

An Bórd Comhairleach Náisiúnta Druganna

# *Annual Report 1975*

National Drugs Advisory Board



Report

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***1975***



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Consultant in Oral Medicine and Pathology, Dublin  
Dental Hospital.

\*Denotes member of the Board.

## INTRODUCTION

By the Chairman

By the end of 1975, the National Drugs Advisory Board had 15 months of experience in the management of mandatory licensing systems for medicinal products and for manufacturers of pharmaceuticals in Ireland. With few exceptions, most applicants now have an appreciation of the intentions of these systems and are providing the type of data which the Board requires.

During 1976 the Board will be commencing a review of established drugs. Although the information required for assessment is less comprehensive than that needed for a new drug substance, the Board is seeking and must receive sufficient information to ensure acceptability of pharmaceutical quality, availability of the active ingredient for effect (bioavailability) and reasonable safety and efficacy in use. In some cases the information is self-evident, in others this may not be so.

With the implementation of the licensing systems for manufacturers and wholesalers, the first legal steps were taken toward the assurance of compliance with international standards of good practice by establishing a regular system of inspection. The increasing availability of established laboratory facilities for the analysis of samples of pharmaceutical products will augment the overall coverage of marketed products. The visit of the EFTA Committee of Officials during 1975 was a welcome confirmation that the surveillance system established here is up to international standards and that it will form a sound base for continued improvement.

The post-marketing surveillance of medicinal products has always been considered by the Board as of great importance in ensuring the continuing safety of all therapeutic agents. During 1975 the voluntary reporting of side-effects associated with medications almost doubled. Of these, over 200 were sent by dentists, alerting the Board to a defect in pharmaceut-

ical quality of a local anaesthetic product, batches of which were withdrawn at the Board's request. Considerably fewer reports -4- were received very early in the year from observant practitioners who detected over-reactions to initial therapy with an antihypertensive. As a result the companies concerned were required by the Board to modify their recommendations for dosage to avoid such unnecessarily exaggerated early responses. In the case of another cardiotherapeutic agent, practolol, practitioners gave invaluable assistance by their reports, enabling the Board to assess the extent and significance of reactions to the drug and to direct the graduated withdrawal of the product from the market.

It should be emphasised that the satisfactory monitoring of the safety of drugs on the market is very dependent upon the co-operation of practitioners in reporting side-effects, **even if these are only suspicions**. Equally an adverse reaction should not be ignored simply because it is known to occur — thus, the difference in bioavailability of various digoxin tablets might have been detected more rapidly if reports of experiences with adverse or unexpected reactions had been made to the Board.

An integral part of monitoring is the recall system whereby the Board can ensure a rapid and complete implementation of any instruction for recall or withdrawal which may prove necessary, with minimal interference in therapeutic management. To facilitate such a system it is essential that an established written procedure exist for each manufacturer and wholesaler, and for each product authorisation holder, and that there should be early and close liaison with the Board on any problem which arises.

The Board appreciates the assistance of practitioners in maintaining a reporting system and hopes that their co-operation will continue to increase, thereby ensuring safer therapy. The co-operation of the pharmaceutical industry has already facilitated improvements in therapy and in patient protection and the Board looks forward to the industry's continued acceptance of this role.

## SUBMISSIONS

### A. European Communities (Proprietary Medicinal Products) Regulations 1974 – Applications for Product Authorisations

The National Drugs Advisory Board considered the documents submitted with 272 applications for product authorisations during 1975, and 27 applications which were under review on 31st December 1974. Seven authorisations have been suspended because of the subsequent development of unsuspected problems in relation to the products. Three of the submissions were withdrawn.

The Board recommended acceptance of 188 applications (161 of the applications submitted in 1975 and the 27 applications under consideration at the 31st December 1974). For the remainder, completion of evaluation of 61 applications had to be interrupted pending provision of further information while 47 applications were under active consideration on 31st December 1975.

It is unfortunate that, despite the availability of guidelines indicating the information required, many applicants still omit such essential information as specifications and analytical results, and such required documents as a sample, the draft literature and evidence of a licence to manufacture. The Board regrets the time spent on reminding applicants of such omissions.

### B. Other Submissions

In addition to the documentation presented in connection with applications for product authorisations, 61 submissions for the marketing of generic products were considered by the Board. Evaluation of 86 submissions for clinical trial was also undertaken – an encouraging indication of the continued interest of both industry and physicians in the exploration of new therapeutic agents.

(Appendix I)

## REVIEW PROGRAMME

On the 15th December 1975, the Minister for Health made regulations – European Communities (Proprietary Medicinal Products) Regulations 1975 (S.I. No. 301 of 1975) – extending controls to proprietary medicines which were already on the market on the 1st October 1974 (the date on which the initial scheme was introduced) in harmony with the provisions of Council Directive 65/65 EEC; Council Directive 75/318/EEC and Council Directive 75/319/EEC of the European Economic Community.

In the implementation of this licensing scheme, the Minister for Health will be advised by the National Drugs Advisory Board which has organised a programme for the review of medicinal products on the market prior to October, 1974. While such a review is necessary so that advice can be tendered to the issuing Authority for the purpose of the above-mentioned Regulations in relation to product authorisations, the Board considers that it is necessary to ensure that those "established" products meet the same criteria of safety, potency, efficacy and quality as products more recently introduced. (See Annual Reports 1973 & 1974).

The information required for such products will in general be concerned with evidence of acceptability of production procedures (pharmaceutics), of clinical experience, of availability for use by the body and of acceptable benefit/risk ratio. The opportunity will be taken to ensure satisfactory labelling and literature for the product so that the practitioner, and where necessary the consumer, may be in the position to use the product to the best advantage.

The order of review is tabulated in Appendix II, together with the dates by which submissions are requested for the products of the several classes. In the case of medicinal products on which full submissions have already been made to, and passed by the Board, the Board will only require updating of information.

## Guidelines

The National Drugs Advisory Board has issued a revised Guideline for use by applicants for product authorisations, which has taken into account the recently introduced regulations S.I. No. 301 of 1975 and the current relevant EEC Directives.

A Guideline is also available specifically for use by those presenting submissions for products intended for clinical trial, including Phase I or Stage I studies.

A special review Guideline will be issued to facilitate applications for products already on the market. The Board expects that those applicants who may be uncertain of or have difficulties with the various requirements will contact the Board's offices.

### MEDICAL PREPARATIONS (LICENSING OF MANUFACTURE) REGULATIONS, 1974

With effect from the 1st October 1975, no person may manufacture a medicinal preparation unless he holds a licence under the above regulations. Licences are issued by the Minister for Health on the advice of the National Drugs Advisory Board which has also been assigned responsibility for supervising the observance of any conditions laid down by the Minister.

In 1975, the Board's Inspector assessed the premises and procedures of thirty three (33) manufacturers who had applied for a manufacturing licence. In some cases, repeat visits were necessary to ensure that modifications recommended by the Inspector or proposed by the company had been completed.

A licence was issued if, at the time of inspection, the company was adjudged to meet certain minimum standards but the target for each company remains the attainment of optimum standards.

Over the past year emphasis was placed on the problem of cross-contamination in relation to certain substances which are generally referred to as "Antibiotics and Low Dose Potents". The major ones are penicillins, tetracyclines, steroids, hormones and substances having a unit dosage form of 10 mgm. or less. During inspections, this topic was discussed at length in each case and it is hoped that no problem area will arise.

Generally, progress was noted in the improvement of the facilities, documentation and procedures and it is felt this will be maintained during the coming year. Despite economic difficulties many companies acquired more equipment for production areas or laboratory use and this will of course enhance their performance.

Licences have been issued by the Minister to twenty eight manufacturers for the maximum period of three years. In two cases, the licences were limited to a period of twelve months. Three applications were withdrawn and at the close of the year, one application was still under review. (See Appendix III).

In addition to inspections undertaken under the above regulations, the inspection of pharmaceutical plants was also necessary to advise the Minister for Health on the certification for export purposes, of drugs manufactured or processed in this country. In each of seven such inspections the premises, facilities, etc. of these manufacturers met the necessary standard for good manufacturing practice.

### Medical Preparations (Licensing of Manufacture) (Amendment) Regulations 1975

These Regulations (S.I. No. 302 of 1975), signed by the Minister for Health on the 15th December 1975, bring the provisions to be satisfied by manufacturers of medical preparations into line with the recently adopted EEC Council Directive 75/319 approximating the provisions of the various Member States in regard to the manufacture of such products. They require that there should be available a "qualified

person" in each unit manufacturing medical preparations and specify duties and set down the qualifications and experience which such a qualified person must possess. They also provide that the importation of medical preparations from countries other than Member States of the Community should be treated as manufacture for the purposes of the licensing of manufacture arrangements.

### **MEDICAL PREPARATIONS (WHOLESALE LICENCES) REGULATIONS 1974**

Under these regulations, no person may sell or supply medical preparations by way of wholesale except under licence granted by the Minister for Health. There are, however, certain exceptions, e.g., a person who holds a manufacturer's licence; doctors or dentists for administration to their patients and co-operative groups of pharmacists not exceeding three in number.

The inception date of this licensing scheme was the 1st January 1976. Applicants for licences are obliged to apply in the form and manner required by the Minister for Health and must satisfy the Minister in regard to the medical preparation or preparations which they propose to sell by wholesale, that they have suitable premises, equipment and staff and suitable arrangements for record-keeping, handling, storage and distribution.

Licences are issued by the Minister for Health on the advice of the National Drugs Advisory Board which has also been assigned responsibility for the observance of any conditions laid down by the Minister. Seventy one applications were received for wholesale licences prior to the 31st December 1975. Sixty five have been inspected and recommendations have been submitted to the Department of Health for the issue of the necessary licences; two applications were withdrawn and the remaining four applications were awaiting inspection at the end of the year. (See Appendix IV)

During the year, draft guidelines for wholesalers were prepared by the Board and circulated to all applicants for licences. The purpose of these guidelines was to advise the applicants

in general terms of the standards which would be required by the Board in each area of the wholesaler's activities. Discussions were then held with wholesalers, both individually and collectively, on these draft guidelines to exchange ideas and identify areas of difficulty in their implementation..

In cases where the issue of a licence by the Minister has been recommended by the Board, the Board's Inspector found that the premises were adequate for the activities carried on therein. In a few cases, re-inspection was necessary as the premises were in the course of reconstruction or the applicants were in the process of moving to more suitable premises. Reasonable controls were exercised over the distribution of products; in the disposal of returns; and the staff employed were suitably qualified to undertake the duties entrusted to them.

However, two aspects of the wholesalers activities did give rise to some concern:-

#### **1. The facilities available and the arrangements made for the storage of medical preparations**

It is a condition of a licence held under the above regulations that the licence-holder should have adequate facilities and arrangements available to avoid deterioration of medical preparations.

Many medical preparations currently handled by wholesalers have specific storage requirements which are usually stated on the product labels. These requirements are often specified in the appropriate pharmacopoeial monograph. In some cases, wholesalers failed to conform with the recommended storage requirements.

In particular, certain medical preparations require refrigerated storage to avoid undue deterioration. This group includes products of biological origin such as insulins, vaccines, sera, etc.

The question of storage was discussed with wholesalers at the meetings referred to above. In addition, the Board's Inspector alerted wholesalers to storage requirements and issued a letter to all wholesalers emphasising the necessity to ensure that the recommended storage conditions are fulfilled.



Wholesalers have accepted the Board's recommendations in this regard and it is expected that standards of storage will improve in the coming year. The Board's Inspector will be paying particular attention to storage conditions in his follow-up inspections during 1976.

## **2. Withdrawal or recall of medical preparations**

Sub-Article 6 (2) (e) of the Medical Preparations (Wholesale Licences) Regulations 1974 states "A wholesaler's licence granted under sub-article (1) of this article shall be subject to such conditions as the Minister may specify and may, in particular, require that the holder of the licence shall keep available records, and, in particular, such records as may be specified in the licence, of the distribution of the medical preparation sold by him as will facilitate its withdrawal or recall as mentioned in paragraph (c) and (d) of this sub-article".

In the discussions between the Board and the wholesalers, it became evident that wholesalers held the view that it would be necessary, to comply with this sub-article, to ensure that all batch numbers of products sold or supplied to their customers would have to be recorded. Representations were made, particularly by general wholesalers who carry all classes of medical preparations, that the recording of batch numbers on invoices to customers would be completely impractical.

Ideally, the recording of batch numbers on invoices to customers by both manufacturers and wholesalers would allow the withdrawal or recall of a product to be undertaken precisely and effectively. The Board recognises, however, the practical difficulties that such recording would present for wholesalers, and, in its discussions with wholesalers, it emphasised that it was not committed to any particular method or system of records but that the method employed by each applicant for licence would be judged on its merits. Any improvements in methods of recording it felt necessary to recommend could be implemented gradually. Nevertheless, in respect of certain groups of products, the Board felt that batch numbers should be recorded and it was agreed that

priority in regard to the recording of batch numbers should be established as follows:

1. Infusion solutions, with effect from the 1st January 1976
2. Vials and ampoules for parenteral use
  - (a) insulins and other hormones
  - (b) antibiotics

with effect from 1st January 1977.

## **RECALL PROCEDURES**

Ireland has on its market a high proportion of pharmaceutical products manufactured and originating elsewhere. As a consequence there is often a failure of communication between pharmaceutical companies and the Irish authorities should it be necessary to recall a product originating outside the country. As a condition of the licence issued, manufacturers and wholesalers have a responsibility to withdraw or recall a product if so directed by the Minister, as does the holder of a product authorisation who must also present a written recall procedure for his product.

During 1975 the Board drew up a guide to recall procedures which was circulated to the pharmaceutical industry. In the organisation of a recall procedure, it is essential to ensure that:-

- (1) There must be a person named as responsible for initiating and continuing communication between the company and the Board.
- (2) This communication of the existence and extent of the problem must be commenced at the earliest possible moment to permit full and adequate involvement of all concerned in the decision as to the procedure for recall in a particular case.
- (3) Within each company there must be a written procedure to be followed, in which is also named the person responsible for communications with outside bodies and the person, generally the quality controller, responsible for directing and monitoring the recall and for reconciliation of results.

- (4) The National Drugs Advisory Board must be kept informed of the progress of the action, if necessary with interim reports, and should receive a full report on completion of the recall which should include details of reconciliation of quantities, as well as the steps taken to investigate the reasons necessitating the recall, the outcome of the investigations and the methods adopted to avoid repetition of such an episode.

A total of twelve (12) recalls or withdrawals of medical preparations were notified to the Board during 1975. In most cases, the recall was undertaken in an efficient manner by the companies concerned. In a few instances, unfortunately, communication from the companies left a great deal to be desired. It is expected that the establishment of an agreed procedure will eliminate this deficiency.

#### **SAMPLING and ANALYSIS of MEDICAL PREPARATIONS**

In April 1968, the Board submitted detailed proposals for the organisation of a Quality Control System in Ireland to the Minister for Health. In its memorandum to the Minister, the Board recommended that, after the institution of product protocol assessment and the establishment of a legislative system of pharmaceutical quality control to cover manufacturing and wholesaling premises, the next priority should be the provision of laboratory facilities to undertake the analytical testing of medical preparations.

There are three circumstances in which analytical testing of medical preparations would be required at present:-

1. When found necessary during the course of inspection of premises. Provision for this has been established in the relevant regulations.
2. Preparations already on the market: during 1973, the National Drugs Advisory Board considered the matter of the equivalent potency for established drugs and made particular reference to the use of antibiotics. A decision was made at that time that sampling "sweeps" should be undertaken as soon as was feasible, assaying all products containing the active principle under study; for example phenoxymethyl penicillin, tetracycline etc.

3. Preparations in respect of which reports of defects had been received.

In July 1975, the Board, after consideration of the present position concerning available facilities and the need for sampling agreed that the time was opportune to proceed with the testing of medical preparations. Discussions were held with the Department of Health and final arrangements for a programme of sampling and testing of medical preparations were under consideration at the close of the year.

#### **LABELLING REQUIREMENTS**

The European Communities (Proprietary Medicinal Products) Regulations 1974 applied the provisions of the European Economic Community Directive 65/65 to all proprietary products introduced on the market after 1st October 1974. However the application of the labelling provisions of that Directive was deferred until 1st October 1975 because of certain practical problems which this presented to the industry.

It is now required of the holder of a product authorisation to ensure that the following information appears on the container and outer package of the proprietary medicinal product:-

- (1) The name of the proprietary product.
- (2) The internationally approved name of the active constituent together with the quantity per unit dose.
- (3) The batch number.
- (4) The product authorisation number.
- (5) The name (corporate) of the person responsible for placing the product on the market, and where applicable, of the manufacturer.
- (6) The method of administration.
- (7) The expiry date for the product if this be less than three years.
- (8) Special storage precautions if necessary.

It is accepted that most companies already include all these items on labels but there are a few which are often omitted, or if included, do not appear sufficiently prominently.

(a) The active ingredient has often been named by chemical nomenclature only – often making it unidentifiable to the practitioner and pharmacist, particularly since there are many systems of chemical nomenclature.

(b) The batch number is often omitted, or else is not readily detectable, because of obscure positioning.

(c) Special storage precautions are generally included somewhere but all too often are not easily discerned by those responsible for ensuring compliance with such instructions.

It is hoped that companies will take steps to correct any possible confusion or omission on labels to facilitate safe handling of the product.

### PROVISION of INFORMATION on DRUGS

Over the past year, discussions have continued with the pharmaceutical industry on the matter of the means used for dissemination of information by the industry to practitioners.

There are many advantages associated with the annual publication of a book or compendium of information, provided it is circulated to all practitioners and pharmacists on a regular basis, and that it includes acceptable and complete statements on all products. The major disadvantage arises from the necessity of constantly updating the descriptions. The information required would be as follows:-

1. Proprietary name of the pharmaceutical product.
2. Approved name of active ingredients together with the quantity of these per unit dose. (In certain cases, e.g. topical preparations, the quantity of active ingredient may also be expressed in terms of percentage per total volume, but such method of expression should be avoided, if possible).
3. Description of pharmaceutical form and appearance.
4. Primary action.

5. Recommended use.
6. Recommended dosage, and routes of administration in adults, children as appropriate by age group, infants, and special groups as relevant.
7. Contra-indications to use.
8. Precautions, warnings, major side effects.
9. Overdosage symptoms and instructions for treatment of poisoning.
10. Pharmaceutical instructions
  - (a) Storage conditions
  - (b) Shelf-life and expiry date
  - (c) Other instructions.
11. Quantity per packet size or container.
12. Name of holder of product authorisation and name of manufacturer.
13. Number of Product Authorisation.
14. Date of preparation of information.

The Board reiterated its concern that this basic information should be made available to the professions in a standardized and regular format. Until this is decided, package inserts should continue to be provided.

### ADVERSE REACTIONS

The National Drugs Advisory Board received 716 reports from medical and dental practitioners during 1975. From these reports, 1,180 side-effects associated with the use of drugs were recorded during the year. This figure is almost double the number reported for the previous year, but was inflated by 233 side-effects reported by dentists consequent to the use of a particular batch of a local anaesthetic.

Drug interactions were reported in 25 instances - 2% in most cases involving either tranquillizers or antihypertensives. The frequency of reporting of such interactions is increasing and many more will undoubtedly be encountered, particularly in those patients on long-term maintenance therapy for such

conditions as mental illness, hypertension and congestive heart failure. It is important that doctors and dentists be aware of all the medications (even those which are self-prescribed) taken by their patients before prescribing additional treatments. It is suggested that all patients on long-term therapy should be provided with treatment record cards to be carried on their persons to ensure that information on their medications be immediately available to practitioner, hospital, or pharmacist as necessary.

Of the side-effects reported about one-third involved the skin and subcutaneous tissues, while the gastrointestinal system, central nervous system and cardiovascular system were affected in 15%, 19% and 9% respectively. (APPENDIX V – TABLE I)

As mentioned above, the Board received over 200 reports associated with the use of a particular batch of a local anaesthetic, all occurring within a few weeks. At the Board's request, the local anaesthetic concerned was recalled as a matter of urgency from the market by the agent and the manufacturers. Such events serve to underline the importance of early notification to the Board by practitioners of any unexpected or unusual effects encountered. Appropriate steps can then be taken to have the cause corrected and the product withdrawn.

Recall of a product may be required as the result of a pharmaceutical defect, or the appearance of an unacceptable side effect as in the case of the next most reported drug, **practolol**. Despite the safe use of this substance in many patients, oral **practolol** was withdrawn from the market because of the high incidence of potentially serious oculocutaneous and other reactions following its prolonged use.

The anti-infectives, ampicillin, cotrimoxazole (trimethoprim plus sulphamethoxazole) each accounted for the 3% of the reports, with penicillin itself providing almost as many. Nalidixic acid, nitrofurantoin and minocycline, none of which is used to the same extent as the first three, each accounted for 1.5 – 1.6% of the total.

The analgesic, pentazocine, was associated with 2.5% of the side-effects reported. Such a relatively high incidence suggests the possibility of unnecessary use.

The various oestrogen-progestogen preparations accounted for 2% of the side-effects reported, and all four of the deaths. These preparations are unusual in that they are most commonly prescribed for healthy persons. It is important to ensure that any drug in such a category has an extremely low incidence of associated side-effects which should be relatively minor. In other words, the benefit of treatment must be vastly greater than the risks to the user. Fortunately, there appears to be a clear trend in recent years toward the reformulation of such preparations with reduction of the oestrogen content. (APPENDIX V – TABLE 2)

### **Congenital Abnormalities**

With the continuing recording of the incidence and type of congenital abnormalities, the Board is increasingly in a position to detect significant fluctuations. The usefulness of such records has been increased by the greater interest of practitioners in detecting minor anomalies, including cleftlip, functional variations in the hip joint, and potential major abnormalities which often require sophisticated diagnostic aids, as well as a high index of suspicion, such as heart anomalies.

The Board hopes that the more intensive follow-up of babies and pre-school children will permit early detection of such functional abnormalities as are often not evident in the neonatal period.

(Appendix VI)

### **The Prospective Study of Primigravidae and Medications**

This study, in progress since 1971 in three maternity hospitals in the country now has records for just over 3,200 primiparous women. The overall incidence of congenital abnormalities in their offspring was 3.2% – the same incidence was seen in offspring of women who took no medications during early pregnancy.

These prospective records have permitted the Board to assess rapidly the experience in this group when questions of the potential teratogenesis arise as with haloperidol, diazepam.

Despite the absence of evidence that any particular drug has acted as a teratogen, the Board continues to recommend that medicinal products should not be used during pregnancy unless the physician feels it to be essential. Furthermore, women who may become pregnant should be discouraged from self-medication.  
(Appendix VII)

## DRUGS SPECIALLY CONSIDERED

### Digoxin

Following the publication of the results of a number of studies of the differing bioavailability of digoxin tablets, not only from different manufacturers, but from different batches made by the same manufacturer, the National Drugs Advisory Board notified doctors and pharmacists of the problem in 1973. It was recommended that digitalized patients should be maintained only on the particular brand they had been prescribed with no alteration of source for the present since interchangeability was not established.

The new pharmacopoeial monograph published in 1974 and with effect from 1st October 1975 has included a new specification to ensure uniformity of digoxin tablets.

The Board issued a notification to all practitioners informing them of the altered circumstances. The withdrawal by companies of digoxin tablets which did not meet the new specification took place during the latter months of 1975, phased so as to allow practitioners time for any necessary modifications in their patient's digitalization dosage regimens.  
(Appendix VIII : Warning Note)

### Metoclopramide

During the six year period, 1968 to 1975 there were 28 reports to the Board of side-effects associated with the use of Metoclopramide. Most of these were cases of dystonia, usually facial, and were often quite severe. Seven, about 30%, occurred in children under the age of 17 years.

It is all too likely that even with this number of cases there has been under-reporting.

The Board issued a reminder to practitioners of the tendency in children to develop dystonic reactions after metoclopramide, and suggested that use of the drug should be kept to a minimum in this group particularly.  
(Appendix IX : Warning Note)

### Phenformin Therapy (UGDP Study)

During 1975 the second report of the University Group Diabetes Program became available, this time concerned with the evaluation of the effect of phenformin therapy on cardiovascular morbidity and mortality. The National Drugs Advisory Board reviewed the available documents.

As in the previous study report of the use of the sulphonylureas, the criteria for the diagnosis of diabetes mellitus and inclusion in the study group were not likely to be readily acceptable by all specialists in this field. In addition, it was noted that certain predisposing factors were more frequently seen in the patients included in the phenformin group, while adequate control of diabetes was achieved in less than half the patients. Such imbalance made interpretation of the results difficult.

The Board was unable to conclude from the evidence provided that the acceptable therapeutic use of either the sulphonylureas or the biguanides rendered patients more susceptible to cardiovascular disease. It was felt, however that the biguanides, in particular phenformin, should be used with circumspection in view of the possibility of development of lactic acidosis with fatal consequences under certain circumstances.

### Practolol

During 1974 and up to July 1975 the National Drugs Advisory Board received 26 reports of cutaneous reactions associated with the use of practolol and 12 reports of ocular reactions of the keratoconjunctivitis type.

Warnings were published by the Board in December 1974 and April 1975. After consultations with cardiologists and

with the company concerned, it was decided to discontinue the use of the oral form of the product in all cases except the relatively few for which no substitute therapy was available. The parenteral form would continue to be available for acute management of cardiac arrhythmias in hospital. Withdrawal was carried out by October 1975.

The Board has as yet received no reports of cases of the serositis such as have been recorded in the literature, but would like to remind practitioners that this complication may become clinically evident even 8 to 12 months after discontinuing use of the drug.

It is not yet possible to indicate if any other B-adrenoceptor blocking agents carry similar hazard, since some have not been available for a sufficiently long period. It is important therefore to bear the possibility in mind and practitioners using these agents should keep their patients under close observation for the development of such complications. (Appendix X : Warning Note)

#### **Prazosin**

This new antihypertensive agent, with a mode of action involving peripheral as well as central mechanisms, was reported as having caused exaggerated hypotensive episodes in 11 patients shortly after commencement of treatment. Similar experiences were also reported elsewhere.

The Board recommended that the product should carry an instruction warning that initiation of treatment should employ a very low dosage with slow increments only. A warning of this was issued to practitioners. (Appendix XI : Warning Note)

#### **Reserpine and Related Rauwolfia Alkaloids and Breast Cancer**

In a continuing appraisal of the relationship of drugs of this type and the development of breast cancer in women, the National Drugs Advisory Board evaluated a number of studies published during 1975, with particular attention to the question of the involvement of levels of circulating prolactin, the relationship of hypertension itself with breast

cancer, and to studies both retrospective and prospective, which were similar in design to those already reported (Lancet, 1974; II, 669).

On the basis of the evidence now available the Board felt that no relationship of significance can be established between administration of reserpine or related compounds and the development of breast cancer.

#### **Stilboestrol and Vaginal Adenosis**

The Board considered the results of a study reported in the literature (1974; Amer. J. Obstet. Gynec., 120, 666; Staff A. and Mattingly, R.F.) of 131 cases of vaginal adenosis in girls who had been exposed in utero to stilboestrol.

On the basis of this further work which demonstrated the teratogenic capacity of high doses of stilboestrol (diethylstilboestrol) to interfere with the normal development of the embryonic vagina, the Board confirmed its previous recommendation (1972) that high doses of stilboestrol should not be used during pregnancy either as medical therapy or as a feed additive for animals, the carcasses or products of which are destined for human consumption.

#### **Oestrogens and Teratogenesis**

The Board has also reviewed the data available at present on the teratogenic potential of oestrogens in general when administered during pregnancy. Most of the published reports deal with women who had received high doses of oestrogen (over 100 ug. daily). No anomalies of sex chromatin, chromosomal number or structure have been seen in most studies but a few have reported chromosomal anomalies, inevitably lethal. The overall incidence of developmental abnormalities have been within the expected range, 2.7% with oestrogens in a dose below 150 ug. a day, but there have been reports of such teratogenic effects as feminisation, ectromelia, heart malformation and foetal death with oestrogens used at higher levels. Reports of infants borne after exposure in utero to low doses of oestrogens have shown no evidence of a teratogenic effect. None of these oestrogens has been in use over a period longer than 20 years.

The Board concluded that there is no evidence at present that babies borne to mothers who have received low doses of oestrogen are at greater than normal risk of developmental or chromosomal anomalies.

### **Use of Hormonal Testing for Pregnancy**

During 1975 the use of various oestrogen: progestogen preparations in the diagnosis of early pregnancy was considered by the Board.

In such cases, the time of most likely use would be between the fifth and tenth weeks of gestation—in other words during the period of organogenesis. Although the content of each hormone is low, both are highly potent and it would be theoretically possible that an effect could be exerted on the embryo at a particularly crucial point in its development, when the placenta is not yet fully developed and capable of metabolising the hormones.

A review was carried out of the congenital abnormalities reported to the World Health Organization Monitoring Scheme as possibly associated with use of these preparations, and also of those cases from the Board's prospective study (see above) in whom there was a history of ingesting one of these preparations. In addition, the various publications in the literature were also consulted and the resultant information evaluated in the light of the times of susceptibility of the various organs and systems as established in human developmental embryology.

It was concluded that good scientific evidence was not available to relate the diagnostic use of oestrogen:progestogen preparations to the development of congenital abnormalities. Nevertheless, the Board recommended that use of these preparations for such a purpose should be avoided as other more accurate external diagnostic procedures were available.  
(Appendix XII : Warning Note)

### **Megestrol Acetate**

In November 1975 interim reports were made available to the National Drugs Advisory Board as well as to similar bodies in other countries, concerning long term dosing studies in dogs and monkeys using megestrol acetate. (Long term dosing programmes with the various progestogens are only now reaching the time at which significant effects may be expected.)

In the case of megestrol acetate, studies to date revealed the appearance of malignant mammary neoplasms in a few dogs after receiving this substance at high doses for over six years. (A somewhat similar finding was reported with chlormadinone in 1970). No unusual features have been reported in monkeys as yet.

It is not possible to predict the relevance to women of these findings in dogs, particularly in view of the peculiar sensitivity of this species to certain progestogens, as well as of the differing oestrous cycle in the dog. Nevertheless, the Board recommended that doctors should not continue to prescribe preparations containing megestrol acetate.  
(Appendix XIII : Warning)

### **Tetracyclines**

In view of the increasing use of tetracyclines in the treatment of infections encountered in general practice the Board issued a reminder that these substances, if used frequently or over a prolonged period in infants or children, or in women during pregnancy, will be deposited in the deciduous and permanent teeth, and in areas of bone undergoing matrix mineralization.

This binding of tetracycline leads to hypoplasia of teeth enamel and decrease in linear bone growth in children.  
(Appendix XIV : Warning Note)

## DRUGS INFORMATION SHEETS

During 1975, the Board issued the following publications to medical and dental practitioners and pharmacists:-

- (a) Drug Information Book No. 19  
Substances Affecting the Gastrointestinal Tract
- (b) Drug Information Book No. 20  
The Topical use of Agents Capable of Exerting a Systemic Effect.
- (c) Drug Information Book No. 8 (Revised)  
Drug Interactions
- (d) Reports of Side Effects associated with the use of drugs 1968 - 1974.

### Other Matters

#### CONVENTION for the MUTUAL RECOGNITION of INSPECTIONS in respect of the MANUFACTURE of PHARMACEUTICAL PRODUCTS

Following the Irish Government's approach early in 1975 to Sweden, the depositary Government of the Convention for the Mutual Recognition of Inspections in respect of the Manufacture of Pharmaceutical Products, to secure an invitation to Ireland to accede to the Convention, the Secretariat of the Convention contacted the Board in June 1975 to suggest that, since a number of experts from the Committee of Officials would be present in Dublin in September to attend the F.I.P. Congress, 1975 it would be opportune for these officials to visit the Board informally to discuss the licensing arrangements for the marketing, manufacture and wholesaling of medical preparations which had been introduced in this country. Such discussions would facilitate the Committee's assessment of Ireland's application should this country be invited to accede to the Convention.

Seven members of the Committee of Officials together with the Director and Assistant Director of Legal Affairs met members and officers of the Board and representatives of the

Department of Health at the Board's offices on the 8th September 1975. A full and frank discussion of the licensing arrangements, the respective roles of the Department of Health and the National Drugs Advisory Board in the implementation of the schemes and the supervision of the observance of the conditions imposed in the licences was undertaken.

Following lunch, the party divided into two groups for an informal inspection of two pharmaceutical manufacturing plants in the Dublin area. During the course of these inspections the members of the Committee of Officials had the opportunity to discuss all aspects of pharmaceutical manufacture with the appropriate personnel at these plants.

The Board have subsequently been informed that a report made to the Committee of Officials by the participants in the visit was considered by the Committee in December 1975. It concluded that, in general terms, Ireland had the necessary legislation and national arrangements to comply with the requirements of the Convention.

### CYCLAMATES

The National Drugs Advisory Board considered a number of reports which have been made available in the last few years and which develop the studies recorded in earlier years in relation to the possible hazards of this substance. Investigations have tended to concentrate on the effects of cyclohexylamine (CHA) and the role of intestinal bacteria in the conversion of cyclamate to cyclohexylamine. Of interest is the apparent racial and species differences.

There seems to be some acceptable evidence now that cyclamate, or most likely its metabolite cyclohexylamine, can act as a mild co-carcinogen in rodents. No positive findings are available in any other species, including man.

### PACKAGING, PHTHALATES & OTHER 'ADDITIVES'

As part of its continuing review of the possible problems associated with packaging materials used for pharmaceuticals, the National Drugs Advisory Board considered the potential toxicity of materials used as plasticizers and stabilizers in



various plastics. The phthalates, particularly diethylhexyphthalate, are probably the most important, in view of the reports of evidence of their leaching into body tissues when plastic tubing has been used for haemodialysis or transfusions. The degree of this migration is of most significance in infants, not only in regard to short term effects on metabolism and on such cells as platelets and erythrocytes, but also in regard to possible long term carcinogenic effects. Indeed, it would appear after evaluation of available documents on all these additives, that there is a great paucity of information on metabolism of this compound in the body (including the intestinal lumen) and on its potential for carcinogenesis. There is a need for intensive organized investigation of these substances.

#### **THE VOLUNTEER SUBJECT IN CLINICAL TRIALS**

Since 1967, the National Drugs Advisory Board has reviewed documentation on drugs proposed for clinical trials in patients or for investigations of the 'Phase I' type in subjects in this country. The applications have been made voluntarily by the companies concerned and by many of the investigators.

After discussions with investigators and with hospital committees and after consideration of the many reports on the subject, the Board adopted a policy of ensuring that the details of a proposed trial should be considered by the ethical or peer committee appropriate to the investigator, and that participants volunteering to take part in such trials have given their informed consent to the undertaking.

Agreement of the Board to clinical trials is now given only if the company undertakes to respect and adhere to this policy. The various hospitals and associations concerned have been requested to notify the Board of their decisions with regard to trial proposals presented to them.

#### **WARNING LABELS ON PRODUCTS CONTAINING SALICYLATES (ASPIRIN) and/or PARACETAMOL**

During the course of the past five years, the National Drugs Advisory Board has held a series of discussions with the Pharmaceutical, Chemical and Allied Industries Association, as representatives of the pharmaceutical industry on the subject of increasing the 'safety in use' of medicinal products on general or free sale.

Having accepted the validity of criteria aimed at protecting the consumer who uses such medications, the industry agreed early on to take active steps in relation to products intended for use by children. Over the last two years manufacturers have agreed to the progressive implementation of several further steps by the addition of warning labels to all medicinal products to ensure –

- (a) that the medicine is kept out of the reach of children
- (b) and in the case of products containing salicylates or paracetamol –  
that the consumer is warned to consult his physician if symptoms persist
- (c) that the consumer is reminded that prolonged use may be dangerous or harmful.

The Board looks forward to the future reduction in pack size of those products available outside pharmacies so that the total number of dose units per container should be below the minimum lethal dose.

The Board hopes that these warnings and limitations will, in addition to serving their specific purpose, help to educate and remind the public that these products are medicines and should be used with care and common sense.

## **GENERAL**

### **Board**

The names of the members of the Board and its two Committees are shown on the facing sheets to this Report. There was no change in the membership of the Board and its Committees during 1975. The vacancy on the Board and on the Committee on Drugs Usage and Adverse Reactions, due to the resignation of Professor P. B. B. Gatenby in November 1974, was still unfilled at the close of the year.

Nine meetings of the Board and eight meetings of each of the Committees were held during the year.

### **Staff**

The work-load devolving on the staff of the Board with the introduction of the new licensing schemes increased considerably during the year. Approval for the creation of a post of Medical Officer and an additional post of Pharmacist had been granted by the Minister for Health in November 1974 and the recruitment of personnel to fill these two positions was undertaken during the year.

Miss Catherine Goldon, B.Sc. (Pharm.), M.P.S.I., took up duty with the Board on the 16th June 1975. Having completed her initial training with the Board, Miss Goldon visited the Department of Health and Social Security and the Wellcome Foundation Limited in the United Kingdom as part of her induction training programme. Arrangements have also been made for her to visit other countries to examine the systems of product licensing during the coming year.

Two attempts were made during 1975 to appoint a Medical Officer to the Board. With the making of the European Communities (Proprietary Medicinal Products) Regulations 1975 in December initiating a review of established products on the Irish market prior to the 1st October 1974, it is essential that this position should be filled as soon as possible to enable the Board to assess submissions within the time-limits laid down in E.E.C. Directives.

In addition, the Board has sought the approval of the Minister for Health to create two further clerical posts. Unfortunately, approval of these posts was deferred due to the embargo placed on the recruitment of staff in the Public Service. Discussions with the Department of Health were continuing at the end of the year in an attempt to resolve this problem of staff recruitment.

The Board's Inspector continued to attend the training courses organised by the Department of Health and Social Security in London for its Medicines Inspectorate.

# Appendix I

## SUBMISSIONS RECEIVED BY THE NATIONAL DRUGS ADVISORY BOARD

### A Applications for Product Authorisations

	1973	1974	1975
Applications under consideration at			
1st January	—	—	27
No. of Applications Received	—	50	272
	—	50	299
Recommendations issued to the			
Department of Health	—	22	188
Held awaiting provision of additional			
information	—	—	61
Withdrawn	—	1	3
Applications under consideration			
at 31st December	—	27	47
	—	50	299
Product Authorisations Suspended	—	—	7
Product Authorisation amendments			
notified and approved	—	—	14

### B Other Submissions

<b>No. for Clinical Trial</b>	<b>89</b>	<b>57</b>	<b>91</b>
Passed	78	41	86
Withdrawn	8	7	—
Under Consideration	3	9	5
<b>No. for Marketing</b>	<b>562</b>	<b>438</b>	<b>69</b>
Reformulations	381	222	—
Passed	466	351	61
Withdrawn	34	49	—
Under Consideration	62	38	8

# Appendix II

## REVIEW PROGRAMME

Classes of Products	Date by which Submissions should have been received
Anti-infectives, Hypnotics, Tranquillisers Sedatives,	1st August 1976
Antidepressants Analgesics Corticosteroids Diuretics Vaccines	1st April 1977
Miscellaneous central nervous system Autonomic Antihypertensives Gonadals Anabolics Hypoglycaemics Other metabolic drugs	1st April 1978
Anaesthetics Stimulants Cardiovascular Haematinics	1st April 1979
Coagulants and Anticoagulants Blood proteins and substitutes Diagnostic Agents	1st April 1981
Vitamins Drugs acting locally Antiprotozoals Fungicides Anthelmintics	1st April 1982
Miscellaneous	1st September 1982

### Appendix III

**Medical Preparations (Licensing of Manufacture)  
Regulations 1974  
Applications for Manufacturing Licences Received  
by the  
National Drugs Advisory Board**

	1974	1975
<b>No. of Applications Received</b>	22	12
Recommendations issued to Department of Health :		
Licences for three years	—	28
Licences for limited period	—	2
Applications withdrawn	—	3
Awaiting Inspection	—	1

### Appendix IV

**Medical Preparations (Wholesale Licences) Regulations  
1974  
Applications for Wholesale Licences Received  
by the  
National Drugs Advisory Board**

	1974	1975
<b>No. of Applications Received</b>	1	70
Inspections undertaken	—	65
Awaiting Inspections	1	4
Withdrawn	—	2
Recommendations issued to the Department of Health	—	65

### Appendix V

**Table I  
SUMMARY OF ADVERSE REACTIONS REPORTED  
(By System Affected)**

	1968-1974 Cumulative Total	1975
Skin and Subcutaneous Tissues	473	400
Musculoskeletal	72	21
Central Nervous System	398	102
Psychiatric	325	112
Special Senses	140	57
Gastrointestinal	364	168
Metabolic and Nutritional	201	50
Endocrine	6	5
Cardiovascular	293	101
Respiratory	56	22
Haemopoietic	152	42
Urinary	71	9
Reproductive System	39	3
Male		
Female	88	2
Foetal	5	5
Generalised	142	81
<b>Totals :</b>	<b>2,825</b>	<b>1,180</b>
	Interactions	25
	No. Reports	716

Table 2

## TOP TWENTY

	Number	% of Reports
Lignocaine and Adrenaline	231	20%
Practolol	48	4%
Ampicillin	38	3%
Trimethoprim + Sulphamethoxazole	37	3%
Pentazocine	30	2.5%
Aspirin	27	2.5%
Indomethacin	22	2%
Penicillin	22	2%
Oestrogen: Progestogen	21 (4)*	2%
Prazosin	20	1.8%
Ibuprofen	19	1.8%
Influenza Virus Vaccine	19	1.8%
Carbenoxolone	18	1.6%
Nalidixic Acid	18	1.6%
Paracetamol	18	1.6%
Nitrofurantoin	17	1.6%
Clonidine	17	1.6%
Minocycline	16	1.5%
Methyldopa	14	1.4%
Diphtheria, pertussis and tetanus	13	1.2%
Erythromycin	12	1%
Oxyphenbutazone	10	
Trimipramine	10	
Metformin	10	

\*Deaths

ATTENTION  
NOTICE TO HOSPITALS

In reviewing the sources of reports of side-effects to drugs as received in the first six months of 1975, the National Drugs Advisory Board was particularly concerned about the poor reporting from hospitals.

The Board's own intensive Monitoring Scheme indicates that approximately 10% of hospitalized patients experience a side-effect to a drug, either a minor or a serious one. This figure is similar to that reported from centres in other countries.

Only 18 hospitals of the over 200 in the country have sent in even one report. Those hospitals, from which no reports have come, have a total of over 40,000 beds. It is remarkable that no reports have been received from any maternity hospital and from only one children's hospital.

The Board appreciates that doctors may be busy and cannot always spare time for yet more paperwork. Nonetheless, the reporting of side-effects to drugs should be considered a part of the routine care of patients. These reports can ultimately assist the practitioner in patient management and provide a safer basis for therapeutics.

There are many reasons, including ethnic and environmental differences, why any one country cannot rely solely on reports from elsewhere. This makes it of vital importance for the Board to receive reports of possible side-effects associated with drugs, even if the doctor is only suspicious that a relationship may exist. Collation of such reports will allow all to benefit from the experience of a few.

The Board urges that hospitals should make greater efforts to assist the Board in its monitoring of side-effects and thereby contribute to improvement in patient care in the future.

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

## Congenital Abnormalities for Coombe, Galway, National Maternity, Rotunda and St. James's Hospitals.

Number		1969	1970	1971	1972	1973	1974
740	Anencephalus	76	81	69	67	77	82
741.0	Spina Bifida with Hydrocephalus	24	22	29	32	29	20
741.9	Spina Bifida without Hydrocephalus	18	16	20	27	30	31
742	Hydrocephalus	15	21	14	19	22	25
743	Congenital Abnormalities of the Nervous System <b>other than those above</b>	12	17	11	19	28	22
743.3	Spinal Cord Congenital Abnormalities (i.e. Myelias)	3	11	7	8	0	15
744	Congenital Eye Abnormalities	1	3	7	0	1	1
745	Congenital Abnormalities of Ears, Face Neck ( <b>NOT</b> including Cleft Palate)	3	5	5	3	7	6
746	Congenital Abnormalities of Heart	19	42	18	27	35	47
747	Congenital Abnormalities of Circulatory System	0	1	0	0	0	1
748	Congenital Abnormalities of Respiratory System	4	5	7	5	19	6
749	Cleft Palate and Hare Lip	11	13	27	25	15	36
750	Congenital Abnormalities of the Alimentary Tract <b>above</b> the Pylorus ( <b>NOT</b> including Cleft Palate)	3	8	7	9	22	9
751	Congenital Abnormalities of the Alimentary Tract <b>below</b> the Pylorus including Anus, Liver and Umbilical Hernias	12	15	15	20	11	22
752	Congenital Abnormalities of Genital Tract Male and Female	2	1	7	6	17	13
753	Congenital Abnormalities of Urinary Tract including Bladder, Ureter and Urethra	8	10	17	9	15	26
754	Talipes (Club Foot etc.)	12	17	20	24	34	26
755	Congenital Abnormalities Limbs <b>NOT</b> Talipes	17	41	55	25	215	87
756	Congenital Abnormalities Musculo Skeletal System inc. Skull if no brain damage and Diaphragmatic Hernias— <b>not</b> inc. Limbs	5	8	9	12	23	20
757	Congenital Abnormalities of the Skin, Hair and Nails	0	0	3	0	6	19
758	Congenital Abnormalities of the Endocrine System and Spleen	0	3	3	2	2	2
759	Gross or Multiple Congenital Abnormalities i.e. Monsters etc.	19	23	11	19	23	13
759.3	Mongolism or Down's Syndrome	16	26	25	40	9	49
759.5	Sex Chromosome Abnormalities	not done	not done	6	20	16	4
		(2xHosps) (2xHosps) (3xHosps)					
TOTAL NO. OF CONGENITAL ABNORMALITIES .....		280	389	393	418	656	582
TOTAL NO. OF LIVE BIRTHS .....		—	—	22882	23825	23934	24620
TOTAL NO. OF DELIVERIES .....		21044	21979	24493	24019	25748	25635
% INCIDENCE OF CONGENITAL ABNORMALITIES .....		1.33%	1.77%	1.61%	1.74%	2.55%	2.27%

## Summary Table of the Prospective Study of Primigravidae &amp; Medications

30th November 1974 to 30th December 1975

Hospitals	None Given	Iron Preps	Anti- Emetics	Folic Acid	Sedatives & Tran- quillisers	Anti- Infectives	Special Treatments	Analgesics
<b>Galway Regional</b>								
No. of Mothers	84	101	20	43	4	15	18	10
No. of Abnormalities in Offspring	0	1	0	0	0	0	0	0
<b>National Maternity</b>								
No. of Mothers	5	16	25	1	4	15	14	19
No. of Abnormalities in Offspring	0	0	0	0	0	0	0	1
<b>St. James's Hospital</b>								
No. of Mothers	238	38	27	8	9	14	13	18
No. of Abnormalities in Offspring	8	3	2	0	1	2	2	1

## Summary Table of Prospective Study of Primigravidae &amp; Medications

July 1971 to 30th December 1975

\*Groups of Drugs taken in First Trimester of Pregnancy.

Hospitals	Total No. of Mothers	None Given	Iron Preps	Anti- Emetics	Folic Acid	Sedatives & Tran- quillisers	Anti- Infectives	Special Treatments	Analgesics
<b>Galway Regional</b>									
No. of Mothers	757	256	524	92	86	44	73	117	57
No. of Abnormalities in Offspring	10	1	7	3	0	0	1	1	0
<b>National Maternity</b>									
No. of Mothers	1557	916	514	274	17	74	170	115	150
No. of Abnormalities in Offspring	57	36	7	8	0	0	5	1	4
<b>St. James's Hospital</b>									
No. of Mothers	893	574	160	65	18	31	86	50	94
No. of Abnormalities in Offspring	33	16	5	5	0	1	5	2	3
<b>Total % Incidence of Congenital Abnormalities</b>	3.2%	3.26%	1.58%	3.7%	0%	0.7%	3.3%	1.4%	2.3%

\*In some cases a mother took several drugs.



## Appendix VIII

### ORAL DIGOXIN TABLETS 0.250 mg.

In July 1973 the National Drugs Advisory Board notified doctors and pharmacists of the problem which had resulted from the disparity in biological availability of different brands of **digoxin tablets**. A number of studies have revealed that the bioavailability of digoxin, that is the amount of digoxin available for absorption by patients, varied in tablets manufactured by different manufacturers even though the manufacture was carried out to the same pharmacopoeia monograph standards.

Because of the lack of equivalent bioavailability the National Drugs Advisory Board suggested that doctors should maintain their digitalized patients on the particular brand with which oral therapy was begun, and should specify the name of the manufacturer of the brand of digoxin tablets on records and prescriptions so that control of maintenance therapy would not be inadvertently interrupted by an alteration in the digoxin brand used and dispensed.

To avoid such continued variations in bioavailability of digoxin tablets, a new pharmacopoeia monograph has been introduced with effect from the 1st October 1975. This includes a new specification to ensure uniformity of digoxin tablets, by requiring that at least 75% of the digoxin in the tablet should be available for absorption within one hour of ingestion.

Any supplies of oral digoxin tablets 0.250 mg. which do not meet the new specification will be gradually removed from the market. The period of phasing out will last for a number of months in order to give practitioners time to assess the digitalization dosage regimen of any patient who has been on such tablets, and who may hold prescriptions issued before the 1st October 1975.

There are certain patients who will require particular care:-

- (1) The elderly and the young on 0.250 mg. dosage.
- (2) Patients on daily dosages of 0.500 mg. or over.
- (3) Patients on concomitant diuretic therapy, with or without potassium supplements.

In these cases careful supervision is required to avoid the possibility of digitalis intoxication when changing the patient to a tablet with more rapid and complete absorption.

Patients who are being maintained on 0.250 mg. tablets of Lanoxin (Burroughs Wellcome) or of Digoxin (Clonmel Chemical Co.) are already receiving preparations which meet the new specification. Some alteration in dosage may be required if a patient is changed to either of these two preparations, or even from one of these brands to the other.

The Board would like to remind practitioners that a **patient stabilized on a particular brand of digoxin tablet is only at risk during the period of changeover, to, and establishment on, a different digoxin brand**. At that time an alteration (usually reduction) in dosage may be required to avoid toxicity.

October 1975

## Appendix IX

### METOCLOPRAMIDE

Of 28 reports of side-effects associated with **Metoclopramide** in Ireland, 23 were cases of dystonia (notably facial), ranging in severity from twitching to painful, continuous oculogyric crises. All recovered after treatment was discontinued. Seven of the dystonic reactions occurred in children and young adults under the age of 17 years.

Reports received by WHO number 76, of which 33 occurred in the age group 0-17 (37 cases of dystonia) and 41 in the ages of 17 and over (26 cases of dystonia). It is interesting that the Irish reporting rate (which is probably not a total rate) accounts for about 30% of the WHO figures.

The Board suggests that the possibility of inducing such dystonic reactions should be borne in mind by the practitioner prescribing metoclopramide. Particularly in the case of children, he should question the necessity of using such a drug for nausea and vomiting, which responds quite rapidly in this group to simple specific anti-infective therapy where necessary or to conservative measures.

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

December, 1975

**PRACTOLOL**

Since the National Drugs Advisory Board published its warning concerning practolol there have been some further developments of which practitioners should be made aware.

The total number of reports of cases of psoriasiform skin eruptions associated with prolonged practolol administration has now risen to 18 in this country, while there have been 5 reports of changes affecting the eye and one of mucosal ulceration. Although all have been associated with administration of practolol for at least 18 months, there has been no evidence of irreversibility once drug treatment has been stopped or the patient transferred to other medications.

Several cases of sclerosing peritonitis have been reported in other countries, ostensibly related to practolol usage, but the Board has been unable to identify any such instances in Ireland, nor have there as yet been any reports of ear disorder.

The mechanisms by which these various effects are induced is not yet clear: some studies have suggested antibody formation to the drug, with cellular type of allergic response.

The Board would like again to remind all practitioners that they should keep any patients receiving practolol under close and regular observation. On the evidence available it would appear unwise to use practolol for treatment unless it is for a patient whose respiratory condition prevents the use of other B-blockers. It is also important to emphasize that the drug should not be used in women of the child-bearing age.

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

April 1975.

**PRAZOSIN**

The National Drugs Advisory Board would like to draw the attention of practitioners to the need for caution in the initiation of treatment with this antihypertensive agent.

A few reports have been received of an exaggerated response to the initial doses of the drug resulting in hypotension and, occasionally, loss of consciousness. This excessive reaction to dosage does not usually occur after the first week of treatment.

Practitioners are urged to commence treatment with very low dosage using slow increments depending on the clinical response. Initial doses should not be taken during the working part of the day or immediately before retiring.

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

April 1975.

**WARNING re:  
HORMONAL PREGNANCY TESTING PREPARATIONS**

Certain oestrogen progestogen preparations are being used as tests for the existence of pregnancy. The Board would like to remind practitioners that there has been no assessment of the safety for use of such preparations for this purpose, and such a use has not been accepted by the Board.

There have been a few publications suggesting a possible relationship between the use of these preparations for such a purpose and the subsequent birth of offspring with congenital abnormalities.

Although strong evidence is lacking for such an aetiological relationship, it would be wiser to avoid the use of oestrogen:progestogen preparations for this purpose since a firm statement of safety cannot be given. Other more efficient methods of diagnosis are available.

The much lower doses of similar preparations which may be used for cycle regulation do not constitute a source of concern.

With this warning, the Board would again emphasize the need to avoid the use of any drug during pregnancy unless considered essential.

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

April 1975.

Dear Doctor,

The National Drugs Advisory Board has had the opportunity of considering new documentation detailing the results of a seven year dosing study in dogs (beagle bitches) using **megestrol acetate**, one of the active ingredients in the products.

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By the end of the dosing time several dogs receiving megestrol acetate at very high doses had developed hyperplastic, malignant mammary tumours. Dogs have an oestrus cycle very different from that of women, and, in addition they are peculiarly sensitive to the effects of certain progestogens. Similar studies in progress in rhesus monkeys have not resulted in the appearance of any tumour at the end of six years, nor have comparable studies with other available progestogens resulted in any malignant tumours.

The Board nevertheless recommends that doctors should not continue to prescribe megestrol acetate-containing products, and should consider the use of alternative treatment to replace these medications as soon as possible. The company concerned – Duncan, Flockhart & Company Limited – will be withdrawing both products in the near future.

Patients who are at present on either of these two products are asked to consult their doctors about their treatment and not to discontinue their tablets until he so directs it.

It is emphasized that no reports have been received in this country or abroad suggesting that megestrol acetate is implicated in human neoplastic disease.

Yours sincerely,  
A. Scott, M.D., F.R.C.P.,  
Medical Director.

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

9th December 1975.

**WARNING  
TETRACYCLINES**

The National Drugs Advisory Board would like to remind practitioners that tetracyclines\* chelate or bind to apatite – the calcium -phosphate complex found in bone, and dentine and enamel of teeth. In the adult this is only of significance during bone repair, but in the infant and child absorption of a tetracycline leads to deposition of the drug in the deciduous and permanent teeth, and in bone, particularly in areas where active mineralization of matrix is occurring. The extent of binding varies with the type of tetracycline.

There is some evidence suggesting that this deposition of tetracyclines leads to a decrease in linear growth of bone and to hypoplasia of teeth enamel as well as their discolouration.

Administration of tetracyclines to women during pregnancy, or to infants or young children should be kept to a minimum and prolonged or frequently repeated administration avoided if at all possible.

• **including**

Chlortetracycline (Aureomycin)  
Clonmocyline (Megacilor)  
Demethylchlortetracycline (Ledermycin, Lederstatin  
(N) )  
Doxycycline (Vibramycin)  
Lymecycline (Tetralysal)  
Methacycline (Rondomycin)  
Minocycline (Minocin)  
Oxytetracycline (Berkmycen, Bisolvomycin,  
Clinimycin, Imperacin, Leocycline, Oxytet,  
Servicin, Terra-Bron, Terramycin, Vendarcin)  
Rolitetracycline (Reverin, Velacycline)  
Tetracycline (Achromycin V, Albamycin T,  
Chymocyclar, Fabacycline, Hostacycline,  
Mysteclin F, Servicin, Sigmamycin, Sumycin,  
Tetrachel, Tetracyn).

National Drugs Advisory Board,  
Charles Lucas House,  
57C, Harcourt Street,  
Dublin, 2.

25th July 1975.

