

## **Audit Report No. 18, 2004-2005**

# Regulation of Non-prescription Medicinal Products - Department of Health and Ageing and Therapeutic Goods Administration

## **Introduction**

- 12.1 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).
- 12.2 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. 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.

### **Audit objectives**

- 12.3 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.
- 12.4 The ANAO tabled its report in December 2004. The report contained 26 recommendations, a high number by ANAO standards.

### **Overall conclusion**

- 12.5 The ANAO concluded that 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, the ANAO found that more rigour around systems, procedures and resource management was required to provide assurance that non-prescription medicines are appropriately and cost-effectively regulated.
- 12.6 The ANAO found that aspects of risk management for non-prescription medicines required better articulation and structure, to support targeting and monitoring of risk treatments. This was 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.
- 12.7 The TGA's regulatory framework is supported by a substantial number of standard operating procedures. However, the ANAO reported that greater clarity and guidance was required for some key

aspects of the TGA's regulatory functions. There were also some gaps in documented procedures.

- 12.8 The ANAO found that 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. The ANAO found that recent initiatives had the potential to improve the integrity of these processes, but required management focus, better information support, and monitoring of effectiveness for the assurance of all stakeholders.
- 12.9 The ANAO reported that decision-making, including reasons for particular action and enforcement, required more structured documentation, especially when discretionary judgments were being made. Key information obtained through the TGA's regulatory functions was often not captured, or not utilised for the purposes of monitoring and analysis of trends. Information was often unreliable, limiting its value for management purposes. The ANAO also found that better management of information was required to inform the TGA in its regulation of non-prescription medicines.
- 12.10 The ANAO reported that performance management arrangements were insufficient to support sound management of regulation, and accountability to stakeholders. Performance indicators provided limited insight into the effectiveness of the regulation of non-prescription medicines, and of manufacturer compliance.
- 12.11 The ANAO found that 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.

### **ANAO recommendations**

- 12.12 The ANAO made 26 recommendations aimed at strengthening the regulation of non-prescription medicinal products. The Committee notes that this is an exceptionally large number of recommendations compared to most ANAO reports. The Committee also notes that the Department agreed with all 26 recommendations, and argued that many of the issues raised during the audit were already addressed by the time the Audit Report was tabled in Parliament.

Table 12.1 ANAO recommendations, Audit Report no. 18, 2004-05

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.

9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.

17. 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.
  18. 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.
  19. The ANAO recommends that the Department of Health and Ageing develop performance indicators and targets for the timeliness of TGA laboratory testing.
  20. The ANAO recommends that reports be provided to the TGA's Product Regulator on the effectiveness of recall-related corrective actions implemented by manufacturers.
  21. 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.
  22. 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.
  23. 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.
  24. 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.
  25. 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.
  26. The ANAO recommends that the Department of Health and Ageing implement a
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performance management system that defines key outcomes, key performance indicators and targets for the regulation of non-prescription medicinal products.

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### The Committee's review

- 12.13 The Committee held a public hearing on 5 April 2005, taking evidence from the ANAO and the Department of Health and Ageing (including representatives from the TGA, a division of the Department).
- 12.14 The Committee received one submission relating to the inquiry. The main issues canvassed at the public hearing included:
- licencing and certification processes;
  - manufacturer audits;
  - deficiency findings in manufacturer audits; and
  - TGA management issues.

### Department's response

- 12.15 The Department of Health and Ageing and TGA advised the Committee of progress against the ANAO's 26 recommendations.
- 12.16 Health's audit committee has established a small sub-committee to oversee the department's response to the ANAO's audit report (comprising three officers: TGA's National Manager; a First Assistant Secretary and the Chief Operating Officer, Business Group). The main task of the audit sub-committee is to manage a short-term consultancy aimed at outlining the actions needed by Health and TGA to implement the ANAO recommendations. At the time of the Committee's hearing, Health was in the process of calling for tenders for the consultant's work. The terms of reference for the consultancy required the consultant to:
- assist the TGA in implementing the ANAO recommendations including development of an implementation strategy;
  - undertake a review of recent key enforcement actions to draw lessons for the future; and

- review broader aspects of the TGA's administration, management and governance structure and make recommendations where appropriate.<sup>1</sup>
- 12.17 Health subsequently advised the Committee that Deloitte had been appointed to the consultancy and work was scheduled to run from April 2005 and complete the assignment by June 2005.<sup>2</sup> In August 2005 Health informed the Committee that the consultancy had found that TGA was planning activities to address all 26 ANAO recommendations. Around half of all recommendations would be addressed by the implementation of new TGA standard operating procedures, planned for August 2005.<sup>3</sup>
- 12.18 The consultant also concluded that 'many of the planned activities could be further enhanced to give effect the broader intent of the recommendations.' To this end, the consultant has developed further recommendations for the TGA to build into its implementation plans. Health reported that a second phase of the consultancy is now underway to assist the TGA in finalising the implementation of all recommendations.
- 12.19 The Department's response to the ANAO report was welcomed in a submission from industry groups. However, the submission noted that 'the recommended improvements must not only be agreed, but must also be seen to have been put into effect.'<sup>4</sup>

## Licensing and certification

- 12.20 Australian manufacturers of non-prescription medicinal products are required to hold a manufacturing licence, issued by the TGA, covering one or more sites where manufacture takes place.
- 12.21 Overseas manufacturers are required to be sponsored by an Australian importer, exporter, and/or supplier of the product. Sponsors must provide evidence that the products are manufactured to a standard equivalent to the Australian Code of Good Manufacturing Practice (GMP). This may be achieved by providing a

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1 Department of Health and Ageing (Health), *Request for Quotation: Consultancy*; Exhibit No. 7..

2 Email correspondence with secretariat, 10 May 2005.

3 Health, submission no. 12, p. 2.

4 Australian Self-Medication Industry et. al; submission no. 1, p. 1.



certificate of GMP compliance issued by an overseas regulator with which Australia has a GMP agreement. If documentary evidence cannot be produced, the TGA will itself undertake an on-site audit.

- 12.22 Most non-prescription medicine manufacturers are overseas manufacturers who have been certified as GMP compliant by overseas regulators (see Figure 2.1, p. 41 of Audit Report).
- 12.23 The ANAO found that the TGA did not have a standard or target for time to conduct licensing audits. The ANAO recommended that the TGA 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.

## Manufacturer audits

### Scheduled audits

- 12.24 Once manufacturers of non-prescription medicines are licensed, they are subject to ongoing regulation to ensure that their products meet the Code of GMP. This is primarily through a program of audits known as GMP audits. Ongoing conduct of GMP audits mitigates the need for an extensive post-market testing program.<sup>5</sup>
- 12.25 The ANAO found that some 80 per cent of audits were conducted later than their due dates. The TGA advised the ANAO that it aims to complete audits within a window of three months prior to the audit due date to six months after the due date. The TGA's performance target is to complete all audits within six months of their due date. However, the ANAO found that the TGA did not meet this target, with 26 per cent of all non-prescription medicine manufacturers due for audits, but not audited by six months after the due date. Of more concern is that compliance ratings are not held on the TGA's electronic systems, meaning that management does not have ready access to information about the risk of rescheduling audits. TGA

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5 ANAO Audit Report no. 18, 2004-05, *Regulation of Non-prescription Medicinal Products – Department of Health and Ageing, Therapeutic Goods Administration, Commonwealth of Australia*, December 2004, p. 40.

advised the ANAO that it was developing a new information system to allow this to happen. The information system was due to be introduced by the end of 2004.

- 12.26 The ANAO found that audits of overseas manufacturers were more overdue than Australian audits. Furthermore, the ANAO found that where the TGA decides to accept an overseas manufacturer's compliance on grounds other than a TGA audit, this is not supported by a systematic risk-based process – nor are these decisions documented.<sup>6</sup>
- 12.27 At the Committee's hearing in April 2005, Health advised that it had cleared the backlog of audits. While there were some that fell into the category of 'zero to six months' past their scheduled due date, there were no domestic or overseas audits overdue beyond six months.<sup>7</sup>
- 12.28 The Committee questioned the rationale used by TGA to determine the frequency of manufacturer audits. TGA responded that audits are conducted on a one-to-three year cycle, depending on a number of risk factors for each manufacturer. These risk factors include:
- audit history;
  - adverse drug reactions;
  - intelligence – tip-offs or problem reports relating to product quality; and
  - the risk of the product – for example a prescription medicine which requires a high level of sterility requires more frequent auditing than a herbal product.
- 12.29 Based on the above information, TGA may target aspects of the manufacturer, that it wishes to focus on for that particular audit.<sup>8</sup>
- 12.30 The Committee noted the ANAO's concern that 'the rationale for assigning the specific audit frequencies for given risk parameters has not been documented'.<sup>9</sup> The ANAO report also stated that the audit frequency matrix used by TGA to determine when manufacturer audits are to be conducted, had not been reviewed since its introduction.

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6 ANAO Audit Report no. 18, 2004-05, p. 62.

7 Health, *Transcript of Evidence*, 5 April 2005, p. 39.

8 Health, *Transcript of Evidence*, 5 April 2005, p. 33.

9 ANAO Audit Report no. 18, 2004-05, p. 14.

- 12.31 The TGA responded that a review of the audit frequency matrix is one of the tasks to be undertaken by the consultant employed to respond to the ANAO audit report. TGA also reported that its standard operating procedures had been amended to reflect the ANAO's concerns.<sup>10</sup>

### **Recommendation 37**

- 12.32 The Committee recommends that the TGA provide this Committee with a copy of the audit frequency matrix, and any other documentation linked to determination of audits (such as procedures for undertaking an unannounced audit), when it is completed.**

### **Unannounced audits**

- 12.33 The TGA does not favour the routine use of unannounced audits. However, because of the suspension of Pan Pharmaceuticals' licence in 2003, there was a sharp increase in unannounced audits in order for the TGA to assess quality risks of other manufacturers' increased production to fill the market gap. The ANAO noted some advantages in conducting unannounced audits, and that some other regulatory bodies conduct unannounced audits as part of their oversight strategy.<sup>11</sup> The Committee was told that TGA undertook 13 unannounced audits in 2004.<sup>12</sup>
- 12.34 The Committee questioned Health about the planning for unannounced audits. The Committee was interested in whether the manufacturers targeted for unannounced audits are chosen at random, as the result of tip-offs, deficiency reports, or other criteria. Health responded that it conducted a large number of unannounced audits in 2003 following the Pan Pharmaceuticals licence suspension. TGA's National Manager commented:

I think it is important that the regulator pays attention to any intelligence it gets. Otherwise, you get a situation where

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10 Health, *Transcript of Evidence*, 5 April 2005, p. 36.

11 ANAO Audit Report no. 18, 2004-05, p. 67.

12 Health, submission no. 12.

complainants stop complaining and the intelligence that is important to underscore the quality of the system falls off.<sup>13</sup>

- 12.35 Health also outlined a number of other situations which would trigger an unannounced audit, such as:
- tip-offs from manufacturer employees, for example about broken machinery or contamination from foreign material;
  - reports of adverse drug reactions; and
  - questions of quality arising out of TGA's random product testing.
- 12.36 Health advised that one of the areas it is asking its consultant to look at is to assess the balance of announced and unannounced manufacturer audits and to advise on the indicators, separate to those listed above, that would trigger an unannounced audit on a manufacturer. The Secretary of Health told the Committee:
- ...the expectation is that in targeting unannounced audits they are not just spread on an equal chance basis across the manufacturers in the sector. A limited resource needs to be targeted at the areas of potentially greatest risk, and we need the indicators of potential greatest risk.<sup>14</sup>
- 12.37 The Committee is concerned that TGA seems to have a mainly reactive approach to unannounced audits. While acknowledging TGA's concerns that over-use of unannounced audits could result in industry distrust of TGA, the Committee feels that there needs to be a systematic approach to unannounced audits, in addition to those conducted in reaction to specific complaints (as outlined above). It appears that Health and TGA are taking positive moves towards developing a framework for planning unannounced audits. The Committee encourages this move and looks forward to Health reporting on these measures.

### Audit planning and collection of evidence

- 12.38 The ANAO found that the TGA did not have a structured audit planning process. Rather, individual auditors wrote their own audit plans, with detail varying according to the individual. The ANAO also found variations in the collection of evidence as part of audits. Auditors are encouraged by the TGA to make handwritten notes on

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13 Health, *Transcript of Evidence*, 5 April 2005, p. 49.

14 Health, *Transcript of Evidence*, 5 April 2005, p. 51.

their observations. When the ANAO suggested the use of checklists to ensure all required evidence is gathered, the TGA responded that the use of checklists is not considered international best practice.

12.39 The ANAO recommended that TGA improve its administrative procedures and develop support tools for audit planning and evidence gathering.<sup>15</sup>

12.40 At the hearing, the TGA advised that its standard operating procedures have now been modified to include the ANAO suggestions for improving data collection.<sup>16</sup>

## Deficiency findings

12.41 A deficiency is recorded if the auditor considers that the manufacturer's practice does not produce an outcome stipulated by the GMP code. Deficiencies may be classed as:

- Critical – it has produced, or may result in a significant risk of producing, a product that is harmful to the user. For example, lack of sterilisation, gross pest infestation;
- Major – non-critical, but of sufficient seriousness to be listed in a Deficiency report. For example, damage to walls/ceilings where a product is exposed; or
- Other – neither critical or major, but a departure from good manufacturing practice.

12.42 Most audits reveal a number of manufacturing practices that do not meet standards. Deficiencies are recorded in a Deficiency Report issued to the manufacturer. If deficiencies are critical, manufacturing may be suspended. In less serious cases, manufacturing may continue provided the manufacturer advises the TGA of steps to address the deficiencies.

12.43 Health told the Committee that in the period from 1 January 2001 to 31 December 2004, there were 13 'unacceptable' compliance ratings for Australian manufacturers of non-prescription pharmaceuticals; and nine for overseas manufacturers. An 'unacceptable' compliance

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15 Recommendation 7, ANAO Audit Report No. 18, 2004-05, p. 70.

16 Health, *Transcript of Evidence*, 5 April 2005, p. 50.

rating occurs if there is one or more Critical deficiencies found; or if there are a number of Major Deficiencies.<sup>17</sup>

- 12.44 The ANAO found that there was a risk that auditors identify deficiencies inconsistently. In its consultations with industry, the ANAO found concerns about consistency in auditing. For example, manufacturers cited instances where an auditor assessed a practice as deficient that had previously been accepted by another auditor.
- 12.45 The ANAO found that manufacturers generally respond to Deficiency Reports within the required four weeks, and that TGA is also prompt in reviewing these manufacturer submissions. However, the ANAO found that on-site follow up inspections are relatively uncommon. The TGA argued that in general, its standard operating procedures allow for sufficient follow-up action, and that it considered this to be in the interests of maintaining a good working relationship with industry.<sup>18</sup>

### Enforcement action

- 12.46 The TGA has a range of enforcement actions available to control the risk of a non-compliant manufacturer. A lower-level response is utilised where risk to public health and safety is not considered serious or immediate. This action includes:
- issuing a warning letter to the manufacturer, which is likely to require regular reporting on corrective action; and
  - increasing audit frequency, or conducting special audits.
- 12.47 Where risks are considered more serious, formal restrictions may be placed on the manufacturer.
- 12.48 For lower-level enforcement actions, the ANAO found that there were no documented procedures to manage short-term reporting. Roles and responsibilities were not defined, and there were no procedures for on-going assessment and response to reports. ANAO also found that recommendations to increase audit frequency were not always implemented.
- 12.49 For more serious matters requiring licence restrictions, the ANAO found that there were inconsistent approaches in administering licence restrictions. In some cases, manufacturers were offered the

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17 Health, submission no. 12, Attachment A and Attachment B.

18 ANAO Audit Report no. 18, 2004-05, p. 77.

opportunity to make a submission regarding a decision to condition their licence, while others were not given this opportunity. The ANAO found there were no operational procedures for placing restrictions on overseas manufacturers.

- 12.50 The ANAO recommended the establishment of procedures for management of short-term reporting action; consistent license restriction; and restrictions on overseas manufacturers audited and certified by the TGA.<sup>19</sup>

### **Pan Pharmaceuticals enforcement action**

- 12.51 The ANAO briefly overviewed the enforcement action for Pan Pharmaceuticals in 2003. The TGA provided the following overview of enforcement action:

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

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19 ANAO Audit Report no. 18, 2004-05, p. 83.

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.<sup>20</sup>

- 12.52 The TGA advised the ANAO that it considered the 12-week gap between initial audit action and enforcement action to be appropriate, given the vast amount of work required to identify and assess the problems, collect information, identify appropriate enforcement action, and prepare for the product recall.
- 12.53 The ANAO noted that the TGA had not undertaken any independent assessment about whether the above actions were appropriate, and whether there were any lessons to be learnt from the experience. The ANAO noted that an expert advisory group advised that there were imminent risks of death, serious illness or injury. These would have been present during the 12-week gap between audit and enforcement action.

### Committee comment

- 12.54 The Committee is concerned about the lack of documentation for TGA enforcement actions. Even if the majority of enforcement actions are of a minor nature – such as letters to manufacturers – these procedures should be consistent and well-documented. It is also of concern that the ANAO found that follow-up audits for manufacturers subject to enforcement action were not always undertaken in a suitable timeframe. In one instance, a follow-up audit was not undertaken until 12 months after the enforcement action. The Committee believes the TGA must strengthen its oversight of enforcement actions and review processes once enforcement has been taken. From a manufacturer's point of view, it is also unacceptable that the ANAO found different procedures undertaken by the TGA for different companies.

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20 ANAO Audit Report no. 18, 2004-05, p. 85.



### **Recommendation 38**

- 12.55 **The Committee recommends that the Therapeutic Goods Administration document its procedures for implementation of enforcement action against manufacturers. This should include:**
- **a clear definition of different enforcement actions, the circumstances in which they are applied, and manufacturers' rights of submission or appeal;**
  - **stipulation of management authorisation for enforcement actions;**
  - **a definition of timelines for short-term reporting and TGA assessment of manufacturer reports; and**
  - **a requirement that all manufacturers subject to an enforcement action will undergo a follow-up audit within three to six months of the initial action.**

## **Post market monitoring**

- 12.56 A third step in regulation of non-prescription medicinal products (after licensing and ongoing auditing), is post-market monitoring. The TGA spends \$6.6 million per year on its post-market monitoring program. The nature of post-market monitoring depends on the categorisation of products according to their level of therapeutic promise and claim. These categories are high-level (for example, products for the treatment of depression); medium-level (eg, products to help relieve stress) or general-level (eg, products which aid digestion).
- 12.57 Post-market monitoring may include:
- reviews of recently listed products to identify potential inaccuracies in information provided by sponsor;
  - laboratory testing of products and ingredients;
  - reporting of consumers' adverse reactions to products; and
  - safety and efficacy reviews to re-assess the approval of products.

- 12.58 The ANAO recommended that the TGA increase its laboratory testing of products where there is an increased risk arising out of limitations in the manufacture audit program. It also recommended performance indicators for the timeliness of TGA laboratory testing.<sup>21</sup>
- 12.59 The Committee questioned TGA as to whether it should be conducting more post-market testing, noting that the ANAO found that only about one per cent of non-prescription medicinal products are tested annually.
- 12.60 The TGA responded that it spends around 20 per cent of its total budget on laboratory testing for all therapeutic goods. For testing of non-prescription therapeutic products, targeting is important. The TGA targets the products for laboratory testing based on adverse drug reaction reports, intelligence and other objective evidence.<sup>22</sup>
- 12.61 The ANAO stated that the audit had not found major problems with the post-market testing program. However, the ANAO believed that the TGA should conduct more post-market testing on products from overseas manufacturers who had not been audited for a considerable period of time.
- 12.62 The TGA also advised that it had developed performance indicators for the timeliness of TGA laboratory testing, as recommended by the ANAO. The consultant will elaborate further on these indicators.<sup>23</sup>

### Committee comment

- 12.63 The Committee agrees with the ANAO that the TGA should undertake more laboratory testing on products from overseas manufacturers who have not been audited for some length of time. While the TGA assured the Committee in April 2005 that there were no overdue audits for overseas manufacturers, the Committee notes that the ANAO audit found that in previous years, overseas audits in particular have been long overdue. Given Australian consumers' reliance on the TGA to oversee the provision of safe non-prescription medicinal products, it seems reasonable to undertake post-market testing on a percentage of these imports.

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21 ANAO Audit Report No. 18, 2004-05, p. 99.

22 Health, *Transcript of Evidence*, 5 April 2005, p. 59.

23 Health, *Transcript of Evidence*, 5 April 2005, p. 58.

### **Recommendation 39**

- 12.64 **The Committee recommends that the Therapeutic Goods Administration increase its post-market laboratory testing for non-prescription medicinal products from overseas manufacturers, particularly with an emphasis on products from manufacturers who have not been subject to certification or audit in the past 18 months.**

## **Communication with industry**

- 12.65 The Committee asked what kind of information sharing the TGA undertook to ensure that industry is aware of the standards they must meet to ensure GMP compliance. The TGA responded that it has held a number of workshops, training sessions and seminars, particularly following the Pan Pharmaceuticals audit, to communicate with industry. Mr Slater told the Committee that the key steps manufacturers must take to ensure GMP quality are:
- to ensure that inputs that go into a product are of the required quantity and quality;
  - that processes need to be documented, and manufacturers need skilled staff and equipment necessary to ensure that products are compliant with the code of GMP – including staff training; and
  - that products must be end tested to ensure that the quantities of active ingredients are there, that they are in the quantities required and that the product complies with end product standards.
- 12.66 The focus of TGA audits is to ensure that those three critical steps are undertaken by the manufacturer.<sup>24</sup>
- 12.67 The ANAO raised the issue of manufacturers not being told of their compliance rating. TGA responded that it agrees with the recommendation, but has not yet implemented it. The consultant employed by Health to plan TGA's response to the ANAO's audit will advise on the best method of communicating compliance ratings to manufacturers.<sup>25</sup>

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24 Health, *Transcript of Evidence*, 5 April 2005, p. 52.

25 Health, *Transcript of Evidence*, 5 April 2005, p. 58.

## TGA management framework

- 12.68 The ANAO reviewed the over-arching aspects of TGA's regulation of non-prescription medicines, including:
- cost recovery;
  - risk management;
  - information management;
  - record management and documentation;
  - quality management; and
  - performance measurement, monitoring and reporting.
- 12.69 Throughout its report, the ANAO found that the TGA could improve its risk management strategies. The ANAO recommended that TGA review and enhance its risk management framework for non-prescription medicinal products.<sup>26</sup>
- 12.70 The ANAO also found that some key TGA decisions were not supported by formal documentation of the decisions, including reasons and supporting documentation. Files relating to manufacturer audits were often poorly compiled. Important documents such as letters of intention to suspend a manufacturer's licence, were filed without signature or a date. The ANAO had to resort to accessing archived email records and personal notebooks in order to find key information required for the audit. The ANAO also found that TGA needed to improve its quality assurance program.<sup>27</sup>
- 12.71 The Committee considers this poor practice from an industry regulator. Important documents relating to manufacturer audits and other actions which may affect the operations of commercial companies must be properly maintained and filed.

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26 ANAO Audit Report no. 18, 2004-05, p. 118.

27 ANAO Audit Report no. 18, 2004-05, p. 120.

## Recommendation 40

- 12.72 **The Committee recommends that the Therapeutic Goods Administration urgently review its information management systems, including documentation of key decisions and correct electronic and hard copy filing of relevant documents. The importance of maintaining accurate and up-to-date records should also be communicated to all TGA staff.**

### External accreditation

- 12.73 The ANAO noted that the TGA's GMP audit unit had ceased its ISO 9000 accreditation and National Association of Testing Authorities (NATA) accreditation in 2003.<sup>28</sup>
- 12.74 The Committee asked Health and TGA why it had ceased all external certification. TGA replied that following recommendations from previous reviews and internal audits, a consultant reviewed the GMP area. The consultant concluded that the external accreditation was of little value, and that TGA's own internal procedures were robust and that the quality system in place at TGA was providing better value, in the consultant's opinion, than the external accreditation. As a result, TGA ceased its external accreditation regime and employed a quality systems manager to oversee the TGA quality system.<sup>29</sup>
- 12.75 The TGA noted that when its ISO and NATA accreditation ceased, it still belonged to the European Pharmaceutical Inspection Convention (PIC/S). PIC/S is a group of countries which recognise each other's skills in the area of GMP. The TGA reported that the PIC/S had audited the TGA in July 2003, and the World Health Organisation (WHO) had also audited TGA's GMP processes, and that 'both regard the TGA as a world leader in GMP quality'.<sup>30</sup>
- 12.76 Despite TGA's belief that its own internal quality systems were as good as the international accreditation standards, TGA is now re-seeking both ISO and NATA accreditation as a result of the ANAO audit and some industry concerns.

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28 ISO 9000 is an International Standards Organisation protocol on quality management. ANAO Audit Report No. 18, 2004-05, p. 121.

29 Health, *Transcript of Evidence*, 5 April 2005, p. 38.

30 Health, *Transcript of Evidence*, 5 April 2005, p. 38.

- 12.77 The Committee asked the ANAO to report on whether it was unusual for a regulatory authority not to follow ISO or some similar international quality standards. The ANAO replied that current audits of two other health regulators, the Private Health Insurance Administrative Council (PHIAC) and the Office of the Gene Technology Regulator (OGTR) indicated that these two organisations had regard to such standards.
- 12.78 The PHIAC has its own risk management standards which are consistent with the Australian Standard for Risk Management, AS/NZS 4360:1999. The Australian standard, in turn, is consistent with the relevant ISO standard. The OGTR has ISO accreditation for compliance and investigation activities, and has adopted ISO standards for its monitoring activities, although it has not yet received certification for these systems.<sup>31</sup>
- 12.79 The ANAO also noted that another regulator agency, the Australian Pesticides and Veterinary Medicines Authority uses the ISO 9000 standards as the framework of its quality system.

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#### **Recommendation 41**

- 12.80 The Committee recommends that the Therapeutic Goods Administration continue with its re-accreditation process for ISO 9000 and National Association of Testing Authorities (NATA) standards. When the TGA achieves these standards this information should be promulgated to manufacturers and other industry bodies.**

#### **Trans-Tasman agency**

- 12.81 The Committee notes that from 1 July 2006 a new regulatory scheme will be established for therapeutic products in Australia and New Zealand. The Trans-Tasman Therapeutic Products Agency will replace the current Australian Therapeutic Goods Administration (TGA) and New Zealand's Medicines and Medical Devices Safety Authority (Medsafe).
- 12.82 The Trans-Tasman Agency will report to a joint Ministerial council comprising the Australian and New Zealand health ministers. The
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31 ANAO, Submission no. 5.1; p. 1.

agency will be governed by a five-member board. While the ministerial council will determine the regulatory requirements of the scheme, the Agency's Managing Director will make orders for more technical requirements.<sup>32</sup>

- 12.83 The new regulatory arrangements will mean that sponsors of therapeutic goods will now only need to seek one licence for manufacturing therapeutic goods for the Australian and New Zealand markets. Similarly, auditing, testing and disciplinary actions will be administered by the single agency.
- 12.84 The Committee notes that the establishment of the Trans-Tasman agency was reviewed in August 2004 by the Parliament's Joint Standing Committee on Treaties, which approved the treaty which gives effect to the Trans-Tasman agreement.
- 12.85 The Treaties Committee found that the new Trans-Tasman Agency would not result in a diminution in standards for regulation of therapeutic products in Australia or New Zealand. The Treaties Committee reported:

Harmonisation under the Agreement is expected to reduce costs for firms wishing to export to the other country through the reduction or elimination of differences in regulatory standards...Additionally, the creation of a single regulatory agency for both countries will ensure that Australia remains a regional centre of excellence for therapeutics regulation by maintaining regulatory capacity in the face of emerging technologies, and enabling Australia and New Zealand to better influence global and regional standard setting.<sup>33</sup>

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32 *National Interest Analysis for the Agreement with New Zealand Concerning the Establishment of a Joint Scheme for the Regulation of Therapeutic Products*; Joint Standing Committee on Treaties Report No. 62: Treaties Tabled on 30 March 2004; August 2004; Canberra, Australia.

33 Joint Standing Committee on Treaties Report No. 62: *Treaties Tabled on 30 March 2004*; August 2004; Canberra, Australia.

**Recommendation 42**

- 12.86 **The Committee recommends that the Therapeutic Goods Administration report to the Committee on the establishment and operation of the Trans-Tasman Therapeutic Products Agency, with regard to how the new agency will continue to regulate non-prescription medicinal products in accordance with the 26 ANAO recommendations. The TGA should also report on any changes to its governance and reporting arrangements. These reports should be forwarded to the Committee in February and July 2006.**