REPORT OF THE

AUDIT OFFICE

DEPARTMENT OF HEALTH: SAFETY AND EFFECTIVENESS OF MEDICINES

THE AUDIT OFFICE

OFFICE OF THE CONTROLLER AND AUDITOR-GENERAL,
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DEPARTMENT OF HEALTH: SAFETY AND EFFECTIVENESS OF MEDICINES

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This report examines how the Department of Health ensures that only safe and effective medicines are made available to the public. The draft of this report was completed in October 1990. It was discussed with the Department which concluded that immediate action needed to be taken on a number of recommendations in the report. The Audit Office therefore decided to defer finalising the report until the Department had the opportunity to address concerns identified by the Audit Office.

The report now contains our summary of a commentary by the Department on parts of the report and actions that have been taken. This summary has been confined to the more significant findings in the report. In some areas, the Department and the Audit Office remain of a different view and these differences are also set out in summary form.

The Audit Office wishes to make it clear that:

- We are now satisfied that the Department's actions in respect of the assessment of generic medicines will remedy the faults found in the assessment process. Action taken by the Department has been far reaching and decisive, and the Department must be commended on the manner in which it has approached the task of upgrading assessment standards.
- We still have major concerns with the standard of medicine manufacture in public hospital pharmacies and with the manufacture of blood products. We appreciate that the Department has endeavoured to respond to these concerns but the Audit Office is not satisfied with the current situation. Our concerns are detailed in the report.

I would like to acknowledge the work of my officers from the Major Projects Group, Pat Hoy, Darrin Goulding and Jacek Giedrojc, who undertook the review and prepared the material for this report.

Readers of the report are invited to refer also to our separate report *Department of Health: Administration of the Pharmaceutical Benefits Scheme*, which is the result of an associated review.

B H C Tyler
Controller and Auditor-General

28 February 1992

CONTENTS

EXECUTIVE SUMMARY

This audit was undertaken to assess the effectiveness and efficiency with which the Department of Health (the Department) ensures that:

- Medicines are assessed to confirm that they are safe and effective prior to registration;
- Its procedures provide adequate oversight of the use of registered medicines; and
- Its procedures confirm that there is safe manufacture of medicines.

Approval of New Medicines

New medicines are assessed by the Medicines Assessment Advisory Committee, which advises the Minister of Health. In general, the Committee has adopted thorough procedures in scrutinising new medicine applications.

Approval of Generic Medicines

Generic medicines are copies of original medicines for which patent protection has expired. Generic medicine applications were assessed in the Department, but are now assessed on a joint basis with the Department of Scientific and Industrial Research (DSIR).

We found major deficiencies in the way in which the generic medicines, that have been approved for distribution, had been assessed by the Department. These deficiencies have been discussed with the Department, which has now completely revised its procedures for assessing these medicines. In addition, the Department is reassessing the top-selling generic medicines to ensure that they meet appropriate standards. This approach has removed all the concerns that we had with generic medicine assessment.

Monitoring Medicines for Unexpected Results

There are two ways the Department monitors the use of medicines:

- Medicines Adverse Reaction Reporting Scheme. Medicines need to be monitored to see if their use causes unexpected effects. This need is addressed through an adverse reaction reporting scheme which is operated by the Otago Medical School and funded by the Department. While there are problems with the under-reporting of adverse reactions, we found the scheme, and especially the associated Intensive Medicine Monitoring Scheme, to be of value.
- The Department also funds, through the DSIR, a scheme to physically test medicines on the market to ensure that they continue to meet quality specifications. The Audit

Office found that the Department does not always use information gained from the testing programme to target future testing.

Information About Medicines

Medicines have labels describing how the medicine is to be used, situations in which the medicine should not be used, and possible side effects. This is valuable information for the patient and labels must be accurate. The Department checks all labels for newly-registered medicines. While there is no ongoing review of labels to ensure that they continue to meet the same standard as at the time of approval, our own check of a random sample of labels for prescription medicines showed that they were still the same as the originally-approved label.

Each medicine also has a data sheet, intended for use by health professionals, which gives detailed information on the medicine. While the Department had a backlog of many hundreds of data sheets for medicines already on the market that still needed to be checked and approved, this backlog has recently been reduced.

Manufacture of Medicines

The manufacture of safe and effective medicines requires raw materials meeting purity standards, clean facilities in which to produce the medicines, and production according to an approved method.

In the case of medicines made in New Zealand, the Department has a system in place to ensure regular and thorough inspection of commercial manufacturing facilities.

Most medicines used in New Zealand are imported. There was not a reasonable level of assurance that these medicines originate from factories that meet acceptable standards of manufacture. The Department is notaddressing this problem by following up on those overseas factory sites for which there is inadequate certification as to standards.

Medicines are also made in public hospitals. Such medicines are not required to be registered, but the Department has been checking the standard of manufacture. These inspections showed a serious lack of adherence to minimum standards necessary to ensure safe manufacture of medicines. The Department is working with hospitals to remedy this situation.

Since 1985, hospital-based blood transfusion units have been required to be licensed by the Department to ensure that blood products meet acceptable quality standards. However, none have yet been licensed. The Department needs to remedy this situation as a matter of urgency.

1

INTRODUCTION

PURPOSE OF THE AUDIT

101 The purpose of the audit was to assess how effectively and efficiently the Department of Health ensures that medicines are made available for use. That task requires the Department to undertake two fundamental steps:

- To ensure that potentially beneficial medicines are considered for use as soon as they are commercially developed; and
- To ensure that, of the medicines considered, only those for which the likely therapeutic benefit outweighs the risk of a medicine harming patients are allowed to be distributed. Such medicines are referred to as safe and effective medicines. Thus, safety and effectiveness are not separate concepts that can be considered in isolation from each other.

102 The audit also examined the efficiency of the processes used by the Department to provide the assurance of safety and effectiveness. The audit was carried out under the authority of section 25(3) of the Public Finance Act 1977.

STRUCTURE AND SCOPE OF THIS REPORT

103 To demonstrate whether the Department achieves the objectives set out above, the report is structured as follows. In Chapter 2, the Department's process of initial approval for distribution of medicines is examined. Two issues are addressed: consideration of potentially-beneficial medicines for approval, and assurance that only safe and effective medicines gain this approval.

104 In Chapter 3, we examine the extent to which the Department ensures that only medicines which continue to be safe and effective are allowed to remain on the market. The judgement about the safety and effectiveness of a medicine can change in the light of new information about the medicine, advances in science and medical practice, and the approval of improved medicines.

105 Chapter 4 considers whether the Department ensures that users of medicines have access to independent information about their effectiveness and safety. A medicine is approved for distribution on certain conditions. These conditions include whether the medicine can be used for the treatment of certain diseases by certain groups of patients in certain circumstances. A medicine used in conditions other than those for which it was approved can be unsafe or ineffective.

106 To be safe and effective, medicines must be manufactured and stored in suitable facilities. Chapter 5 considers how the Department satisfies itself that the parties involved in the provision of medicines are competent. Competency is addressed by the Department through a system of licensing. For example,

manufacturers of medicines must be licensed. This is an element of providing assurance that medicines are safe and effective.

BACKGROUND TO MEDICINE ASSESSMENT

107 The Medicines Act 1981 requires that all medicines marketed in New Zealand must be approved by the Minister of Health. Each year, there are hundreds of applications made to the Minister for approval to distribute medicines and to notify changes to existing medicines.

108 Evaluation of "innovative medicines" (that is, medicines containing a new chemical entity and which may represent a significant advance in treating illness) requires a wider expertise than is available within the Department of Health. Applications in respect of most innovative medicines are referred to the Medicines Assessment Advisory Committee (MAAC). Members of MAAC are leading specialists in medicine, chemistry, or other fields relevant to the evaluation of medicines. Parts of such applications, relating to labelling and data sheets, are reviewed within the Department.

109 The remainder of the applications are, in the main, for either approval to distribute "generic" medicines, which are copies of innovative medicines, or "changed medicine notifications". Changed medicine notifications must be submitted when, for example, a manufacturer wishes to make changes to the method of making a medicine. Changed medicine notifications are assessed by the Department of Health. Until recently, generic medicine applications were also assessed by the Department. They are still assessed by the Department, but with assistance from the Department of Scientific and Industrial Research, under contract to the Department of Health. Vaccines, which are classed as medicines, are also assessed by the Department of Health.

110 Both the Department and MAAC make recommendations to the Minister after assessing applications, called medicine dossiers. In dossiers, applicants state the case for the safety and effectiveness of the medicine.

111 Dossiers will contain information on the following matters:

- *Ingredients*

  There are two kinds of ingredients in each medicine. The active ingredient is the chemical which produces biological effects. There are therapeutic effects and side effects. For a medicine to be of use, therapeutic effects must outweigh the risk of side effects. To prove that, applicants test medicines, and submit the results of tests for assessment. Medicines are tested first on animals and then on human volunteers. These tests are by far the largest part of a new medicine application.

  Other ingredients of a medicine are called "excipients". They are not intended for any biological effect, but are used for colour, taste, binding, etc.

- *Manufacture of Ingredients*
  There are three factors to be considered here:
  - ★ The "Synthetic Path" or process used to derive the active ingredient. Each synthetic path produces not only the desired chemical, but also impurities. Some impurities can be harmful.
  - ★ Manufacturing Facilities, which must be capable of handling the processes required to produce the desired medicine.
  - ★ Quality Control. There must be a system of checks to ensure that the substance produced meets minimum standards; for example, in terms of purity.
- *Formulation*
  This is the way in which the active ingredient is made available (i.e. by means of a tablet, solution, etc). There are at least two factors to be considered here:
  - ★ *Bio-availability*
    This is the amount of the active ingredient released in a patient's blood stream. Too little active ingredient released will not produce the expected therapeutic effect. This can happen if, for example, a tablet is made in such a way that it does not dissolve or dissolves too slowly.
  - ★ *Interaction Between Ingredients*
    Each excipient, by itself, may not have any biological effect. However, in combination, excipients may react with one another or with the active ingredient, producing harmful substances. Therefore, excipients for each particular formulation must be chosen carefully.

112 All these considerations should be dealt with in the medicine dossier. In the case of an innovative medicine, the dossier may contain thousands of pages of information about the medicine and its clinical effects.

113 The dossier for a generic medicine is smaller, less than a hundred pages in many cases. This is because generic medicines do not have to undergo extensive clinical testing. As the generic medicine is a copy of the innovative medicine, the safety and effectiveness of the active ingredient that is used are assumed to have been proven.

114 The manufacturer of a generic medicine has to prove that the generic medicine is the same as the innovative medicine. This is usually demonstrated by means of "bio-availability studies". In such studies, a small number of volunteers will be given the generic medicine and then blood samples are taken to measure the amount of the active ingredient in the blood stream. If, in comparison to the innovative medicine, a similar amount of the active ingredient is found in the bloodstream of the volunteers, then the generic medicine is regarded as equivalent to the innovative medicine.

115 The other important check concerns how the generic medicine is made. This is important because when a new medicine is discovered, it is protected by patent. Later, perhaps several years later, a method of manufacturing the

medicine on a commercial basis may be developed and patented. When the patent on the medicine expires, other manufacturers are free to copy the medicine. However, as the manufacturing process may still be protected by patent, a generic medicine manufacturer has to develop a new manufacturing process. As this may mean that the medicine is now formulated in a different way from the innovative medicine, a check must be made to ensure that the method of formulation is reasonable.

116 Assessment of medicines is a complex task. At first sight, it may be wondered why a country the size of New Zealand should assess medicines. Larger, western countries have far more resources to devote to this task. It could therefore be argued that New Zealand should wait until medicines are first approved in those countries and then allow all such medicines to be marketed in New Zealand.

117 But there are drawbacks to such an approach. As mentioned in paragraph 101, the safety and effectiveness of a medicine are not absolute criteria. Whether a medicine is considered safe and effective depends on alternatives available to treat the disease. As a result, a medicine considered safe and effective, and therefore worthy of approval in one country, may be considered unnecessary in another country because it already has similar but better medicines.

118 It is also important to bear in mind that no two medicines are the same. They may have the same active ingredient, but may be formulated in a different way. This can apply to both innovative and generic medicines. An innovative medicine made in the USA, for example, may have a somewhat different formulation compared with the same medicine made by the same company in New Zealand.

119 The facilities in which medicines are made can also differ between countries. Thus, approval of a medicine in the USA may be on the basis of knowledge of the facility where it is made. But the company marketing this medicine in New Zealand may decide to obtain the medicine from an entirely different source.

120 There is accordingly a need to assess at least some parts of a medicine application in New Zealand. This does not exclude the possibility of co-operation between countries. For example, there is hardly a need for each country to separately verify the authenticity of data supplied by applicants.

121 The New Zealand record in the assessment of new medicines compares favourably with other countries. The MAAC has been operating since 1970 and, in that time, only two medicines have been recommended for approval which, in hindsight, should not have been recommended. No problems were caused, as neither medicine was subsequently distributed. The MAAC has, however, declined to recommend for approval several medicines that were later approved in overseas countries and had to be withdrawn because of unforseen problems in their subsequent use.

2

APPROVAL TO DISTRIBUTE MEDICINES

201 All medicines marketed in New Zealand must be approved for distribution by the Minister of Health. In respect of the approval process, it is reasonable to expect that the Department should fulfil two functions: consideration for approval of medicines needed, and provision of assurance that only safe and effective medicines are approved. At the end of this chapter, we also address the question of the efficiency of the approval process. We recognise that some of the recommendations would necessitate the application of additional resources to this task.

CONSIDERATION FOR APPROVAL

202 The Department has, as one of its tasks, to ensure there is a sufficient range of up-to-date medicines available, at least cost, to treat the majority of patients.

203 In the view of the Audit Office, to complete this task, the Department needs continually to collect information about:

- Medicines needed, to be determined on the basis of Government health priorities established, for example, in the New Zealand Health Charter. This charter sets out the operation and goals of the public health system;
- Medicines available locally; and
- Medicines available internationally (by a review of new medicines introduced in other countries).

204 By comparing these three bodies of information, the Department could determine what medicines, additional to those already approved, should be considered for approval. It could then determine the order in which applications for approval submitted by companies should be considered, from the medicines most needed to least needed. Moreover, it could encourage applications for approval of needed medicines, if such medicines are not available in New Zealand. This last consideration is important given the small size of the market. Otherwise, the public relies entirely on pharmaceutical companies for decisions on which medicines should be available. Given that companies may also decide to withdraw medicines, even though this may mean the loss of medicines that are of use to patients, it is important to maintain an oversight on which medicines are needed in New Zealand.

Findings and Discussion

205 The Department does not systematically determine what medicines are needed most.

206 The Department does not have a list of all medicines approved for distribution in New Zealand, and therefore does not have complete knowledge of approved medicines available for distribution locally.

207 There is no review of new advances in medicine development with a view to encouraging firms to lodge applications for registration for those medicines that would have a high priority for use in New Zealand. The exception is new vaccine assessment, where the Department will seek out manufacturers of vaccines to ensure an up-to-date vaccine is available.

Conclusions and Recommendations

208 The existing system cannot ensure that people have access to all the medicines they need. To overcome this, the Department should set up a programme for the systematic monitoring of medicine needs, medicines available locally and medicines available overseas. This programme should produce a list of priorities for registration of new medicines.

Department of Health Comment and Action

209 *The Department states that it has neither the mandate nor the resources to change the public's reliance on pharmaceutical companies for decisions on which medicines should be available in New Zealand. In addition, the Department believed the Medicines Act had sufficient flexibility to allow New Zealand practitioners to obtain whatever medicines they required.*

210 *The Department says that its practices are flexible enough to permit a system for giving priority consideration to applications, to ensure that significant new medicines are made available speedily. In addition, the Department has proposed a more formal system of departmental officers summarising pertinent details of all new medicine applications and a recommended priority.*

Audit Office View

211 *We accept that the Department does give priority consideration to some new medicine applications. That being the case, the Department should have specific criteria for its procedure. The assessment and documentation of a particular new medicine's merits against the criteria would then be possible. This is necessary to ensure that such decisions are impartial, fair and transparent. Given the significant commercial advantages which priority consideration can provide for a new medicine applicant, such a process is essential.*

SAFETY AND EFFECTIVENESS

212 The purpose of approving medicines for distribution is to prevent uninformed choices by consumers as to the medicines they use and how they use them. In the view of the Audit Office, to meet this purpose approval must be based on an assessment such that:

- Information provided by applicants in the dossiers is verified as reliable evidence;
- The evidence is examined to determine whether an adequate case is made to establish the safety and effectiveness of a medicine; and
- Users of medicines (patients and the medical profession) have confidence in the approval process so that medicines, once approved, are made full use of.

VERIFICATION OF INFORMATION SUBMITTED BY APPLICANTS

Findings and Discussion

213 Assessment of medicines does not involve any re-performance of tests completed by the applicant. Assessors rely on information supplied by applicants. It was the Audit Office's expectation, therefore, that this information would be verified. Verification can be of two kinds: checking documentation provided by the applicant to see if there is anything in it to suggest that data is incorrect, and positive (external) confirmation of facts.

214 The assessors in the Department and the MAAC consider the internal consistency of applications from a scientific or medical point of view. They also consider the reputation of researchers and research institutions in which the tests were done. However, this is not done on a consistent basis.

215 There is no systematic testing of the "audit trail"; e.g, checking the authenticity of signatures.

216 No positive verification of the information stated in the applications is undertaken. Such confirmation, which again would be on a test basis, could include confirmation of the existence and standard of facilities in which the applicant claims that the tests were performed.

217 The need for such verification can be illustrated by reference to the practices of document brokers operating in Europe. Document brokers offer for sale "medicine dossiers" (in respect of generic medicines only) that contain details of bio-availability data on how to make the generic medicine. Brokers may also sell medicines or their ingredients.

218 New Zealand importers buy dossiers and have them approved here, and may buy the medicine or its ingredients from a broker. Brokers, however, do not manufacture medicines. Instead, they buy medicines or ingredients from manufacturers. Thus, without verification of application details, medicines of unknown origin made from ingredients of unknown purity subject to unknown quality controls can be approved.

219 We have found the names of such dossier brokers gazetted as the manufacturer in approved generic medicine applications.

Conclusions and Recommendations

220 The Department should establish a programme of data verification to be carried out, on a test basis, before applications are referred to assessors (whether in the Department, MAAC, or external experts) for scientific and medical appraisal. This programme would involve examination of the documentation submitted for an audit trail, external confirmation, and checking summaries to raw data. The verification should be done on a test basis, with the amount of testing done on an application dependent on the knowledge about an applicant. Risk profiles of applicants would be developed on the basis of the results of previous verifications of applications submitted.

Department of Health Comment and Action

221 *The Department believes if a verification programme were implemented, there would need to be a significant increase in the resources available to the Therapeutics Section and undoubtedly an increase in the time required to assess applications because of the additional verification and checking procedures envisaged. Action on these recommendations awaits the results of the Australian Inquiry into Drug Evaluation Processes which has the objective of streamlining the Australian evaluation process and moving it away from dependence upon verification of raw data.*

222 *In the case of dossier brokers, the Department expects that the gazetting of dossier brokers as manufacturers will not occur again because addresses on GMP [Good Manufacturing Practice] certifications are checked against the address given as the manufacturer.*

Audit Office View

223 *We agree that if an intensive verification programme was put in place, such a programme would exhibit limited returns relative to potential costs. But verification on a sample of registrations would not be costly and would serve as a useful deterrent.*

ASSESSMENT OF MEDICINES

224 This subsection examines whether information in new medicine applications is effectively assessed to form a supportable recommendation on the application.

Findings and conclusions are presented separately for the assessment of medicine applications by MAAC, the Department, and DSIR.

Assessment by the MAAC

Findings and Discussion

225 Until the end of 1989, each MAAC member independently reviewed the complete application for each medicine referred to the MAAC. At their meetings, members discussed their conclusions and only if there was unanimous agreement would a medicine be recommended for approval. Disagreement about a medicine meant the medicine would be deferred pending further information.

226 Since the establishment of MAAC in 1970, its workload has been continually increasing. Although the number of new applications considered each year by MAAC has remained stable, the size of an average application has increased.

227 These changes prompted the chairman of MAAC to propose changes in its procedures. The changes involve having 2 or 3 members (instead of all 8 members) review a medicine application in its entirety while the others review only a summary of the application. Also, some members will only review certain parts of applications or certain types of applications.

Conclusions and Recommendations

228 The procedure of independent review and confrontation of conclusions by specialists ensures that all the merits and demerits of applications are considered and debated before recommendations are made. Thus, we consider the procedure adopted by the MAAC to have been sound.

229 The previous method by which the MAAC operated, that is, all members considered the whole application, had certain strengths. Each member could form his or her opinion on the basis of the application in its entirety and voice their views at the meeting. Thus, there was a certain safeguard that, if some members missed a point, it would be raised by the others at the meeting and a consensus view formed. Now that only 2 or 3 members consider the whole application, the MAAC (and the public) are relying on the judgment of these members. Hence the Committee needs to agree on the basis on which these judgments are to be formed. Standards and procedures will need to be established.

Department of Health Comment and Action

230 *The Department of Health financed a special meeting of the MAAC to review standards of evidence required and procedures to be followed. The Committee*

favours members providing a written report on their assessment, such reports to be in a standard form that requires reporting on specified matters.

Assessment by the Department of Health

Findings and Discussion

231 As discussed in Chapter 1, generic medicine applications were, until recently, assessed by the Department. They are now assessed both by the Department and by the DSIR as the Department's agent. Assessment of generic medicines has been carried out by a limited number of scientists working alone and without challenge by each other. As discussed earlier, the strength of the MAAC assessments is the challenge provided by other members of the committee.

232 MAAC recommended in August 1989 that a sub-committee be set up to review and make recommendations for approval of those generic medicine applications assessed by the DSIR and the Department. This sub-committee held its first meeting in late August 1990.

233 The medicine assessment process is critical to ensuring that only safe and effective medicines are available to the public. In assessing a medicine, it is easy for one person to miss potentially weak areas in an application. The fact that, prior to the recent involvement of MAAC, assessments of generic medicines have been carried out without the benefit of challenge by other scientific staff raises questions as to the standard of these assessments. For this reason, we arranged for an independent review of a sample of generic medicine application files assessed by the Department and the DSIR.

234 The files for 10 generic medicines that had been assessed by the Department were reviewed. This provided a statistically significant sample. These 10 medicines were randomly selected from 70 of the leading generic medicines currently on the market and which had been approved for distribution in the 1980s.

235 The same standards were applied by our independent reviewers to the generic application files as would be applied to new medicine applications. The reviewers applied the medicine assessment standards current at the time of approval; that is, assessments were not against 1990 standards. This meant reviewing the documentation on file for factors such as:

- *Raw Materials:* Are the raw materials supplied by a known manufacturer from a plant that is subject to a code of good manufacturing practice, is the synthetic path for the raw materials specified, and have impurities been identified?
- *Manufacture of the Medicine:* Are there appropriate quality controls throughout the various stages of production, and is the manufacturing plant subject to a code of good manufacturing practice?

- *Bio-availability Studies:* As mentioned in paragraph 114, these studies demonstrate whether the generic medicine has a similar "profile" in the body as the innovative medicine. Three measures are of particular importance:
  - "AUC" This value records the total amount of the medicine that has been absorbed in the body.
  - "Cmax and Tmax" These values record the maximum concentration of the medicine in the body and the length of time of maximum concentration.

236 In general, values for AUC, Cmax and Tmax for a generic medicine should not vary from the innovative medicine by more than plus or minus 20%. For some medicines, a smaller margin is required and for other medicines the margin is greater. If a generic medicine meets these criteria, that is, it has a similar profile in the body to the innovative medicine, then it is assumed to be equivalent to that medicine. The bio-availability studies in the applications were reviewed in terms of study design (i.e. number of subjects, pattern of administration of treatments, etc.) and sampling times, and the Cmax, Tmax and AUC calculations were checked. The statistical studies for some medicines were re-analysed by a biostatistician.

237 On reviewing these 10 files, it was considered that all 10 had been inappropriately assessed.

238 The faults found in the way these applications had been assessed were serious. They included:

- No synthetic path (that is, the process used to derive the active ingredient) specified. This is a serious omission, as the raw materials used for some medicines can be synthesized in a number of different ways. In the case of one raw material used, it can be synthesized by at least five different methods, two of which produce by-products of significant toxicity. As the Department did not obtain details of the synthetic path, there is no assurance that a safe method of synthesis has been used.
- One file contains two completely different descriptions of the raw material used in the medicine—in one document it is described as an almost white crystalline powder and in another document as a creamy yellow powder. Hence it is not clear if the same raw material is being described for use in this medicine. Yet this discrepancy was not queried by the Department.
- Many of the bio-availability studies were badly flawed. For example, Cmax and Tmax values were not always provided, and inadequate sampling times were used. The analysis of the statistical data shows that some studies could not detect a 20% difference between the generic medicine and the innovative medicine even though bio-equivalence was claimed.
- The Department on one occasion noted that a manufacturer of the active ingredient was unknown to it, but did not follow this up to ensure that the manufacturer was genuine and not a document broker. It was later found,

three years after the medicine had been approved for distribution, that the "manufacturer" was in fact a document broker. On another occasion, the Department asked for confirmation that the manufacturing plant was inspected by an overseas inspection agency. When informed that the plant was not required to meet such standards, the Department took no further action and recommended the medicine for approval.

Assessment by the DSIR

Findings and Discussion

239 Over the last 2–3 years, the Department has engaged the DSIR to carry out assessments of generic medicines. We arranged for a sample of 6 files assessed by the DSIR to be independently reviewed.

240 Of the 6 files, 3 were considered to have been inappropriately assessed, although only in respect of relatively minor matters. Nevertheless, they were points that should have been commented on by the DSIR.

Further Issues Concerning Generic Assessments

Findings and Discussion

241 There are other problems with the way in which the generic medicines are assessed. This can be illustrated by reference to a company that sought approval to market two products. The company sought approval for amoxycillin capsules in November 1987 and for amoxycillin powder in November 1988.

242 The application for amoxycillin capsules was not referred to the DSIR. A bio-availability study was provided for this product but had major flaws. Only seven volunteers were used in the study when such studies require an even number of volunteers (for comparison purposes). Cmax and Tmax data was not included. These and other faults meant bio-equivalence was impossible to substantiate. The Department had concerns about heavy metal impurities present in the raw materials and, while it sought quantification of these impurities, its queries were never satisfactorily answered and the medicine was approved for distribution in 1989.

243 The application for amoxycillin powder was referred to the DSIR for assessment. The DSIR drew attention to a number of problems with the application and, in particular, commented that "no bio-availability studies have been submitted. Since the product when reconstituted is a suspension, not a solution, a bio-availability comparison is probably necessary. The company refers to files on amoxycillin capsules for data on bio-availability. Since this deals with a different dosage form, it cannot be considered strictly relevant."

244 The matters raised by the DSIR were followed up with the company and all the matters were dealt with except the question of the bio-availability study. The company replied on this point that "no bio-availability study has been carried out. This is not relevant for an oral suspension." That explanation was accepted by the Department and the medicine was approved in 1989 without a bio-availability study being obtained.

Conclusions

245 There has been inadequate assessment by the Department of applications to distribute generic medicines. Such medicines have been approved for distribution despite an insufficient case being made to demonstrate equivalence to an innovative medicine. This conclusion is based on a review by two expert assessors hired by the Audit Office and working independently of each other. While it may be argued that our assessors' opinions are just that, and someone else could come to a different conclusion, the concerns expressed are of such a serious nature that they cannot be ignored.

246 The DSIR has applied a higher standard of assessment, but there are instances where clarification of some points should have been sought from the applicant. There are also instances of the Department not heeding the DSIR concerns about an application, or not referring an application to the DSIR and continuing to rely on its own assessment instead.

CONFIDENCE IN ASSESSMENT

247 It is essential that decisions to approve medicines are based on adequate evidence of safety and effectiveness and that they are seen as such by applicants, the medical profession, and the public.

248 Confidence in assessments by the Department may be undermined because the Department fulfils two functions in relation to medicines. It regulates access to the market by administering the registration process and it pays for medicines on behalf of users. In this latter function, one of the Department's objectives is to minimise the cost of medicines that are subsidised. This may conflict with its function of recommending only safe and effective medicines for approval when, for example, an approval of a generic medicine promising substantial savings is considered.

249 Without confidence in assessments, uninformed choices can be made by consumers. For example, if users consider generic medicines to be unsafe or ineffective they will not use them, notwithstanding that some of those medicines may be preferable because of their therapeutic properties or cost. Thus, lack of confidence in assessments can disadvantage users of medicines.

Findings and Discussion

250 The Department has been repeatedly challenged about its assessment of generic medicines. There have been court cases (which were resolved in favour

of the Department), questions in the House of Representatives, scientific papers, television programmes, and petitions from medical associations questioning the Department's assessment of generic medicines. As discussed in paragraphs 231–238, there are in our opinion grounds for these concerns.

251 Having an independent body of experts review all assessments and make a final recommendation is one way to achieve confidence in those assessments. Any charge that there are conflicts of interest would have less force when recommendations for approval are made by an independent body. One such body, MAAC, has not been subject to such charges.

252 Applicants can appeal MAAC recommendations to the Medicine Review Committee. Since the inception of the Medicine Review Committee in 1984, it has received only five appeals against the approximately 190 MAAC recommendations. Only two appeals were successful.

Conclusions and Recommendations

253 The procedure used to assess generic medicines without the participation of outside experts has not been adequate, and has not created a climate in which there is confidence that generic medicines are equivalent to the innovative medicines. Generic medicines have therefore not been able to compete freely with innovative medicines so as to bring maximum benefits to users.

254 The MAAC sub-committee on generic medicines should make recommendations on approval for all applications to distribute generic medicines. The sub-committee should also re-evaluate generic medicines assessed by the Department with no outside assistance. Such re-evaluation could be a part of the continued assurance programme recommended in Chapter 3.

Department of Health Comment and Action

255 *Since the auditors were in the Department, the process of evaluation of all medicines (except the novel medicines which go to the MAAC) has altered considerably. These changes include:*

- *In April 1991, the Department asked manufacturers and distributors of the top 130 selling generic medicines to update and improve the quality of the information held about each of these products. On 8 July 1991, the Department sought and obtained Ministerial approval to reassess approximately 130 generic medicines. The aim of this reassessment is to determine whether these medicines are therapeutically equivalent to the respective innovative brand name medicines and whether the Department can endorse retail substitution of these generic medicines (which are already on the market) for the innovative medicines. In order to determine which generic medicines are suitable for substitution, the Department has established a new committee known as the Generic Substitution Review*

Committee. This committee first met on 23 August 1991 and determined the process by which it will reassess the identified generic medicines.

- *The Generic Sub-Committee of the MAAC that assesses new generic medicine applications now examines files of a representative sample of new applications after seeing all finished checklists.*
- *Each medicine is separately reviewed by two appropriately qualified evaluators, one from the DSIR and one from the Department's Therapeutic Section. This allows for peer review between scientists.*
- *Evaluators work to written checklists that cover those aspects of an application that must be scrutinised.*
- *Formal monthly meetings of departmental and DSIR evaluators to agree that evaluation has been satisfactorily completed on each medicine and that recommendation for consent to market should take place; to consider requests for fast-tracking of evaluations; and to assess progress on evaluations.*
- *Standard operating procedures for evaluation of new and changed medicine applications have been established.*
- *Amendments to the Evaluator's Guide concerning bio-availability studies, aerosol inhalers and controlled release formulations have been drafted with the help of the Generic Sub-Committee of the MAAC.*

Audit Office View

256 *The new evaluation procedures introduced in response to the initial audit will ensure that all new generic medicine applications, and the 130 existing generic medicines that have been identified for review, will be appropriately evaluated.*

257 *The Audit Office is now completely satisfied that these new procedures will ensure that generic medicines are correctly assessed. The Department is to be commended for the decisive way in which it is rectifying the assessment of generic medicines.*

MANAGEMENT OF THE APPROVAL PROCESS

258 The previous sections of this chapter address the questions of the effectiveness of application process; i.e. whether the job gets done. This section considers the efficiency of the process. We looked at utilisation of the most important resource in the assessment process—assessors' time.

259 Assessment is essentially the analysis of information. Applications are the major source of information for assessors. We therefore expected the

Department to ensure that applications contain all information necessary for assessment in a format that facilitates assessment.

COMPLETENESS AND PRESENTATION OF APPLICATIONS

260 For efficient utilisation of assessors' time, it is essential that applications considered are complete and well presented. We expected that the Department would do two things to ensure that only complete and well-presented applications are sent to assessors:

- Provide guidelines for companies on preparation of applications; and
- Screen applications so that incomplete and poorly-presented applications are referred back to applicants before being assessed.

Findings and Discussion

261 Of the 50 applications received by the MAAC in the last two years, 13 were referred back by the MAAC for further information. That is, 26% of applications did not contain sufficient information to allow an assessment to be completed.

262 The MAAC has repeatedly commented on the low quality of some applications. In our view, incomplete applications, or applications not in the correct format, should not reach the MAAC.

263 The Department has developed guidelines for applications, setting out the information they should contain and the general format. However, MAAC members state that applications tend to be exact copies of applications submitted to overseas regulatory agencies.

Conclusions and Recommendations

264 The Department does not ensure that all applications considered by assessors are complete and presented in a format facilitating assessment. While it would be unreasonable to expect applicants to re-format whole applications to suit New Zealand requirements, it would not be difficult for them to prepare a summary specifically in the format needed to comply with that specified by the Department.

Department of Health Comment and Action

265 *It may be quite advantageous for the MAAC to review applications which are an exact copy of what has been submitted in another country, particularly if:*

- *That country is Australia, Canada, the United Kingdom, or the United States of America; and*
- *That country has given approval to the medicine.*

266 *Acceptance of a common format for new medicine applications is pivotal for international harmonisation of drug regulatory activities. The Department has accepted that Australia and New Zealand are likely to be using the European*

Economic Community format. In December 1991, the Department wrote to the pharmaceutical companies involved, to request that future applications which are to go to the MAAC should follow the EEC format, with the addition of a New Zealand–specific summary section as specified by the MAAC.

Audit Office View

267 *Our concern was that applications differed and did not conform to, and hence did not necessarily contain all the information required by, the guidelines issued by the Department. Agreement on a standard application format for all countries would make the whole process more effective and efficient.*

VERIFICATION OF SUMMARIES

268 Applications for new medicines are voluminous. Assessment is therefore done largely on summaries of data. We expected applications referred to the MAAC to be not only screened for completeness and compliance with the correct format by the Department, but also verified to confirm the integrity of the data and the summaries of data. Ideally, the MAAC should be able to consider the merits of a case made by an applicant in the summary and refer to raw data only to clarify specific issues.

Findings and Discussion

269 The Department does not verify data submitted in applications for medicine approval.

270 The Department does not check that summaries included in applications are supported by the raw data before referring applications to the MAAC. In the absence of reliable summaries, such checking is undertaken by members of the MAAC. It is routine work. Having MAAC experts undertake it is not the best use of their time. It limits the number of applications they can consider.

Conclusions and Recommendations

271 The assessment process could be better managed. Assessors' time would be put to better use by providing them with complete and well-presented applications with summaries checked to raw data. The Department should consider ways of ensuring that applications referred to the MAAC are presented in a way that minimises unnecessary work by assessors.

CHANGED MEDICINES NOTIFICATION PROCESSING

272 Whenever a company proposes to change a medicine it has to notify the Department of the change. The Department then has 45 days to consider the application.

273 Companies only notify the Department of particulars of the changes proposed. They do not re-submit a summary of the data about the medicine. When many

changes are made to one medicine, it is difficult for the Department to keep track of all the changes that have been made. For example, a manufacturer may make changes to the method of making the medicine or the strength of the medicine, and the complete file would have to be examined to know the cumulative changes made to the medicine.

Findings and Discussion

274 The Department has dealt with changed medicines notifications within the time allowed. All changes which were notified were considered.

275 If any of the scientists assessing a notification is doubtful as to the case presented, the application is referred to the MAAC.

Conclusions and Recommendations

276 The Department has handled changed notifications effectively.

277 It is difficult for the Department to readily identify all the approved changes to a medicine. Each notification should be accompanied by a revised summary (3–4 pages) of data on that medicine. The Department would then have ready access to an up-to-date record of the medicine.

3

ASSURANCE OF SAFETY AND EFFECTIVENESS

301 The Department has the function of providing assurance to users that all medicines distributed in New Zealand are safe and effective. Two things need to be done to enable such an assurance to be given:

- Firstly, the Department must ensure that only registered medicines are distributed.
- Secondly, the Department must ensure that only medicines which are safe and effective remain registered. This reaches further than providing assurance that medicines approved for distribution are safe and effective at the time of approval. It requires a continual review of all medicines registered so that each medicine would be re-examined at regular intervals.

ASSURANCE THAT ONLY REGISTERED MEDICINES ARE DISTRIBUTED

302 There is little point in having an elaborate registration process if unregistered medicines can easily appear on the market. Therefore, we expected to find a system of ensuring that only registered medicines are distributed. The most basic requirement of such a system would be that registered medicines are easily identified. Then, obviously, unregistered medicines could also be identified and denied access to distribution by wholesalers or pharmacists. The second requirement of such a system would be the detection and deterrence of distribution of unregistered medicines.

Findings and Discussion

303 Medicines registered for distribution are not identified by a licence number or other inscription on packages. The Medicines Act 1981 does not require such information on packages. This is in contrast to the Animal Remedies Act 1967 which requires a licence number on animal remedies.

304 As already noted in paragraph 206, there is no complete list of approved medicines available to distributors. A pharmacist or wholesaler offered a medicine for sale cannot easily determine whether it has been approved for distribution.

305 The Department monitors imported medicines to ensure that only registered medicines are distributed, and that they are distributed only by persons licensed to do so.

306 In 1989, the Department became aware that several people, not licensed to do so, were importing and distributing an asthma inhaler medicine. A batch of

this medicine had been subject to a product recall in the country in which it was made.

307 A detailed investigation by the Department compiled substantial evidence to suggest that several breaches of the Medicines Act had occurred. Nevertheless, the Department did not proceed with any prosecutions and we were unable to establish why.

Conclusions and Recommendations

308 There is no assurance that only registered medicines are distributed. Legislation to prevent distribution of unregistered medicines is more restrictive for animal medicines than it is for medicines to be used by humans. Assigning to each medicine a unique licence number on registration would be one way of allowing users of medicines to identify approved medicines. Such a number should be required to be shown on all medicine labels. An amendment to the Medicines Act would be necessary to implement this recommendation.

309 The Department should then arrange, with Area Health Boards, for inspections by District Advisory Pharmacists to include checking that all medicines stored by pharmacists and wholesalers bear approved licence numbers.

310 Instances of illegal distribution of medicines detected by the Department should result in prosecutions to deter such distribution.

Department of Health Comment and Action

Licensing of Medicines

311 *The recommendation to have a unique New Zealand licence number on each medicine is incompatible with the Department's 1991 intention to harmonise with Australian regulations, providing as few barriers as possible for Trans-Tasman trade, particularly in the area of labelling and packaging requirements.*

Prosecutions

312 *The Department believes that prosecutions are not the most cost-effective means of achieving compliance with the Medicines Act.*

313 *The Department's preferred practice is to warn offenders about breaches of the Act and, where appropriate, to use the powers of seizure under the Act to confiscate goods. The latter is in fact, punitive because the value of the goods usually greatly exceeds the maximum fine which could be levied.*

314 *The Department, in spite of the trivial penalty (i.e. often a $100 fine) provided in the Act, has since 1985 taken three prosecutions where the accused were considered to be "repeat offenders".*

315 *However, the Department believes that, to make a more active regime of surveillance and prosecutions viable, it is necessary to amend penalty provisions*

of the Act, educate the pharmaceutical industry, and provide resources for training and administration for officers competent to mount a prosecution.

Audit Office View

Licensing of Medicines

316 *In 1989, the Department, in its published briefing notes to the then Minister, stated that the distribution of unregistered medicines "is of concern to both the Department of Health and local drug manufacturers and distributors because, in the increasing number of instances that have come to our attention, the imports have been in breach of the Medicines Act". Hence, in the view of the Audit Office, users of medicines need to be able to distinguish approved medicines from unapproved medicines.*

Prosecutions

317 *Given that the Department, for some time, has acknowledged the minimal deterrent impact of the current fines, we believe that, in its capacity as the administering agency, it should have sought an appropriate review of the fine levels. This is necessary, given that the Department's preferred action of confiscating goods obviously does not deter offenders as the Department acknowledges the necessity to have to prosecute repeat offenders.*

REVIEW OF REGISTERED MEDICINES

Findings and Discussion

318 There is no periodic review of all registered medicines to determine whether they should remain registered. The Medicines Act does not provide for such regular reviews. This is in contrast to provisions in the Animal Remedies Act which allows for such review.

319 We reviewed the dates on which the most commonly-used medicines were introduced to the New Zealand market. In the case of prescription medicines, we found that medicines introduced before 1970 accounted for approximately 18% of total prescription medicine sales.

320 For non-prescription medicines, those introduced before 1970 accounted for approximately 44% of total non-prescription sales.

321 Since 1970, there have been major advances in science and medical knowledge. Researchers we interviewed stated that they would not put their names to tests conducted 10 years ago. Also, before 1970, there was no requirement or provision to formally review each new medicine to ensure it was safe and effective.

322 Because all medicines have some side effects, the safety and effectiveness of a medicine can only be judged in comparison with other medicines which treat

the same disease. With an increasing number of medicines available, combined with advancements in the methodologies for assessing medicines, the assessment of new medicines has become stricter.

323 A recommendation by the MAAC in November 1987 illustrates the point. The MAAC decided to recommend that approval be declined for a medicine which had been on the United States market for 20 years and on the Australian market for 10 years. In justification of its recommendation, the MAAC stated "the medicine is not needed because better ones are available".

Conclusions and Recommendations

324 The Department cannot assure the public that medicines distributed meet one standard of safety and effectiveness. Prescription medicines comprise mainly recently-approved medicines, but a high proportion of non-prescription medicines were approved over 20 years ago. A regular re-evaluation of medicines would ensure that only useful medicines that are safe and effective would remain on the market. In this respect, a higher standard is required of animal remedies than medicines for humans.

325 All medicines should be periodically re-assessed at, for example, 5-yearly intervals. This would require an amendment to the Medicines Act. The re-assessment should be based on applications made by companies. Such applications would not be as extensive as original applications but should contain at least:

- A data sheet (a document giving a detailed description of the medicine);
- Details on manufacturing of formulation and ingredients; and
- Information on adverse reactions collected by companies, as required by the Medicines Act.

326 The re-assessment should be undertaken by a committee similar to the MAAC, possibly constituted as a sub-committee of the MAAC. Medicines regarded as not meeting current standards of safety and effectiveness should be recommended for withdrawal from the market.

Department of Health Comment and Action

327 *Periodic assessment of quality assurance measures would be a valuable addition to the role of the Department, but it would require additional resources. The tracking system could be the same one as that used for licensing. The Department is developing policy proposals to put to the Government for a system of product licence with renewals at set intervals (annually, biannually). This will require amendments to the legislation.*

SURVEILLANCE OF MEDICINES IN USE

328 The Department undertakes a number of activities to monitor the performance of various medicines. They include:

- Monitoring adverse reactions to medicines; and
- Testing medicines on the market.

MONITORING MEDICINES FOR UNEXPECTED RESULTS

329 When a medicine is being developed, it undergoes extensive clinical trials on a relatively small group of patients to assess its safety and effectiveness. Specific groups of patients, such as the very young, or pregnant women, are excluded from such trials unless they are intended to be the main users of the medicine. However, once a medicine is registered and available on the market, it will be used by large numbers of very different patients, over long periods of time. For these reasons, the use of a medicine needs to be monitored to see if there are unexpected effects. This need is addressed through a Medicines Adverse Reactions Reporting Scheme.

Findings and Discussion

330 The Department operates, through the Otago University Medical School, a voluntary reporting system in which medical practitioners notify any adverse reaction to a medicine.

331 In the last five years, notifications have led to the withdrawal of 1 medicine and modifications to the labels of 9 medicines to warn of possible adverse reactions.

332 The adverse reactions reporting scheme lacks a mechanism for relating the number of notifications about a medicine to the quantity of the medicine used. Few notifications may be received in respect of a particular medicine, from which it might be concluded that there are few problems with that medicine. In fact, the few notifications may simply result from the medicine being seldom prescribed.

333 Both the Otago Medical School and the Department estimate that large numbers of adverse reactions in patients are not reported. For example, during a recent vaccination programme, doubts arose over the effectiveness of the vaccine being used. The Department conducted its own survey in areas where the vaccine was being used and found that between 40% and 50% of people receiving the vaccine developed an adverse reaction. However, the formal notifications showed an adverse reaction rate of only between 0.05% and 4%.

334 The Department, again through the Otago Medical School, also operates the Intensive Medicine Monitoring Scheme. This scheme was introduced in 1977 and monitors up to six newly-marketed medicines at a time. Medicines chosen for intensive monitoring are those of a novel or particularly problematical nature.

335 Selected medicines are intensively monitored over four years. The scheme is actively promoted amongst medical practitioners. When writing a prescription for a medicine on the list for intensive monitoring, a medical practitioner will

use a special form and the presence or absence of any reactions will be noted. A copy of this form is sent to the Otago Medical School. There is an 80% rate of return of forms which enables close monitoring of these medicines.

Conclusions and Recommendations

336 The adverse reactions reporting scheme provides useful information about medicines in use. However, because of the problems with the low reporting rate and the lack of correlation between the number of notifications and the amount of medicine used, the scheme is not a substitute for on-going assessment.

337 When reporting an adverse reaction in medicines other than those selected for intensive monitoring, doctors should be asked how many times they prescribed the medicine in the past month and if they had noted any adverse reactions then. This would provide information about the population to which reported adverse reactions relate and would allow conclusions to be drawn about frequency of adverse reactions.

338 The intensive monitoring scheme works effectively and allows a detailed knowledge to be developed about medicines being monitored.

Department of Health Comment and Action

339 *Asking doctors who report adverse reactions to indicate the number of times they have prescribed the medicine in question, and to state adverse reactions occurring previously, is to ask them to make two estimations both of which would be subject to serious bias.*

Any improvement in the current monitoring system would require a further injection of resources.

Audit Office View

340 *We agree that asking doctors to estimate the number of times they have prescribed a medicine in the last month would be inaccurate. A more accurate correlation between the number of adverse reaction notifications and the quantity of medicine used could be obtained by reference to the medicine usage data generated by the Wanganui Prescription Pricing Office. That office processes prescription payments on a large computer system, which, until the introduction of the standard $15 prescription charge, would have given an indication of the volume of each medicine supplied on prescription. The information is now incomplete, because prescriptions which are of a lesser value*

than the standard prescription charge are no longer submitted by pharmacists for pricing.

MEDICINE TESTING

341 To establish whether a medicine that has been registered and is in everyday use continues to meet the quality specifications set at the time of registration, the Department operates a medicines testing programme. This involves acquiring medicines and testing them in a laboratory. Testing is carried out either by the DSIR or by the Department's Communicable Diseases Centre.

Findings and Discussion

342 There is a planned approach to testing medicines. Each year, a programme of the medicines to be tested is drawn up. Included in the programme are medicines which have been the subject of specific complaints, or the manufacture of which might be difficult, leading to a greater likelihood of problems with the finished medicine.

343 If serious faults are found in the medicine tested, the Department will institute a recall of the particular batch of that medicine. Medicines are made in batches and a fault in a medicine in one particular batch means the whole batch is suspect and needs to be recalled.

344 On some occasions, stronger action than a batch recall is taken. For example, in one case, a batch of medicines imported from Australia was found to be faulty. The Department sought the assistance of the Australian Department of Health to inspect the factory making the medicine. The factory procedures were found to be deficient and a whole consignment of medicine intended for New Zealand was stopped.

345 Major faults found with medicines were correlated with the companies that either made or imported those medicines. Over a six-year period, there were 58 companies that had at least one major fault with a medicine. Only two companies had more than 10 major faults; one company had 21 major faults and the other had 14. Both companies were manufacturers or importers of generic medicines. Although in mid-1988 the DSIR drew attention to the fact that most faults lay with the products from two generic medicine companies, the Department decided not to follow up that advice.

346 Further, the two companies were not subjected to any special attention by the Department; for example, by requiring special inspections of the source of their medicines and establishing whether the overseas factories making the medicines met acceptable standards of manufacture.

Conclusions and Recommendations

347 Testing of medicines is an important means of providing assurance that unsafe medicines will be detected. However, testing and subsequent action on

medicines found to be unsafe does not result in checks on those companies found to have the most problems. Hence, the results of testing of medicines should be a source of information triggering further investigations by the Department.

Department of Health Comment and Action

348 *The Department stated that it was never provided with the data to support the DSIR's contention. It is the Department's view that the information available since at least 1987 has not supported the view that generic medicines are of poorer quality.*

349 *It must also be remembered when totalling "complaints received" that the number of product lines sold by any New Zealand sponsor must be taken into account when deciding whether the total represents a higher than average "score". Generic companies have a wider product range than research-based companies.*

350 *The Department does not accept the Audit Office's claim that it has focused only on the results of batch-testing of medicines. The nature of each defect noted for a medicine is always considered with respect to the implications it raises for evidence of GMP deficiencies at the manufacturing site. Where a deficiency is considered to indicate a fundamental lack of GMP [Good Manufacturing Practice] adherence, follow-up action is taken to ensure that any deficiency is remedied.*

Audit Office View

351 *The Department has not been able to provide us with any analysis to support its views. When the analysis quoted above is weighted for each company's number of products, we found that 3 out of the 4 generic companies are above this average compared to 8 out of 33 brand name companies.*

352 *For the period 1983 to 1991, we reassessed the available medicine testing programme data exclusive of complaints received by the Department. Our reassessment did not support the Department's view of an improving record. Twenty testing programmes were conducted and 557 prescription medicines were tested, of which 29 failed (i.e. medicine recalled or not satisfactory due to manufacturing faults).*

353 *Ten failures were attributed to three out of four generic companies. One generic company in particular was involved in ten testing programmes involving 36 of its products and had 7 medicine failures, of which 6 have occurred since late-1986.*

354 *The Department should collate its medicine testing and validated complaint information in a manner which allows the identification of correlations between medicine failures and companies. Any above-average company medicine failure rate should be a signal to target the Department's medicine testing programme. This is now being indirectly achieved in response to the Department's reassessment of the top 130 generic medicines. These medicines are all being tested by the DSIR.*

4

INFORMATION ON MEDICINES

401 To avoid ill-founded choices about medicines they use, patients and health professionals need accurate information about medicines. Three types of information about medicines can be identified:

- *Advertisements for a Medicine:* These aim to promote the use of medicines. The Medicines Regulations 1984 specify the minimum amount of information to be given in such advertisements.
- *Medicine Labels:* These provide information to patients on the use of a medicine. The information required on a label is specified in the Medicines Regulations.
- *Medicine Data Sheets:* These are intended primarily for health professionals and give a detailed description of the medicine. Medicine manufacturers are required by the Medicines Regulations to submit a data sheet to the Department for approval. A data sheet is required when a medicine has been approved for distribution or when a changed medicine notification has been approved.

402 It was our expectation that, to ensure accurate and unbiased presentation of information on medicines, the Department would have a systematic process for checking information about medicines.

ADVERTISEMENTS FOR MEDICINES

Findings and Discussion

403 There is no systematic checking of advertisements for medicines to ensure that they meet the minimum information requirements prescribed in the Medicines Regulations.

404 Regulation 11 of the Medicines Regulations imposes extra requirements if the advertisement is intended for distribution to members of the medical profession. We have seen one study (conducted by a member of the staff of the Department) that reviewed a sample of such advertisements. This study found

that the most frequent defects of such advertisements were lack of details about side effects or significant interactions.

Conclusion

405 There is no assurance that provisions in the Medicines Regulations 1984 governing the standards of medicine advertising are being complied with.

MEDICINE LABELS

Findings and Discussion

406 When a medicine manufacturer seeks registration for a new medicine, or submits a changed medicine notification, the Department also checks the label that is proposed to be used. We found that all labels submitted are checked. Where necessary, the Department insists on changes to the label.

407 The Department has no programme of checking labels in use to ensure that they still comply with the originally-approved label. However, our check of a random sample of labels on 30 prescription medicines showed that they were the same as the originally-approved label.

Conclusions and Recommendations

408 There is adequate initial checking of medicine labels to ensure that they contain the required information. While there is no ongoing review of labels to ensure that they continue to meet the same standard as at the time of approval, our own review showed that labels do continue to meet this standard. Nevertheless, the Department should undertake a systematic review of labels in use.

Department of Health Comment and Action

409 *The comments and recommendations of these sections are not disputed but, given the paucity of resources of the Therapeutics Section, implementation of the courses advocated cannot rate highly in terms of priority.*

DATA SHEETS

Findings and Discussion

410 When a data sheet has been approved by the Department, it distributes copies to Area Health Boards and medical schools. The Department does not distribute copies to medical practitioners or pharmacists.

411 Medical practitioners and pharmacists rely on a privately-produced publication for detailed information on medicines. While this publication does contain copies of data sheets, these may not have been approved by the Department, and it is not possible for readers of the publication to know

whether any particular data sheet has or has not been approved by the Department. The publication receives data sheets directly from medicine manufacturers.

412 The Department currently has a backlog of 2,000 data sheets awaiting approval for both new and changed medicines. The Department estimates that there are 461 medicines on the market for which there has never been an approved data sheet.

Conclusions and Recommendations

413 The Department has not ensured the availability of minimum independent information requirements about each medicine. Thus, doctors have to rely on information produced by medicine manufacturers which has not been checked by the Department.

414 Data sheets should be approved as part of a new medicine application or a changed medicine notification approval, not after the approval for distribution has been given. Whenever a medicine is approved for distribution, there should automatically be a data sheet approved for it. An amendment to the Medicines Act would be required to implement this recommendation.

415 The Department should arrange with the companies which publish data sheets to use the Department-approved data sheets whenever these are available. If unapproved data sheets are published, they should be identified as such.

Department of Health Comment and Action

416 *In order to overcome the backlog, the priority with which data sheets are being assessed has been changed, and they are being assessed concurrently with new and changed medicines applications, when supplied. A large backlog in data sheets awaiting approval has since been reduced by this process.*

5

INSPECTION OF MEDICINE MANUFACTURERS

501 The manufacture of a safe and effective medicine is dependent on raw materials meeting purity standards, clean facilities in which to produce the medicine, and production according to the approved method. Once the medicine has been produced, it must be packaged and distributed in a way that does not compromise the quality of the medicine.

502 Some medicines are made in New Zealand, but the bulk of the medicines used are imported. We reviewed the inspection system used by the Department to ensure that medicines are manufactured safely.

COMMERCIAL MANUFACTURE OF MEDICINES

503 There are over 20 factories in New Zealand that make medicines on a commercial basis. Each factory requires an annual licence from the Department.

Findings and Discussion

504 The Department's records show that each factory is inspected at least once a year. Inspections are carried out to ensure that certain minimum standards of facilities and quality controls necessary to produce good quality medicines are being maintained. These minimum standards have been developed in conjunction with the pharmaceutical industry and applied since 1974.

505 Inspections have found faults in the procedures at some factories. Where faults are serious, re-inspections are carried out to ensure that they are remedied. In the last year, there were only two factories that warranted re-inspections to ensure correction of faults.

506 Approval of a medicine for distribution includes approval of a method of manufacture of that medicine.

507 The Department's inspections do not compare the method of medicine manufacture used in the factory against the method of manufacture approved.

Conclusions and Recommendations

508 There has been effective inspection of medicine manufacturing premises to ensure compliance with the minimum standards of facilities and quality controls. However, no checks are done to ensure that medicine manufacturers make medicines in accordance with the method approved in the original

application to register the medicine. Such checks should be carried out on a sample basis.

Department of Health Comment and Action

509 *A revised policy to increase the emphasis on auditing all aspects of the manufacture and testing of each medicine has been instituted. The current random review of batch documentation is to be extended to include a comparison with the "terms of approval" data for at least one medicine made by the company, including method of manufacture. In any case where discrepancies are noted, a more detailed audit of this aspect of the operation will be performed and appropriate corrective or enforcement action taken as necessary. This will be done by the GMP [Good Manufacturing Practice] auditor at the time of the routine annual audit.*

510 *By adopting this action, the probability of detecting any non-compliant activity which might have the potential to affect public safety will be increased.*

MEDICINES MADE OVERSEAS

Findings and Discussion

511 There are over 150 companies importing medicines into New Zealand. To ensure that these importers are acquiring medicines only from factories that meet New Zealand standards, the Department wrote to these companies in 1989 and asked them to provide documentation to this effect. A number of companies have replied, but the Department has not yet been able to analyse the replies.

512 The Department recognises that this system is not the complete answer to providing assurance that imported medicines originate only from factories that operate to required standards. The Department does not have a system to detect a company obtaining medicines from a factory that did not operate to required standards, although the company may choose to inform the Department of the fact.

513 The problem of ensuring that imported medicines are made only in factories that meet certain minimum conditions is a concern to many countries that import medicines. A number of countries belong to the "Pharmaceutical Inspection Convention". Membership of the Convention allows for exchange of information on the inspection of factories where medicines are made. Such an exchange would allow New Zealand to benefit from up-to-date information

on the standards of medicine factories in the countries concerned. New Zealand has not applied for membership.

Conclusions and Recommendations

514 The Department is unable to provide a reasonable level of assurance that medicines imported into New Zealand originate from factories that meet acceptable standards of manufacture. Hence, the Department needs to ensure New Zealand membership of the appropriate international convention covering inspection of medicine factories. This would facilitate the ability of the Department to confirm that imported medicines are made in factories that meet minimum standards. The recommendations in Chapter 3, relating to regular review of medicines, address the concern that all medicines be made in an approved factory.

Department of Health Comment and Action

515 *A Standard Operating Procedure has been developed, clearly stating what information on GMP for an overseas site is currently considered acceptable at time of registration. It is intended that further resources be committed to creating the database and querying the status of sites for which there is no, or inadequate, certification.*

516 *A trial database with limited information has been generated.*

517 *At the expense of the New Zealand sponsor, arrangements can be made to contract out the inspection of any overseas site for which certification is not available. To date, the Department has arranged contracts to have two sites inspected on this basis by GMP auditors chosen by the Department and arrangements are being made for a third site to be audited.*

518 *The present and proposed approach will ensure that only plants operating to a satisfactory level of GMP compliance will supply New Zealand.*

HOSPITAL MANUFACTURE OF MEDICINES

519 Pharmacists employed by public hospitals make medicines for hospital patients in a hospital pharmacy. Medicines may be made for an individual patient, while more commonly used medicines are made in bulk to supply wards within the hospital. Some hospital pharmacies make medicines for other hospitals. The Medicines Act specifically exempts hospital pharmacies from the requirement to have a licence to make medicines. Nor do medicines manufactured in hospitals have to be registered.

520 Blood products, for use in blood transfusions, are also made in hospitals, usually in a separate unit. Blood products are defined in the Medicines Act as medicines, and the manufacture of blood products requires a licence under the Act. The New Zealand Blood Transfusion Service provides overall co-

ordination of the six regional blood transfusion centres that make blood products.

HOSPITAL PHARMACIES

Findings and Discussion

521 In 1989, the Department began a programme of inspecting hospital pharmacies to provide assurance that appropriate medicine production standards were being met. These standards were recommended for hospital production in 1978.

522 By July 1990, 15 hospital pharmacies had been inspected. None met the minimum standards necessary to provide assurance that the facilities and procedures used are such that safe medicines are being made.

523 The inspections are based on the 1978 recommended standards. The faults observed were classified in three categories: critical deficiency, major deficiency, and minor deficiency. A critical deficiency is any deficiency which may cause the medicine to be unsafe or ineffective. At one hospital pharmacy, 71 critical faults were recorded. At another large city hospital pharmacy, 65 critical faults were listed by the inspector. The hospitals concerned have undertaken to try and remedy the faults. But medicines are still being produced at these hospitals. The extent to which faults have been remedied is not known by the Department.

524 A common fault is that most hospital pharmacies do not test the raw materials from which medicines are made to provide assurance of quality and purity. In 1990, the Department arranged for independent testing of raw materials used in hospital medicines and found that 50% of the batches tested did not satisfy minimum requirements.

525 Some hospitals were using raw materials which are labelled by the manufacturer "not for human use".

526 The practice of using such raw materials to make medicines was justified to us at one hospital on the ground that there was no alternative supply. The hospital staff also believed that products from this manufacturer are safe for human use as they contain no impurities. They also believe that the only reason for the company stipulating that its products are not for human use is because of the religious beliefs of the proprietors, who would not wish to knowingly make products that might be used in the human body.

527 In fact, our enquiries of a senior official at the company concerned established that its products are labelled as not for human use for the very reason that they are not intended for human use. Its products are intended for research laboratories, where they might be used in laboratory animals or in the course of other experiments. Because of that intention, the company does no product

testing to see what impurities might be in these raw materials. Some impurities can be harmful to patients.

528 Medicines produced by hospitals, for use in the hospitals, do not have to be registered. Hence, there is no independent verification of their safety or effectiveness. The Medicines Act allows dispensing of unapproved medicines provided they are made only as required for a particular patient. But there are medicines made in bulk as a matter of routine in hospital pharmacies. As these medicines are used by many patients, there is no reason why they should not be subject to approval to provide an independent check on their safety and effectiveness.

Conclusions and Recommendations

529 The decision by the Department to inspect hospital pharmacies was an important initiative and provides the basis for determining what improvements are required. The inspections have shown a serious failure to adhere to certain minimum requirements for the safe production of medicines. In the last 10 years, failure to adhere to such requirements in hospital pharmacies in some overseas countries has resulted in patient deaths.

530 The lack of adherence to certain minimum standards, and the fact that the hospital-produced medicines do not have to be registered, mean that there is only limited assurance that these medicines are safe and effective.

531 The Medicines Act should be changed to require:

- Licensing of hospital pharmacies where medicines are made in bulk; and
- Registration of hospital medicines that are made in bulk.

532 Hospital pharmacies should immediately cease using raw materials not intended for human use.

Department of Health Comment and Action

Hospital Manufacture of Medicines

533 *The Department has distributed two "GMP Bulletins", in October 1990 and March 1991, as an education tool and has sent them to all hospital pharmacies. The content concentrates on the major areas of concern, explaining the principles of GMP and giving examples.*

534 *The Department has written to all Area Health Board Managers, on 31 May 1991, and advised that "hospitals which do not comply with the code must, therefore, upgrade their operation or immediately cease to manufacture medicines". Since this time, the Department is now reconsidering the suitability of the GMP standards for hospital pharmacies.*

535 *A programme of follow-up audits of some hospital pharmacies is under way in late-January/February 1992. These audits are being performed by consultants*

from the United Kingdom who will audit hospital pharmacies against the current United Kingdom Code of Good Manufacturing Practice.

"Not for Human Use" Medicines

536 *The Department does not, and has never, approved the routine use of raw materials for medicine manufacture which have not been obtained from a validated supplier and been tested for compliance with recognised specifications. This has been conveyed to:*

- *Individual hospital pharmacists, where instances of such use are known;*
- *The New Zealand Hospital Pharmacists' Association; and*
- *The Pharmaceutical Society of New Zealand.*

537 *The only situation where the use of such materials may be reasonable is if all the following criteria are completely satisfied:*

- *Without treatment, the patient will certainly die;*
- *There is no other source of this material available in the world;*
- *Informed consent of the patient has been obtained, where the patient understands that the product is supplied by the manufacturer with the caution "Not for Use in Humans"; and*
- *Area Health Board Ethical Committee approval has been obtained in this instance.*

538 *Any pharmacist who ignores the advice of the Department on this matter will be referred to the Council of the Pharmaceutical Society (under section 30 of the Pharmacy Act 1970) for disciplinary action. However, it could be a just defence if the pharmacist dispensed the product under the instruction of the patient's medical practitioner pursuant to the exemption provision of section 29 of the Medicines Act.*

Audit Office View

539 *At this stage, the Audit Office still has concerns regarding the standard of medicine manufacture in some hospitals.*

540 *In particular, our subsequent reviews of departmental files show that one large city hospital, identified in October 1989 as being grossly deficient in its standards of medicine manufacture, has still not provided assurance to the Department that standards have been upgraded.*

541 *The Department's audit of this hospital's pharmacy had disclosed critical faults which included:*

- *An unacceptable standard of cleanliness and good housekeeping practices in manufacturing areas;*
- *Windows being left open in the medicine manufacturing area, which would allow dust and insects to enter the compounding and packing areas;*
- *No details available to demonstrate that the autoclave unit was reaching the correct operating temperature. An autoclave is a piece of equipment used in*

the sterile manufacture of medicines and must reach a certain specified temperature to ensure complete sterility of the items placed in it.

542 *The nature of the hospital's response to the Department's audit gives no assurance that the hospital will try and remedy the faults identified. For example, the hospital's written responses to the Department on the three critical faults mentioned above were:*

- *To deny that there was a cleaning problem, as statements about cleanliness are subjective. However, as the Department pointed out, to comply with the code of GMP, not only must areas be clean, but documentation on cleaning procedures must be available.*
- *To state that windows in the medicine manufacturing area only opened at a downward angle. As the Department later pointed out to the hospital, an open window will still allow the entry of dust and insects.*
- *To state that the autoclave is maintained at 6-monthly intervals, supported by copies of the maintenance reports. The Department pointed out to the hospital that maintaining the unit is not the same as ensuring that the unit is able to reach the correct heat to ensure sterilisation. The maintenance reports did not cover this aspect.*

543 *Hence, the Audit Office concern is that these straightforward problems are not accepted or understood by the hospital. In our view, these faults should have been remedied.*

BLOOD PRODUCTS

Findings and Discussion

544 Blood transfusion units are required, under the Medicines Act, to be licensed to make blood products. This requirement was to have been implemented by August 1985.

545 However, the transfusion units could not complete the necessary documentation of procedures by 1985. Such documentation is an essential first step in the licensing process. For this reason, the then Minister of Health extended the time by which transfusion centres had to be licensed until August 1986. Although some transfusion units applied for a licence, no unit has yet been licensed. The Department only began in June 1990 to inspect transfusion centres in preparation for deciding if centres are of a sufficient standard to warrant the issue of a manufacturing licence.

546 A 1988 report to the Minister of Health by the New Zealand Blood Transfusion Service drew attention to the serious concern that existed with problems of infection transmitted through blood and blood products. Requiring transfusion units to meet certain standards and to be subject to

regular inspections is an element of providing assurance that these problems are being addressed.

Conclusions and Recommendations

547 Hospital blood transfusion units have not been licensed to make blood products. They are therefore acting illegally in producing blood products and there can be only limited assurance that blood products are safe. Deadlines should be set for the licensing of blood transfusion units. Units that do not meet the standards after the deadline should be closed.

Department of Health Comment and Action

548 *The practical difficulties associated with implementing the 1985 provisions within the framework of the Blood Transfusion Service were formidable and generated considerable debate about the best way of tackling them.*

549 *The attention given to topics such as AIDS and Hepatitis B, and the possibility of contracting these illnesses from contaminated blood, have added urgency to the need to resolve these problems.*

550 *Various options about appropriate remedial actions are being examined.*

Audit Office View

551 *This potentially serious issue has been drawn out for far too long and must be effectively resolved. There is serious concern about the problems of infection transmitted through blood and blood products and assurance must be provided that standards are set and enforced.*

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