedures for Therapeutic Goods establish the responsibilities and action to be taken by health authorities and sponsors when products are to be recalled.[91] It is the sponsor's responsibility to undertake a medicine recall and any subsequent corrective action required by the TGA.

7.13 The TGA does not separately record information on recalls for non-prescription medicines.[92] Accordingly, data are only available on the total number of recalls for all medicines, including prescription medicines. These data are summarised in Figure 7.1 for the years 1999–2003.

7.14 The large increase in 2003 is due to the recall of products manufactured by Pan Pharmaceuticals Limited.

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91 The procedures, which are publicly available, are supported by internal TGA SOPs.

92 The TGA does not record the type of product being recalled on its recalls database. The TGA advised that this information is not relevant, because a defect in a complementary medicine can be as harmful as a defect in a prescription medicine.

Figure 7.1

Medicine recalls, 1999–2003

Year	Total number
1999	48
2000	105
2001	75
2002	196
2003	1805

Source: TGA

Notes: Excludes blood and blood products, and medical devices.

The 2003 figures are as at 17 December, and include 1618 Pan Pharmaceuticals Limited products.

Planning the recall

7.15 The first step in undertaking a recall is for the TGA to assess the situation and determine recall parameters, that is, the classification, urgency and level of the recall.

7.16 The ANAO found that the TGA had developed a generally sound approach. For example, in all the recalls examined, the TGA determined and documented: details of the product and the problem; testing results; and action proposed by the sponsor.

7.17 However, until recently the TGA had not formally documented risk assessments it had undertaken to determine the danger and consequences presented by the defective products. The TGA advised that SOPs were introduced during the latter half of 2004 to address this. The SOPs require that the product defect, consequences, likelihood of occurrence, the level of risk and the overall risk assessment be assessed and documented.

Classification of recalls

7.18 Recalls are *classified* by the Recalls Coordinator in consultation with the sponsor and/or the regulator, according to the seriousness of the harm or injury that may be caused by the product. Expert advice is sought when the classification is not easily determined, or when there are safety related concerns for the product. Recalls are classed as:

- potentially life-threatening, or could represent a serious risk to health;[93]
- defects could cause illness or mistreatment; and

[93] The ANAO found that, when there is insufficient information to accurately assess the risk, the recall defaults to the most serious category, that is, Class I.

- defects may not pose a significant hazard to health, but withdrawal may be warranted for other reasons.

7.19 Class I or II recalls are 'urgent' recalls. Class III recalls are considered routine. Examples of the latter include minor labelling deficiencies and contamination of goods with non-toxic substances.

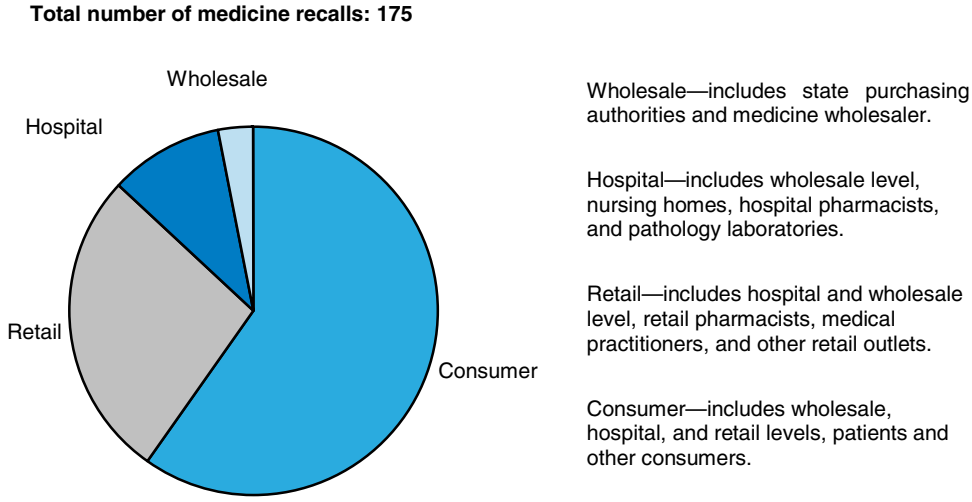
7.20 In recent years, most recalls have been classified 'urgent'.

Recall level

7.21 The recall *level* establishes who will be notified of the recall, for action. It provides for a graduated response based on the product's known distribution and the likelihood that the product will cause harm. The majority of recalls in 2002–03 were at the consumer level; that is, all parts of the distribution chain, including the consumer.

Figure 7.2

Recalls by level, 2002–03



Source: TGA data for all recalled medicines excluding the major Pan Pharmaceuticals Limited's recall.

Implementing the recall

7.22 Each recall has a separate strategy based upon the recall parameters, as well as matters such as consumer safety, distribution networks, and availability of alternative products.

7.23 The ANAO found that the TGA met the requirements of the Uniform Recall Procedures for those recalls examined. This is usually supported by use of a comprehensive checklist that serves as a process control tool. For very large recalls, there may also be a separate strategy document.

7.24 Sound procedures and templates support the broadcast of the recall to interested parties. These address, *inter alia*:

- template letters to the target recall audience, to which the product sponsor adds the reasons for the recall, together with details that easily identify the product being recalled;
- template advertisements for use by the sponsor, with the actual advertisements checked and approved by the TGA prior to use;
- issue of a media release(s), if necessary. This occurs when the deficiency presents an imminent danger to the user;
- notification of overseas regulators, if the product was exported; and
- posting of the broadcast on the TGA website, and placing a statement on the Recalls Information 1800 Service.

7.25 The ANAO found that these procedures were generally followed. There were instances where advertisements were placed in newspapers later than required because of difficulty in getting space in the required parts of the newspapers at short notice.[94] The TGA advised that it has had discussions with the media industry in an effort to develop an agreement on priority placement.

7.26 The TGA aims for all broadcasts to be released publicly within 24–48 hours of notification of a recall. However, the ANAO found that the average time between the notification of a recall and the dissemination of the notice by the sponsor was four working days for a period examined in the audit.

7.27 However, these recalls were appropriately prioritised. Critical or life-threatening recalls (Class I) were dealt with promptly, and within the TGA target. Class III recalls (not a significant hazard to health) were delayed when Class I and II recalls were prioritised. The ANAO notes that timeliness of recalls is also dependent on timely action by the sponsor.

7.28 In 2003, the TGA conducted a recall of all products manufactured by Pan Pharmaceuticals Limited. This was the largest therapeutic goods recall ever conducted by the TGA. All but one of the recalled products were non-prescription medicinal products. The majority of these were listed products.

7.29 Overall, the ANAO found that the TGA managed the Pan Pharmaceuticals Limited recall effectively. Problems that were encountered were largely due to its unprecedented size, and difficulties in obtaining and collating information from sponsors. Appendix 12 provides further information on the TGA's management of the recall.

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[94] It is intended that the advertisements be run in conjunction with the notification of impacted parties. For consumer level recalls, advertisements are inserted in the first five pages of the print media of each State/Territory where the product was distributed. Generally, dissemination in regional/rural papers or in the Australia wide press is not required.

Recall close-out

7.30 The sponsor is required to report to the TGA on the recall outcome, including providing evidence of corrective action to ensure the problem does not recur.

7.31 State and Territory Recall Co-ordinators may also be called on by the TGA to inspect suppliers of products, to ensure that recalled products have been recalled from sale.

7.32 The ANAO found that, for those recall files examined, the TGA had appropriate evidence from the sponsor of completed action. This included requesting further information or clarification from the sponsor before close out.

7.33 However, many recalls stem from manufacturer deficiencies. The TGA Recalls Unit rarely conducts on-site recall audits to follow-up corrective action by suppliers to prevent recurrence of recalls. Instead, it relies on this being addressed during the next manufacturer audit. The TGA gives priority to audits of the manufacturer if the recall was due to a serious safety issue.

7.34 However, formal feedback to the Product Regulator only occurs if the audit identified unsatisfactory corrective action. The ANAO considers that a formal report to the TGA Recalls Unit for those audits undertaken pursuant to a recall would be better practice. It would provide a greater level of assurance that the manufacturer has implemented the corrective action reported by the sponsor. This is particularly so for recalls linked to serious health issues.

Recommendation No.20

7.35 The ANAO recommends that reports be provided to the TGA's Product Regulator on the effectiveness of recall-related corrective actions implemented by manufacturers.

Departmental response

7.36 Agreed.

Timeliness

7.37 The average time to complete those recalls that were commenced in 2003 is summarised in Figure 7.3. The table covers all medicines. The TGA has a target of a 90-day average. This target was not met in the three quarters to September 2003.

7.38 The performance measure has limitations in assisting the TGA assess its effectiveness in coordinating the removal of non-compliant products from use. Measurement of the number of recalls meeting a minimum timeliness standard, especially for each of the stages of recall, would assist in this regard.

This would allow the TGA to assess, for example, the time to initiate and disseminate recalls, the time taken to recall products, and the time taken to destroy recalled products.

Figure 7.3

Medicine recalls processing time 2003, working days

	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec
Average time to completion	115	95	93	80

Source: TGA

Note: The figures relate to all medicines, including prescription medicines.

Monitoring

7.39 The Recalls Coordinator sends weekly reports on recalls to the TGA Executive, covering the number of recalls and details of significant recalls.[95] Further, a hard copy of recall files is provided to the GMP audit section and the relevant Product Regulators.

7.40 However, the ANAO found that the TGA does not conduct, and disseminate to relevant stakeholders, regular trend analysis of recalls. For example, addressing recalls per manufacturer, recalls by product and category of product, or type of fault.

7.41 Limitations in the TGA's information systems restrict, to some degree, its ability to conduct such analysis.[96] However, the TGA has also questioned the value of trend analysis, noting that there are a large number of parameters that such analysis could investigate.

7.42 The TGA is developing a new recalls system that will improve data captured for recall analysis. The ANAO consider the conduct of trend analysis using the enhanced information would provide the TGA with greater assurance that any systematic problems are identified and addressed, facilitating longer-term risk management.

Recommendation No.21

7.43 The ANAO recommends that the Department of Health and Ageing conduct, and disseminate to relevant stakeholders, regular trend analysis of recalls information, in order to assist in identifying systematic issues.

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[95] Fortnightly reports to a wider range of internal stakeholders are part of TGA's processes. However, these have not been disseminated regularly; the TGA advised that this was due to resource constraints.

[96] For example, sponsors frequently nominate more than one manufacturer for their products. However, the recalls database identifies only one manufacturer, not necessarily the one responsible for the problem. As well, the recorded reason for a recall may be out of date or incomplete.

Departmental response

7.44 Agreed.

Cancellation

7.45 The TGA will cancel a product when the product represents an imminent risk of death, serious illness or serious injury, or the sponsor fails to comply with the conditions of listing or registration.

7.46 There is limited information available from the TGA on non-prescription medicinal products cancelled because of non-compliance.[97] The information available refers only to the number of listed products cancelled due to non-compliance identified in desk-based reviews. This indicates that, over the last five years, approximately three per cent of newly listed products were cancelled when the reviews identified non-compliance (see paragraph 6.14).

7.47 Therapeutic goods may also be cancelled for safety related reasons. These may be detected, for example, during manufacturer audits or laboratory testing. A prominent example in 2003, related to unsatisfactory GMP audits of a large manufacturer, led the TGA to take regulatory action (see Figure 5.3). The regulatory action included suspension of the manufacturer's licence, and the cancellation of a large number of products. The cancellations are discussed at Appendix 13.

7.48 The cancellations for this manufacturer were undertaken following expert advice that there was an imminent risk of death, serious illness or serious injury. However, the TGA's documentation of its decision-making process on the enforcement options adopted was not complete (see Appendix 13). A sounder approach to documentation of the decision-making process would provide a more robust and accountable basis for regulatory enforcement.

[97] Normally, information is recorded for all therapeutic goods, rather than for non-prescription medicinal products.

8. Management Framework

This chapter discusses aspects of the TGA's management framework for the regulation of non-prescription medicines.

Introduction

8.1 This chapter discusses some of the overarching aspects of TGA's regulation of non-prescription medicines, and some broader themes from this audit. In particular:

- cost-recovery;
- risk management;
- information management;
- record management and documentation;
- quality management; and
- performance measurement, monitoring and reporting.

Cost recovery

8.2 The TGA is the sole provider of the regulatory activities defined in the Act. It operates on a full cost-recovery basis for these activities. Consequently, the costs to undertake the necessary regulatory activities are always recoverable through fees and charges.

8.3 The TGA imposes fees and charges under two legislative instruments (see Appendix 14):

- taxation charges are imposed under the *Therapeutic Goods (Charges) Act 1989*, and include annual charges for manufacturer licences and product registrations/listings; and
- fees are imposed under the *Therapeutic Goods Act 1989*, and include application, product evaluation and audit fees.

8.4 The TGA allocates revenues and expenses for regulatory functions using information captured by an activity-based costing system. This has enabled the TGA to estimate the revenues and expenses of the non-prescription medicines *product* regulation.

8.5 However, it is not able to separately identify regulatory effort expended on non-prescription medicine *manufacturers*. Accordingly, the TGA could only provide estimates for revenues and expenses for regulation of

manufacturers for all types of therapeutic goods. The available data for 2001–02 to 2003–04 are summarised in Figure 8.1.

8.6 The TGA advise that, because most manufacturers produce a mix of prescription and non-prescription medicines, the manufacturer regulator function is treated as a single cost centre in its activity-based costing model.

8.7 On the basis of the estimates in Figure 8.1, the non-prescription medicinal products regulation operates in deficit. In contrast, regulation of all manufacturers operates in surplus. The ANAO notes that, not withstanding this surplus, some audits were not conducted by their due date and the number of audits of non-prescription medicine manufacturers in 2003 declined (see Figure 3.1 and paragraphs 3.51 and 3.60).

Figure 8.1

Net operating result for regulator functions ($m)

Revenue/expenses	Non-prescription medicinal product regulation			All manufacturer regulation		
	2001–02	2002–03	2003–04	2001–02	2002–03	2003–04
Total revenue	8.09	8.70	10.10	2.92	3.37	4.35
Pre-market						
Application fees	1.89	2.07	1.81	0.04	0.05	0.03
Evaluation fees	1.32	1.47	1.85	n/a	n/a	n/a
Post-market						
Annual charges	4.88	5.16	6.43	1.68	1.87	1.95
GMP audit fees	0.00	0.00	0.00	1.13	1.44	2.37
Other revenues	-	-	-	0.08	-	-
Total expenses	9.29	9.06	10.30	2.26	2.53	3.37
Net operating result	(1.19)	(0.36)	(0.20)	0.67	0.84	0.98

Source: TGA.

Notes: Totals may not sum due to rounding.

Revenue and expense data for manufacturer regulation relate to the regulation of all manufacturers of all therapeutic goods.

It was not possible to separate the pre- and post-market components of GMP audit fees.

8.8 The TGA advised that it conducts a review of its activity-based costing model every two years to ensure costs and revenues are appropriately aligned and cross-subsidisation is minimised. However, in relation to the non-prescription medicines groups in the above table, fees and charges do not align with costs. More generally, there is insufficient capture and analysis of costing information to inform the TGA and stakeholders on alignment below the level in the table. For example, there is no information on costs at the non-prescription medicine manufacturer level.

8.9 Thus, manufacturers and sponsors do not have assurance that their payments are not, at least in part, cross-subsidising other TGA activities. Greater transparency about the relationship between fees/charges and the costs of activities would be appropriate to meet the TGA's obligations as a regulator operating under cost-recovery arrangements.

8.10 Given the limitations in the data for non-prescription medicine manufacturers, the ANAO sought to estimate expenditure on the regulation of non-prescription medicines only for 2003–04. This is summarised in Figure 8.2.

Figure 8.2

Estimated expenses for the regulation of non-prescription medicinal products, 2003–04 ($m)

Expenses	Product regulation	Manufacturer regulation	Total	Proportion of expenses (%)
Pre-market activities	5.98	0.01	5.99	**52**
Post-market activities	4.35	1.29	5.64	**48**
Total expenses by regulator	**10.33 (89%)**	**1.30 (11%)**	**11.63 (100%)**	**100**

Source: TGA, and ANAO analysis of TGA data.

8.11 Figure 8.2 suggests approximately 11 per cent of the total resources budgeted for the regulation of non-prescription medicines are expended on manufacturer regulation. This compares with 89 per cent for product regulation. Strategic plans and risk assessments do not provide documented details to support this distribution of regulatory effort, including whether that effort is aligned to identified risks.

8.12 As outlined elsewhere in the report, there are often instances when resources are diverted from normal regulatory work to priority work. In addition, TGA audits of non-prescription medicine manufacturers have generally been undertaken later than planned. That is, the resources available have not supported TGA's planned risk treatments.

8.13 In a cost-recovery environment, the TGA has an obligation to resource its planned risk treatments. This is part of a broader risk management, as discussed below.

Risk management

8.14 Sound and structured risk management is central to a regulator's function. It supports planning and decision-making with respect to:

- balancing education, encouragement, and compliance checking; and
- allocating resources to specific risk treatments.

8.15 The Act sets an overall strategic framework for the management of risk posed by therapeutic goods. This includes the requirement for products to be approved and classified as either registered or listed, and for manufacturers to be compliant with the Code of GMP.

8.16 The TGA has a short *Statement of Principles* policy document on risk management. As well, during the course of this audit, the TGA published a statement of its risk management policies.[98]

8.17 Assessment of risk is also an important element in the TGA's operational procedures. For example, risk considerations influence the setting of audit frequency and product testing.

8.18 However, the earlier chapters of this report indicate that there are a number of ways in which more structured and consistent risk management would substantially enhance regulation of non-prescription medicines. These include:

- allocation of resources to various risk treatments (for example, between product and manufacturer regulation, and particular compliance tools);
- systematically addressing differences that may arise in risk treatments between Australian and overseas manufacturers;
- ensuring information is collected and utilised to support management of risk and monitoring of risk treatments;
- explicitly identifying risks (for example manufacturers' risks);
- identifying residual risks, and contingency plans to deal with these risks;
- providing a structured means of sharing information on risk strategies and outcomes between the various parts of the TGA;
- ensuring new or targeted strategies are based upon structured risk assessments, and evaluating their outcomes for lessons learned for future management of compliance; and
- providing a means of assessing the impact of slippage on planned risk treatments.

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[98] Therapeutic Goods Administration, *The Therapeutic Goods Administration's Risk Management Approach to the Regulation of Therapeutic Goods, Version 1 of July 2004* [Internet]. <http://www.tga.gov.au/about/tgariskmnt.pdf> [accessed 12 September 2004].

Recommendation No.22

8.19 The ANAO recommends that the Department of Health and Ageing review and enhance the TGA's risk management framework for non-prescription medicinal products. The revised framework should, *inter alia*,:

- be systematic, structured and integrated with the TGA's overall risk management strategies;
- allocate resources to various risk treatments;
- identify any necessary differences in risk treatments between Australian and overseas manufacturers, and their impact;
- provide information necessary to support effective management of risk and monitoring of treatments;
- ensure new or targeted strategies are based upon structured risk assessments, and evaluate their outcomes for lessons learned for future management of compliance; and
- identify the impact of slippage on planned risk treatments.

Departmental response

8.20 Agreed.

Information management

8.21 As discussed elsewhere in this report, much of the information obtained by the TGA through its regulatory processes is not captured by the TGA's management information systems. For example, key information on manufacturer deficiencies and levels of compliance are not on the systems.

8.22 Accordingly, information that would inform management of compliance is not readily available. As previously noted, collection of information presented in this audit has been a time consuming, often paper file-based manual process, and subject to errors.

8.23 As well, important information is often: not entered on systems, as required by the TGA's procedures; out of date; or entered incorrectly. The TGA's information systems are not well integrated, limiting its ability to effectively share information to assist in managing regulation.

8.24 These weaknesses limit the TGA's ability to make risk-based decisions based upon all the information available to it, including trend analyses of key areas. It also limits monitoring of, and accountability for, performance.

8.25 The TGA has advised that a new GMP audit management information system is expected to come into production end 2004. It considers that it will address many of these shortcomings.

8.26 However, the design specifications for the new system do not yet include some key information identified in this audit that would assist audit management, such as type and categorisation of deficiencies identified in audits. As importantly, weakness in the accuracy and completeness of information on current systems needs to be addressed, to obtain the benefits from the new system.

Recommendation No.23

8.27 The ANAO recommends that the Department of Health and Ageing strengthen the capture, recording, management and use of information to support regulation of non-prescription medicines by:

- holding key information collected from its regulatory processes on management information systems;
- maintaining the reliability and completeness of data holdings; and
- enabling better integration and sharing of information between the different areas of the TGA involved in regulatory functions.

Departmental response

8.28 Agreed.

Record management and documentation

8.29 Good recordkeeping[99] supports communication and decision-making and is fundamental to the successful achievement of an organisation's objectives. An effective regulatory system includes sound records management, including documentary records of key regulatory decisions and the reasons underpinning them.

8.30 However, the ANAO found, as discussed elsewhere in this report, that some key decisions have not been supported by formal documentation of the decisions, including reasons and supporting evidence.

8.31 Also, manufacturer inspection files were often poorly compiled. Papers were not folioed or chronologically maintained;[100] required proformas were missing or incomplete; and some key documents relating to an audit were not

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[99] See ANAO Audit Report No.7 2003–2004 *Recordkeeping in Large Commonwealth Organisations*.

[100] This is a requirement of Health's Departmental Record Keeping Procedures.

on file.[101] Important documents, such as letters of intention to suspend, were filed without signature or a date.

8.32 Obtaining key information required for this audit, therefore, necessitated examination of archived email records and personal notebooks and diaries.

Recommendation No.24

8.33 The ANAO recommends that the Department of Health and Ageing strengthen its documentation procedures to ensure key regulatory decisions taken by the TGA are fully documented, and that files are appropriately maintained.

Departmental response

8.34 Agreed.

Quality management

8.35 The TGA's operations have been subjected to several detailed reviews over the last three years. In particular, two major reviews recommended the extension of, and improvements to, existing quality management systems.[102] The TGA accepted these recommendations and undertook to upgrade quality management processes in each of the main regulatory functional areas.[103]

8.36 As outlined elsewhere in this report, several initiatives have been instituted to better manage quality, but progress on some initiatives has not matched expectations, or has been partial. For example:

- new procedures were only introduced during this audit that requires every audit to be reviewed by senior audit management; and
- there has been delay in implementing a formal auditor assessment and feedback program.

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[101] For example, correspondence between the TGA and the manufacturer was not always complete.

[102] The two reports were:

a. *Risk Analysis in the Therapeutics Goods Administration*, Oceania Health, final report dated September 2001. Referred to as the Wall Report; and

b. *Review of TGA Audit and Licensing of Good Manufacturing Practice*, Brian Corcoran, March 2002. Referred to as the Corcoran Report.

[103] In addition, internal management reviews of the conduct of GMP audits had identified consistency as an issue and considered a stronger quality management regime was warranted. Senior audit management had trialled an internal audit program of auditors in late 2001, but the trial was not completed and the initiative was not institutionalised.

8.37 The ANAO notes that the GMP audit unit ceased its ISO 9000[104] and NATA[105] accreditations in 2003.

Recommendation No.25

8.38 The ANAO recommends that the Department of Health and Ageing review and improve the TGA's quality assurance program to improve the quality, consistency and reliability of its GMP audits.

Departmental response

8.39 Agreed.

Performance measurement, monitoring, and reporting

8.40 The TGA publishes its Corporate Plan and its Customer Service Charter on its website. Also, each operational unit of the TGA develops an annual business plan that includes the setting of performance targets, and strategies for achieving the targets.

8.41 A compilation of workload statistics is prepared quarterly and distributed internally within the TGA. These quarterly reports, and other performance information, are discussed with industry representatives during the year.

8.42 However, the reports from the non-prescription medicines or manufacturer Regulators do not include outcome information, or analyses of trends in the statistics. They are also restricted by the limitations in the management information systems discussed above.

8.43 The TGA does not measure the overall compliance of industry with the Code of GMP, nor with non-prescription medicinal product requirements. It publishes one effectiveness indicator. This is the proportion of goods on the ARTG failing to meet standards as a result of post-market testing by the TGA.

8.44 This indicator provides only limited insight into the TGA's effectiveness in achieving its regulatory objective. For example, it does not provide an indication of whether the TGA is being more or less effective at regulating non-prescription medicinal products, nor whether the industry is improving its compliance with standards.

8.45 A strengthened performance management system that includes statements of outcomes, key performance indicators and performance targets

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[104] International Standards Organisation protocol on quality management.

[105] National Association of Testing Authorities–NATA.

will assist and inform planning and management and provide for better accountability to stakeholders.

8.46 Enhanced performance reporting to stakeholders would also be more consistent with the TGA's role as a regulator, improving its transparency and accountability for all stakeholders.

Recommendation No.26

8.47 The ANAO recommends that the Department of Health and Ageing implement a performance management system that defines key outcomes, key performance indicators and targets for the regulation of non-prescription medicinal products.

Departmental response

8.48 Agreed.

Canberra ACT
16 December 2004

P. J. Barrett
Auditor-General

Appendices

Appendix 1: Levels of therapeutic promise and therapeutic claims

Level of claim	Type of claim	Example
High-level	• Product treats, cures, or manages a high-level disease or condition; • product prevents a high-level disease, disorder or condition; or • product treats a specific vitamin or mineral deficiency disease.	Products for the treatment of depression.
Medium-level	• Product enhances health; • product reduces the risk of a medium-level disease, disorder or condition; • product reduces the frequency of a discrete event; • product aids or assists in the management of a named symptom, disease, disorder, or condition; or • product relieves the symptoms of a named disease, disorder or condition.	Products which may be beneficial during times of stress.
General-level	• Product maintains health, including via nutritional support, and vitamin or mineral supplementation; or • product promises the relief of symptoms not related to a named disease, disorder or condition.	Products which aid digestion.

Source: TGA

Appendix 2: MRAs and MOUs/cooperative arrangements

The following tables summarise GMP agreements at 31 July 2004.

All countries in the tables regulate OTC medicines to a GMP standard equivalent to Australia. However, this is not the case for complementary medicines (CM).

Countries with which Australia has an MRA

European Union MRA

Country	Regulates CM as medicines
Austria	Yes
Belgium	Yes
Denmark	Yes
Finland	Yes
France	Yes
Germany	Yes
Greece	Yes
Ireland	Yes
Italy	Yes
Luxembourg	Yes
Netherlands	Yes
Portugal	Yes
Spain	Yes
Sweden	Yes
United Kingdom	No

Countries that joined the EU 1 May 2004	Regulates CM as medicines
Cyprus	(unknown)
Czech Republic	(unknown)
Estonia	(unknown)
Hungary	(unknown)
Latvia	(unknown)
Lithuania	(unknown)
Malta	(unknown)
Poland	(unknown)
Slovak Republic	(unknown)
Slovenia	(unknown)

European Free Trade Association (EFTA) MRA

Country	Regulates CM as medicines
Iceland	Yes
Liechtenstein	Yes
Norway	(unknown)

Pharmaceutical Inspection Convention (PIC) MRA

Country	Regulates CM as medicines
Romania	(unknown)
Switzerland	Yes

Bilateral MRAs–New Zealand and Singapore

Country	Regulates CM as medicines
NZ MRA	No. Food-type dietary supplements not regulated as medicines.
Singapore MRA	Yes. For proprietary traditional Chinese medicines only.

Note: The new Trans-Tasman therapeutic goods regulatory regime, expected to become effective from 1 July 2005, will replace the NZ MRA.

Countries with which Australia has an MOU/cooperative arrangement

Multilateral cooperative arrangement

Pharmaceutical Inspection Cooperation Scheme

Country	Regulates CM as medicines
Canada	No. Regulated as natural health products. Manufacturers not audited by the regulator.
Malaysia	Yes. For traditional and herbal medicines only.

Note: The TGA expects an MRA with Canada to be signed by December 2004.

Bilateral MOUs/cooperative arrangements

Country	Regulates CM as medicines
Japan MOU	Yes. For herbal medicines only.
USA Cooperative Arrangement	No. Regulated as dietary supplements under the Dietary Supplement Health and Education Act.

Source: All tables sourced from the TGA.

Appendix 3: Classification of GMP compliance, 1992–2003

Years	Compliance ratings	Comments
1992-1994	High Acceptable Marginal Unacceptable	TGA-defined classification. For a short period in 1994, a fifth classification was used-critically unacceptable.
1995-1998	Acceptable Marginally acceptable Marginally unacceptable Unacceptable	TGA-defined classification.
1998-2001	Acceptable Unacceptable	EU standard. Adopted April 1998.
2001 to date	High (A1) Satisfactory (A2) Minimal (A3) Unacceptable (U)	TGA-defined classification. Adopted July 2001.

Source: TGA SOPs and other documentation.

Note: Years are an estimation by the ANAO due to incomplete TGA documentation.

Appendix 4: Audit effort for non-prescription medicine manufacturers, 1999–2003 (hours)

The ANAO estimated the audit effort expended by the TGA on licensing/certification audits and routine/special audits of non-prescription medicine manufacturers for the period 1999–2003.

Type of audit	1999	2000	2001	2002	2003
Initial licence/certification					
Australian manufacturers	135	99	97	133	47
Overseas manufacturers	286	424	247	236	39
Routine/special audits					
Australian manufacturers	916	821	731	691	1,588
Overseas manufacturers	116	310	301	414	157
Total audit hours	**1,453**	**1,654**	**1,376**	**1,474**	**1,831**

Source: ANAO analysis of TGA data.

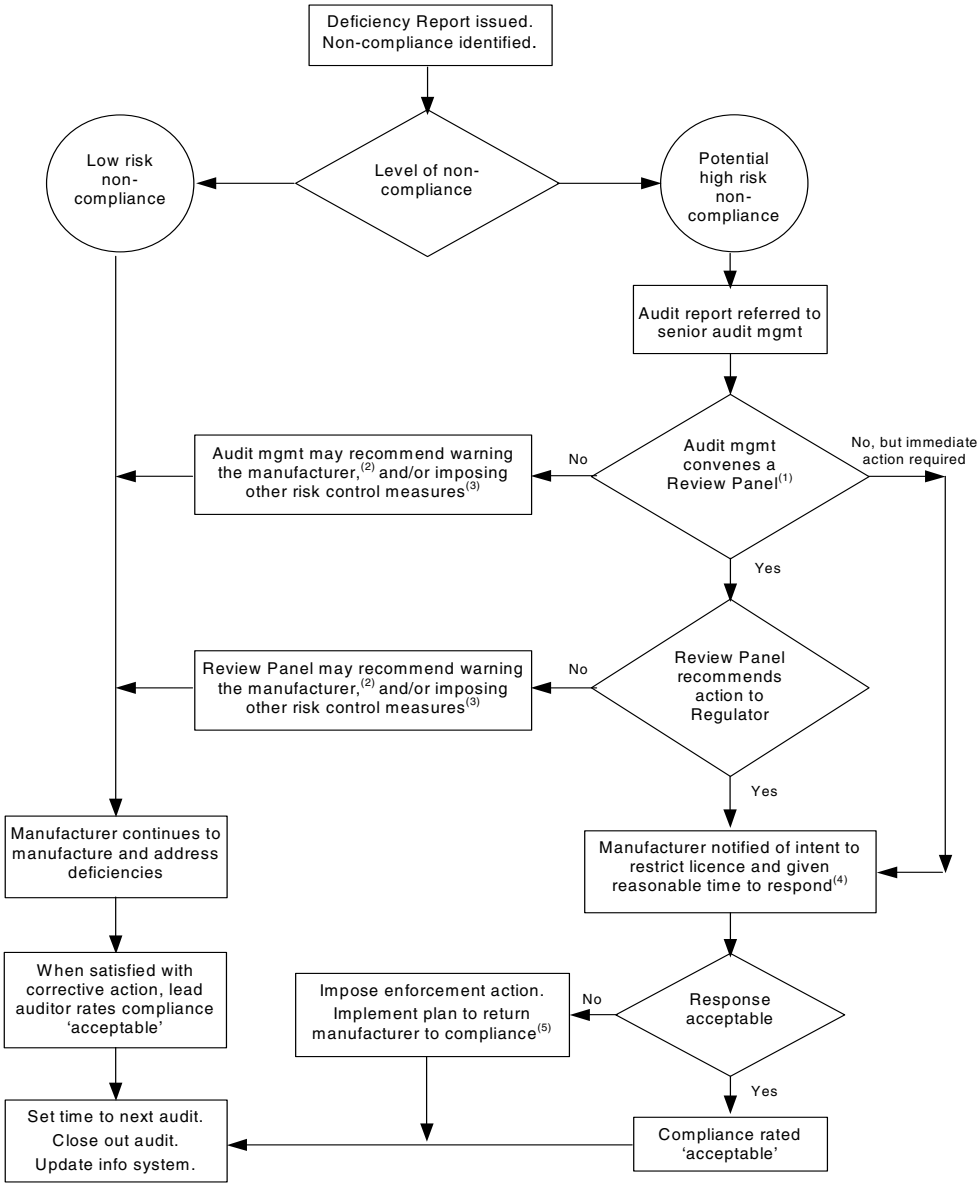
Note: Audit effort has been calculated from the TGA's manufacturer databases as at the end of 2003. The TGA advised that the effort expended on overseas certification audits in 2003 is now recorded as 102 hours.

Appendix 5: Classification of deficiencies, 1995–2003

Commenced in	Classification
1995	Critical Significant Minor
1998	Significant Minor
1999	Significant Other
2000	Critical Other significant
2002	Critical Major Other

Source: TGA

Appendix 6: Key TGA steps in addressing manufacturer non-compliance



Notes:
(1) During the audit, the TGA changed its SOPs to mandate the convening of a Review Panel by audit management.
(2) In addition to a warning, short term reporting may be imposed on manufacturer.
(3) For example, shorten time to next audit or conduct a special audit.
(4) If deficiencies present an imminent risk of death, serious injury or illness, the Regulator's decision is immediate.
(5) GMP audit required to confirm corrective actions are effective, allowing enforcement action to be removed.

Source: ANAO

Appendix 7: Example of addressing a manufacturer's non-compliance

The TGA conducted a special audit of a complementary medicines manufacturer in August 2002, focussing on an adverse reaction to one particular product.[106] The manufacturer was assessed as having two critical, and a number of other, deficiencies and unacceptable compliance.[107] A Review Panel recommended a full audit as soon as possible, in order to make a comprehensive assessment of the manufacturer's GMP compliance.

The full audit was conducted in December 2002. The audit revealed an additional eight critical and 25 major deficiencies. The company was formally advised that the deficiencies were considered serious, would be referred to a Review Panel and that licence suspension was a possibility.[108]

The Review Panel agreed with the seriousness of the deficiencies and recommended, *inter alia*, a notice of intent to suspend the company's licence be sent as soon as possible. The TGA did not issue a notice of intent, but rang the company to express concern regarding the seriousness of the deficiencies. Subsequently, the Chief GMP Auditor wrote to the company in February 2003 advising that its compliance was unacceptable and warned that, if its responses to the audit's Deficiency Report were not satisfactory, he intended to initiate action to suspend the licence.

The manufacturer submitted corrective action plans. However, in March 2003, the TGA wrote to the company advising that many aspects of its response were unsatisfactory. (The manufacturer advised that it did not receive this letter, and did not receive further communication from the TGA until July 2003.)

The letter advised that the matter had been referred back to a Review Panel. However, regulatory action was not taken, rather an audit was recommended to review corrective actions. The limited nature of the TGA's records makes it difficult to assess whether the evidence available supported the decision not to take regulatory action.

The recommended audit was conducted in July 2003. Overall progress and effectiveness of proposed and implemented corrective actions was considered unsatisfactory. Consequently, compliance was again assessed as unacceptable. The TGA advised that it undertook extensive testing of the manufacturer's

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[106] Prior to the audit and in accordance with its procedures, the TGA took samples of the product for testing and directed the product be recalled. The manufacturer ceased production of the recalled product.

[107] The TGA's electronic management information system incorrectly records the compliance status as 'acceptable'.

[108] At the time of the audit, the company was requested to submit a formal risk analysis to the TGA. It was provided in mid-January 2003.

products. No specific product was identified as having safety or quality concerns warranting recall.

The TGA issued a notice of intent to suspend the licence in August, and gave the manufacturer 28 days to respond.

In August and September 2003, the manufacturer provided responses to the July audit's Deficiency Report and to the notice of intent to suspend the licence. The manufacturer's responses to many deficiencies were assessed as unsatisfactory. However, suspension was not pursued. A further audit was scheduled for October 2003.

The October audit was conducted, as planned, and the findings referred to a Review Panel. The audit noted that the company had made substantial efforts and progress since the last audit in correcting most of the critical deficiencies. However, the TGA decided to condition the licence, preventing the manufacture of microdose products. (It was later established that it did not manufacture these products). Also, the Review Panel recommended that: the company be placed on short term reporting (every month); quality alert sampling to be undertaken for microdose products; and an unannounced audit be conducted before the end of the year–to confirm the effectiveness of corrective actions.

The recommended audit was not conducted until February 2004. It found the company to have acceptable compliance.

The TGA advised that the three audits (July 2003, October 2003 and February 2004) were, in effect, 'follow-up audits' for the December 2002 audit. Further, the TGA advised that it had monitored the risks posed by the manufacturer over the period December 2002 to February 2004 and had assessed the manufacturer's non-compliance as not posing a risk to public health and safety sufficient to warrant imposing strong regulatory action.

Appendix 8: Triage criteria for Adverse Reaction Reports

Reaction	Criteria
Serious	Admission to hospital Prolonged hospitalisation Persistent or significant disability or incapacity Life-threatening Fatal Birth defect Critical reaction term Unusual or unexpected reaction
Non-serious	All other reactions

Source: Standard Operating Procedures for Adverse Reaction Reports, TGA

Appendix 9: Adverse Reaction Reports referred to the CMEC, 2002–2003

Month	2002	2003[a]
February	15	39
March	32	19
May	25	14
June	17	75 (44)
August	20	99 (40)
September	24	72 (7)
November	18	60 (8)
December	21	70 (4)

Source: Compiled by ANAO from TGA data

Notes: Figures in parenthesis refer to the number of reports where Pan Pharmaceuticals Limited may have manufactured one or more medicines used by the patient.

Appendix 10: Reviews of non-prescription medicinal products and substances, 1999–2004

Year	No. of reviews
1999	8
2000	8
2001	16
2002	10
2003	20
2004 [a]	11[a]

Source: TGA

Note: To June 2004

The ANAO assessed 14 reviews. Most had one phase, but three reviews had more than one phase to address new information found during the course of review. The outcomes of a single-phase and a multi-phase review are described below.

Single-phase safety review

Magnolia officinalis

The regulator received a warning from Health Canada relating to the ingredient *Magnolia officinalis*. The regulator considered the warning significant enough to reassess the existing approval of the ingredient for use in listed medicines.

Relevant literature and adverse reactions data were reviewed in light of the warning. The review recommended that no changes were required to the use of *Magnolia officinalis* in listable medicines. The regulator agreed with this finding.

Multi-phase safety review

The review for Kava (Piper methysticum)

The TGA began to monitor kava in 2001, after several adverse reactions and deaths were reported overseas. A specific expert group, the Kava Expert Group, was formed to consider the findings and provide CMEC, and the TGA, with expert advice.

CMEC recommended that the TGA treat medicines containing kava with caution, and that it issue appropriate practitioner and consumer alerts. The TGA issued this advice via the TGA website.

By July 2002, the laboratory had tested medicines containing kava. These tests showed variations between the content and label claims.

In response to an adverse reaction report of a kava-related Australian fatality in 2002, the TGA:

- implemented a voluntary recall of all medicines containing kava;
- reviewed the conditions of approval for use in listed medicines; and
- added warning statements to the labels for medicines containing kava.

In 2003, the TGA agreed certain forms of kava were suitable for use in listed medicines. The Therapeutic Goods regulations were changed accordingly.

The TGA cancelled and recalled any products containing kava that were no longer suitable for supply.

Appendix 11: Recall and cancellation options

Prior to June 2003, the TGA could cancel or recall products under the following provisions of the Act:

- s.30 enabled the TGA to cancel and recall products where it appeared to the Secretary[109] that, *inter alia*, failure to cancel that product's registration or listing would create an imminent risk of death, serious illness or serious injury; and
- s.30B enabled the TGA to recall products where the Secretary was satisfied that, *inter alia*, the goods did not conform to a standard applicable to goods of that kind.

Section 30EA was added in June 2003, which allows goods to be recalled where manufacturing principles have not been observed.

A product may be cancelled immediately, or after the sponsor has been provided with reasonable opportunity to respond to the proposed cancellation. The circumstances where a product may be cancelled immediately include:[110]

- where the failure to do so would create an imminent risk of death, serious illness or serious injury;
- when the medicine contains substances that are prohibited imports;
- whether the sponsor has refused or failed to comply with the conditions that apply to a listed or registered product; and
- whether incorrect information was provided when the product was initially entered on the ARTG.

A summary of the available regulatory activities follows.

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[109] The Secretary delegates this role to certain officers of the TGA.

[110] *Therapeutic Goods Act 1989*, Section 30(1).

Regulatory action	Example of circumstances	Outcome
Administrative action—notice of non-compliance and a request to remedy.	Minor label deficiency	Sponsor is able to correct the deficiency without interruption to supply, no impact on consumers
Administrative action—notice of non-compliance and a request to remedy. Warning of cancellation if not corrected.	The deficiency does not pose any hazard to health, but action may be initiated for other reasons such as a harmless precipitate indicating minor quality problem.	Manufacture and supply is temporarily ceased to allow rectification. Impact on supply and consumers is minimal.
Administrative action—notice of non-compliance and a request to initiate wholesale recall and remedy. Warning of cancellation if not corrected.	The deficiency does not pose a significant hazard to health, but withdrawal may be initiated for other reasons (class III recall). For example, preservative inefficiency.	Manufacture and supply is temporarily ceased and wholesale level recall conducted. Product already in the supply chain is not withdrawn. Supply to consumers will be disrupted when retail stocks are exhausted.
Administrative action—notice of non-compliance and a request to initiate retail level recall. Warning that listing/registration will be cancelled if not corrected.	The deficiency could cause illness or mistreatment, but is not potentially life-threatening nor a serious risk to health (class II recall).	Manufacture and supply is ceased immediately, and a retail level recall conducted. Product already purchased by consumers is not affected.
Administrative action— notice of non-compliance and a request to initiate consumer level recall. Warning that listing/registration will be cancelled if not corrected.	The deficiency is potentially life-threatening or could cause a serious risk to health (class I recall).	Manufacture and supply is ceased immediately, and a retail level recall conducted. Consumers are alerted not to take the product and return it to retailers.
Medicine listing/registration is cancelled	Product has flaws in safety, efficacy or quality that cannot be corrected by regulatory action, for example the product must be reformulated	Product is no longer authorised for supply. Recall may also be required as above. Consumers will no longer be able to purchase the product.
Medicine listing/registration is cancelled and civil or criminal prosecution initiated.	Product deficiency is the result of criminal or negligent action by the sponsor.	Product is no longer authorised for supply. Recall may also be required as above. Consumers will no longer be able to purchase the product.

Source: TGA.

Appendix 12: A large product recall

Following a series of GMP audits at Pan Pharmaceuticals Limited's (Pan) manufacturing site, the TGA initiated a consumer level recall of all products manufactured by Pan since the last acceptable GMP audit in May 2002. The recall was mandatory for all products sponsored by Pan, and voluntary for non-Pan sponsored products.

The recall of all Pan manufactured products was the largest therapeutic goods recall ever conducted by the TGA. All but one of the recalled products were non-prescription medicinal products, and the majority of these were listed products.

The TGA developed a recall strategy outlining the process to be followed for the recall. In addition, a very detailed checklist was developed listing the tasks, officers responsible for undertaking the tasks, and expected completion dates and times.

The tasks undertaken by the TGA prior to, and during, the recall were extensive, for example:

- identifying all products possibly manufactured by Pan, the sponsors of these products, and the countries to which products may have been exported;
- sending a Recall Package to affected sponsors, summarising their recall responsibilities, and the procedures to follow;
- notifying authorities in 55 countries which imported Pan products;
- briefing media, parliamentarians, industry and consumer associations;
- establishing a call-centre to answer recall queries; and
- regularly updating the TGA's website.

Sponsors identified as having Pan as a possible manufacturer of at least one of their products were asked to confirm, within 48 hours, whether any of their products had been manufactured by Pan since 1 May 2002.

The TGA found that some sponsors did not have ready access to information on the manufacturer of products, or the batch numbers of the products produced by each manufacturer. This caused delays in reporting to the TGA. Subsequent to the recall, the Act was amended to require sponsors to retain this information.

Details of recalled products and batch numbers were released in 13 metropolitan newspapers. The list of products was updated as more information was received from sponsors. Advertisements also appeared in 360 non-metropolitan daily and weekly papers starting 6 May 2003.

In addition to the newspaper advertisements, the TGA disseminated a booklet to more than 6000 pharmacies listing all products subject to recall up to 5 May 2003.

The TGA used State and Territory Recall Coordinators to report and monitor the effectiveness of the recall.

In summary, 1 618 products were recalled. The TGA advised that all of these products were removed from supply and have either been destroyed or are being held in supervised storage areas, pending the outcome of legal or other issues with the Pan administrators.

Appendix 13: Product cancellations in connection with a large manufacturer

A large manufacturer supplied products to the domestic market by two means–firstly, directly as the sponsor and manufacturer of the product, and secondly, by manufacturing products for other sponsor.

Where the manufacturer was also the sponsor, the TGA cancelled the products under s.30(1)(a) of the Act, and then recalled any products already supplied to the public under the then s.30(6) of the Act.[111] 219 products supplied to the domestic market were cancelled and recalled, and 1 659 export products were cancelled in this action.[112]

Where the manufacturer was not the sponsor, the TGA did not cancel the products. Instead, the TGA imposed a condition that the manufacturer could no longer make the products. Affected sponsors were requested to voluntarily recall products manufactured since 1 May 2002—the date of the last acceptable audit. This action affected 1 399 products.[113] While the recall was voluntary, sponsors were 'strongly encouraged to immediately initiate' the recall. Section 30 of the Act allowed the TGA to cancel the product if the sponsor did not comply with this request.

The TGA's records around the decision-making process are not complete. There was a draft contingency plan, but that was not implemented. There is no subsequent documentation that outlines the reasons for the two different approaches to enforcement. Notwithstanding the incomplete documentation, the ANAO considered the two different approaches were consistent with the available facts and practical considerations. For example, the manufacturer had failed to rectify problems in its manufacturing processes that led to a consumer level product recall earlier that year. On the other hand, cancelling the product listings or registrations where the manufacturer was not the sponsor would have required the sponsors to re-apply for approval, should they wish to continue to sell the product.

It may be that it was considered more convenient and efficient to protect the public by undertaking a voluntary recall of these products, and allowing the to continue supplying the product through a different manufacturer.

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[111] Section 30(6) was removed in June 2003. The recall provisions are now covered by Section 30EA of the Act.

[112] Products exported to other countries cannot be recalled by the TGA under its Act.

[113] Letters provided to sponsors only explained the overall reason for regulatory action. That is, there was an imminent risk of death, serious illness or serious injury.

Appendix 14: Fees and charges

An Australian manufacturer seeking a licence is required to pay an application fee for the initial licensing audit based on the number of hours taken to complete the on-site component of the audit.

In addition, Australian manufacturers pay an annual licence charge. There are two levels—low and high—determined by the type of product(s) produced. For example, a herbal or homoeopathic medicine manufacturer is subject to the low level licence charge reflecting the relatively low level of effort required to complete a GMP audit of that type of manufacturer. An OTC manufacturer, however, is levied the high level charge because of the greater effort required to complete a GMP audit of this type of manufacturer.

The low level and high level licence charges allow for 16 and 48 audit hours respectively over three years before GMP audit fees are imposed. In addition, the TGA imposes an audit fee, charged hourly, when the accumulated number of on-site audit hours exceeds the allowance.[114]

For overseas manufacturers, the product sponsor, rather than the manufacturer, is charged for GMP-related activities. The sponsor is required to pay the full costs of the TGA conducting a GMP audit, or the costs expended by the TGA in obtaining and assessing GMP evidence from countries with which Australia has an MRA or MOU/cooperative arrangement (see Chapter 2).

Product-related fees and charges

A product sponsor pays an application fee to the TGA to list or register a product on the ARTG. In the case of a registrable product, the sponsor is required to pay for the evaluation of the claims made in the application. Once a product is registered/listed, the sponsor pays an annual charge to maintain the product's registration/listing.

[114] The average number of hours may be exceeded because audits take longer to complete, number of audits of the manufacturer is above average or number of auditors assigned to the audit team increases.

GMP-related fees and charges for manufacturers, 1999–2000 to 2003–04 ($)

Fees/charges	1999–00	2000–01	2001–02	2002–03	2003–04
Licence application fee (Australian manufacturer)					
Application fee	540	540	580	620	645
GMP clearance fees (overseas manufacturer)					
Assessment of GMP evidence	165	165	180	190	240
Obtaining GMP evidence	-	-	-	-	210
GMP audit fees (hourly rate)					
Australia	355	355	380	400	415
Overseas	745	745	790	840	870
Annual charges (Australian manufacturer licences)					
Low level	3,500	3,500	3,730	3,970	4,100
High level	6,800	6,800	7,250	7,710	7,965

Source: TGA.

Notes: Clearance fees apply when the TGA obtains or assesses evidence of manufacturer compliance from MRA/MOU/cooperative arrangement partners. Prior to 2003–04, no separate charge was levied for obtaining GMP evidence.

Product-related fees and charges for non-prescription medicinal products, 1999–2000 to 2003–04 ($)

Fees/charges	1999–00	2000–01	2001–02	2002–03	2003–04
Application fees					
Registered products	540	650	690	730	755
Listed products	270	400	430	460	475
Evaluation fees (for registration of OTC and complementary medicines products)					
If no clinical or toxicological data	4,300	4,300	4,580	4,870	5,030
With clinical or toxicological data (depending on page count of data)	4,300–30,000	4,300–30,000	4,580–31,980	4,870–34,000	5,030–35,105
Annual charges					
Registered products	455	465	500	530	690
Listed products	270	350	370	390	505

Source: TGA.

Notes: Applications for listing through the ELF system are not charged an evaluation fee. Low volume and low value products are exempted from annual charges.

Setting fee levels

The TGA has established procedures with industry to increase the transparency of the process to vary fees and charges. Annual increases in fees and charges are generally limited to an agreed indexing formula to take account of economy-wide CPI and wage cost increases.

However, the TGA may impose additional increases to ensure the costs of its operations are fully recovered from industry. For instance, in 2003–04, the TGA increased annual product charges applicable to non-prescription medicines (registered and listed) by approximately 30 per cent to arrest the decline in the level of its financial reserves and to fund the cost of additional post-market monitoring responsibilities arising from legislative changes. Therefore, an additional (to the price and wage indexation) increase was 'applied to most annual charges to ensure full cost-recovery of post-market monitoring and compliance activities'.[115]

Increases to fees and charges are discussed with industry on at least three occasions as part of the TGA's annual budget process. Bilateral meetings with industry associations are conducted early in the budget's preparation. The draft budget, including the proposed fees and charges schedule, is discussed at the May meeting of the TGA-Industry Consultative Committee (TICC).[116] In November, the TGA presents a report to TICC on the TGA's budgetary outcomes for the first fiscal quarter, highlighting actual versus budgeted revenue outcomes resulting from of the adoption of the new schedule of fees and charges at the beginning of the fiscal year.

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[115] Therapeutic Goods Administration, *Notes accompanying summary of fees and charges at 1 July 2003* [Internet]. TGA, 2003, available from <http://www.tga.gov.au/docs/html/fees03n.htm> [accessed 28 May 2004] Refer to section titled 'Annual charges—All Therapeutic Goods'.

[116] Industry and consumer associations represented on TICC include Australian Self Medication Industry, Consumer Health Forum, Complementary Healthcare Council, Medicines Australia, and Medical Industry Association of Australia.

Appendix 15: Departmental response

Department Of Health And Ageing's Response To The ANAO Performance Audit Of The Therapeutic Goods Administration's Regulation Of Non-Prescription Medicines

REGULATORY FRAMEWORK

The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, with responsibility for administering the *Therapeutic Goods Act 1989*. The TGA's key objectives in the regulation of therapeutic goods in Australia are to ensure that these goods:

- meet appropriate standards of safety, quality and efficacy; and
- are made available to the community in a timely manner.

The TGA currently regulates over 59,000 therapeutic goods including prescription and non-prescription medicines, medical devices, blood, and blood and tissue products. The number of goods regulated by the TGA is continually increasing as new therapies evolve, new applications for existing therapeutic goods are found, and as international markets continue to expand. Manufacturing techniques are also continually changing and improving with new technology.

In 2003–04, 14,692 applications for registration, listing, variation or inclusion in the Australian Register of Therapeutic Goods were processed to completion and a total of 1,865 samples covering 990 products were tested by the TGA as part of post-market surveillance.

The TGA's regulatory framework is enshrined in legislation, regulation and documented procedures. It is based on a risk management approach that devotes more resources and attention to products and manufacturers that are most likely to give rise to harm in the community.

The TGA has a multi-faceted risk framework combining both pre and post-market activities that, together with domestic and international intelligence, represent a comprehensive approach to the regulation of medicinal products and their manufacture. The TGA's risk framework comprises:

- pre market activity whereby medicines and other products are evaluated before approval for the market;

- exchange of domestic and international alerts and intelligence with peer countries in the OECD;
- scheduled Good Manufacturing Practice (GMP) audits;
- unscheduled GMP audits;
- safety and efficacy reviews by Product Regulators;
- laboratory testing of product samples;
- adverse reactions reporting;
- medicine problem reporting;
- complaints, including tip offs; and
- recalls and enforcement.

The risk framework necessarily needs to be dynamic, reflecting the need to respond to (sometimes rapidly) changing priorities in order to ensure that the TGA's legislative obligations are met in regard to the standards of safety, quality and efficacy of medicinal and other products supplied to the Australian community.

In the area of complementary medicines, a major part of the non-prescription medicine field, Australia has a more developed regulatory regime than many other OECD countries. The Department notes that non-prescription medicines are at the low end of the risk profile when compared with prescription medicines, and are regulated accordingly. For example, there will be circumstances where the TGA needs to direct resources to higher risk products, which can result in the regulatory effort allocated to lower risk products and their manufacturers being rescheduled or deferred. Resource allocation is applied according to risk and the balance between different risk treatment activities is varied to manage emerging risks on an ongoing basis.

The Department notes the ANAO's overall conclusion that the TGA has a structured framework for the regulation of the risk presented by non-prescription medicinal products.

INTERNATIONAL CONTEXT

The TGA's practices and procedures have been tested and reviewed by regulators in other countries and international regulatory bodies. The TGA was the first non-European member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S); a European mutual recognition convention that enables audit findings and decisions of one country to be accepted by other member countries. In a number of areas, eg Quality Systems for Inspectorates, PIC/S has adopted Australian practices and procedures.

From time to time the TGA's audit processes are assessed by international bodies. The World Health Organisation (WHO) and experts appointed by the PIC/S Committee of Officials, have found the TGA's processes and systems for GMP audits reflect international best practice.

In addition, the TGA's laboratory is a WHO Collaborating Centre for Drug Quality Assurance and a WHO Collaborating Centre for Quality Assurance of Vaccines and other Biologicals.

TGA staff are members of:

- The Global Harmonisation Task Force group of regulators;
- International Standards Organisation (ISO) technical committees on therapeutic goods;
- Council for International Organisations of Medical Sciences Working Groups (CIOMS is an organisation set up by WHO and UNESCO);
- WHO Global Collaboration For Blood Safety;
- Medical Advisory Panel of The World Federation of Haemophilia;
- Centre for Medicines Research International Regulatory Advisory Board;
- WHO Influenza vaccine working parties;
- WHO Consultation on Methodologies for Research and Evaluation of Traditional Medicines;
- WHO Consultation on Selected Medicinal Plants;
- WHO Consultation on Quality Control of Herbal Medicines;
- WHO Working Group on Harmonisation of Standards and Regulatory Framework for Herbal Medicines;
- Standing Committee, Western Pacific Regional Forum for the Harmonisation of Herbal Medicines;
- International Advisory Board on Hong Kong Chinese Materia Medica Standards; and
- the editorial board of the Journal of Medical Device Regulation.

INDUSTRY CONTEXT

The TGA uses a formal TGA-Industry Consultative Committee (TICC) to engage in consultation and dialogue with industry representatives and consumers.

The terms of reference of the TICC are to examine and comment on the:

- TGA corporate strategic plan developed within the context of Government policies;

- TGA performance against the key performance indicators set out in the Corporate Plan and Budget Statements; and
- TGA budgets, including new initiatives and other budget measures, and on proposed industry fees and charges.

Regular formal consultations also take place between TGA Product Regulators, industry bodies and therapeutic goods manufacturers.

For regulatory activities, the TGA operates on a full cost-recovery basis with fees and charges being reviewed annually. The TGA charges product sponsors for costs associated with pre-market evaluation and approval of therapeutic goods. Other costs associated with the regulation of therapeutic goods in the post-market context, such as product testing, manufacturer audit, adverse drug reaction reporting and recall actions, are recovered through annual product charges and manufacturer licence charges.

TGA'S GOVERNANCE

The TGA has an integrated governance framework the main components of which comprise:

- oversight by the Secretary of the Department of Health and Ageing;
- a formal corporate and business planning framework that sets strategic direction and includes performance targets and measures;
- a formal plan that articulates the TGA's risk management strategies for the regulation of therapeutic goods;
- a number of formal executive committees within the TGA that deal with matters of Therapeutics Policy and Planning, and Corporate Governance;
- TGA policies, Standard Operating Procedures (SOPs), work instructions and procedures;
- Department-wide Chief Executive Instructions and Procedural Rules; and
- the public accountability and reporting requirements that apply in a department of state.

In addition, there are a number of expert statutory advisory committees to provide independent advice to the Minister and the TGA. The Therapeutic Goods Committee advises the Minister on, inter alia, standards for national health and safety for therapeutic goods. In the area of non-prescription medicines, the Medicines Evaluation Committee provides expert advice and recommendations for over the counter medicines and the Complementary Medicines Evaluation Committee provides similar advice for complementary

medicines. The experts are drawn from clinical practice, academia and research and provide a mechanism for peer review of the TGA's professional work.

ANAO AUDIT REPORT

The ANAO report covers a number of aspects of the TGA's regulation of non-prescription medicines.

Reviews of Newly Listed Products

In relation to reviews of recently listed products, the ANAO noted that the TGA had automated an earlier inefficient process relating to the checking of product listing applications, and was strengthening the conduct of in-depth reviews of a proportion of newly listed products. No recommendations were made in this area.

Adverse Reaction Reporting

In relation to adverse reaction reporting, the ANAO "… found that the assessment process for adverse reaction reports for non-prescription medicinal products is thorough". No recommendations were made in this area.

Safety and Efficacy Reviews

In relation to safety and efficacy reviews, the ANAO "… found the review process to be effective. All the reviews examined by the ANAO met their objectives. They considered an extensive selection of literature, testing information and/or regulatory data". No recommendations were made in this area.

Laboratory Testing

In relation to laboratory testing, the ANAO noted that "Overall, the ANAO considers that the process for developing testing plans is soundly based". The ANAO made two recommendations on laboratory testing, relating to increased testing in instances of increased risk exposure, and the development of performance indicators and targets. The Department agrees with these recommendations.

Warning letters on Product Non-compliance

In relation to warning letters, the ANAO noted that "…for the cases examined, the TGA had acted appropriately in addressing these kinds of non-conformity through warning letters. It had identified the reasons for non-compliance, gathered sufficient evidence to assess the severity of the problem, and corresponded with the sponsor until the non-conformity had been resolved". No recommendations were made in this area.

Product Recalls

In relation to the planning of product recalls, the ANAO noted that "… the TGA has a generally sound approach".

In relation to implementing recalls, the ANAO "found that the TGA met the requirements of the Uniform Recall Procedures for those recalls examined", and that "…. procedures were generally followed".

In relation to recall close-out, the ANAO noted that there was appropriate evidence of completed action by the sponsor and recommended the provision of reports to TGA's Product Regulators on the effectiveness of recall related actions.

In relation to the monitoring of recalls, the ANAO noted that "The TGA is developing a new recalls system that will improve data captured for recall analysis".

In relation to the Pan recall, the ANAO "…found that the TGA managed the Pan Pharmaceuticals Limited recall effectively".

The ANAO made two recommendations relating to the reporting of information on recalls. The Department has agreed to both recommendations.

Cancellation of Products

The ANAO noted some areas for improvement in documentation. No recommendations were made in this area.

GMP Inspection and Auditing

This is the area that the ANAO identifies as being in particular need of attention by the TGA. The ANAO covered the GMP related activities of licensing and certification of manufacturers, preparation and execution of the GMP audit program, conducting GMP audits of manufacturers, and addressing manufacturer non-compliance.

In relation to GMP audit processes, the Department notes that TGA's GMP audits and audit frequencies are consistent with the PIC/S standard that provides local manufacturers with a level playing field both in Australian and overseas markets.

The Department also notes that the audit scheduling of established Australian and overseas manufacturers is substantially the same. The TGA conducts pre-licensing audits in Australia which require follow up audits as the manufacturers are establishing themselves. These are not required for overseas manufacturers in countries where there is mutual recognition of regulatory standards, as these are already audited by their local authority and have established manufacturing processes in place before requiring TGA audit.

Generally, audit scheduling is based on each manufacturer being audited every two years, on average, with each audit scheduled to commence in a period three months before and six months after a nominated date. Audit scheduling statistics can vary over time as audits are rescheduled to meet changing priorities.

The GMP audit process for non-prescription medicines is governed by TGA's Standard Operating Procedure (SOP) 401 of 17 April 1998. Over the years it has been amended 12 times as part of the TGA's continuous improvement process.

During the period of the ANAO audit a number of amendments have been made to this SOP that have addressed many of the issues raised in the audit report.

Cost Attribution and Recovery

The ANAO suggests that, in relation to non-prescription medicines, the TGA's fees and charges do not align with costs. Department of Finance and Administration Circular 02/2002 on *Cost Recovery by Government Agencies* advises agencies of the Government's cost recovery policy and contains, at Attachment A to the circular, the agreed schedule for phasing in the arrangements. TGA fully complies with this schedule. The TGA is scheduled for review in 2004-2005 and is currently reviewing its arrangements in line with that policy.

The TGA consults with industry and is transparent in its setting of fees and charges through the TICC processes described above.

No recommendations were made in this area.

Information Management

The ANAO report raises issues regarding aspects of the information management practices that span the range of the TGA's regulatory processes.

Since 1999 the TGA has been progressively implementing a major information systems project (the Strategic Information Management Environment- SIME) to provide improved support to its regulatory activities. The TGA is well advanced with this project. On 11 October 2004, for example, a component of the project, the Manufacturer Information System went live with the progressive transfer of information from the replaced systems scheduled to be completed by January 2005.

The system supports GMP audits by enabling the profiling of manufacturer and GMP audit risk and the corresponding scheduling of auditing resources. It also captures information on audit progress, results and decisions and enables the sharing of this information across the TGA. This system, which was already in final preparation during the audit, has addressed many of the issues raised by the ANAO.

The Recalls components of the SIME project will be implemented in mid-2005.

The ANAO has made two recommendations regarding information management practices. In the context of its overall information management improvement approach, the TGA will examine issues raised by the ANAO and augment the improvement strategies where issues have not already been addressed. This process will encompass any necessary improvements to both the information systems and paper record keeping environments.

CONCLUSION

The Department acknowledges the extensive work undertaken by ANAO in conducting this audit and the contribution this has made and will make to the ongoing improvement of the TGA's procedures.

The Department notes that the audit commenced in October 2003, and many of the issues raised have already been addressed over the period of the audit as part of the TGA's continuous improvement practices.

The Department agrees with all recommendations set out in the ANAO report.

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