Ireland

David Lyons
Irish Medicines Board
Dublin, Ireland

ABBREVIATIONS AND NOMENCLATURE

In Ireland the term 'marketing authorisation' (MA) is not a legal term; the equivalent is 'product authorisation'. Thus, 'product authorisation' is used when specifically referring to Irish activities. For European and general purposes, the term MA is used.

The Irish Medicines Board (IMB) is responsible for regulating both human and veterinary medicines. However, this chapter deals with veterinary medicines only where necessary to explain the legal structures of the Board.

CMS	**concerned Member State**
CPMP	**Committee on Proprietary Medicinal Products**
EMEA	**European Medicines Evaluation Agency**
IMB	**Irish Medicines Board**
IPHA	**Irish Pharmaceutical Healthcare Association**
MR	**Mutual Recognition**
MRP	**Mutual Recognition Procedure**
MS	**Member State of European Union**
MSs	**plural of above**
MRFG	**Mutual Recognition Facilitation Group**
NDAB	**National Drugs Advisory Board**

PA	**product authorisation**
PIL	**package information leaflet**
RMS	**Reference Member State**
SPC	**Summary of Product Characteristics**

INTRODUCTION

Between 1922 and 1948, the Republic of Ireland emerged from union with the United Kingdom as of a series of quasi-independent states, including the Irish Free State and Eire. The Republic is located on the northwestern fringe of Europe in the Atlantic Ocean and covers 27,136 square miles. Its population in 1991 was 3.5 million. The climate is mild, due to the moderating influence of the prevailing warm, moist winds from the Atlantic. The mean winter temperature is approximately 14° C higher than that of places at the same latitude in the interior of Europe; the mean summer temperature is approximately 4° C lower.

ECONOMY

Ireland's annual gross national product (GNP) (World Bank estimate; 1991–1993 average prices) was about US $45 billion in the early 1990s, equivalent to US $12,600 per capita. Real gross domestic product rose by 3.5 percent a year during the 1980s, and was slightly less during the early 1990s. Manufactured goods account for some 80 percent of total exports, including electronics, which form some 25 percent of the total. Tourism and the financial services sectors are both major sources of employment. The economy is mixed, with a large private sector and a shrinking public sector. The annual budget figures for 1994 showed approximately US $17.1 billion in revenue and US $17.4 billion in expenditure. Expenditure on healthcare has comprised about 6 to 8 percent of GNP since 1980 of which approximately 10 percent is accounted for by expenditure on medicines, amounting to a market valued of approximately US $500 million.

The cost of medicines is determined on a five-year basis by agreement between the industry, represented by the Irish Pharmaceutical Healthcare Association (IPHA), and the government Department of Health. As in other countries, there have been recent initiatives to reduce the cost of medicines, the latest of which is a five year price freeze imposed by government.

THE PHARMACEUTICAL INDUSTRY IN IRELAND

The Irish Industrial Development Authority, which has responsibility for job development in the industrial sector, has for many years pursued a policy of attracting the pharmaceutical industry to the Republic. This resulted in over 40 international companies setting up a manufacturing base between 1970 and 1990. US companies predominate, with 15 of the top firms. There is also a substantial European

presence, and in 1988 the first Japanese firm, Yamanuchi, established a manufacturing presence in Dublin. The industry employs about 8,000 people and is particularly valued as it provides high quality jobs; 30 percent of the workforce are university graduates. Currently, pharmaceutical exports of finished and bulk product are estimated to be worth US $4 billion annually.

OVERVIEW OF THE REGULATORY ENVIRONMENT

In 1966, following the thalidomide disaster of 1960–1, and the World Health Organization (WHO) recommendation that all countries have agencies to ensure the safety of medicines, the Irish Government established the NDAB with a task to "organize and administer a service for obtaining, assessing and disseminating information as regards the safety of new and reformulated drugs and drugs already in use". In 1987, the NDAB became responsible for approving clinical trials under the Control of Clinical Trials Act. In 1991, the decision was taken by the Irish Government that the Board should become the responsible authority for licensing human medicines (It had served that function for veterinary medicines since 1985). It was also decided that the Board should be self financing. These changes were effected by the IMB Act of June 1995 which transferred the functions of the NDAB to the new Board. In order to meet its new responsibilities, the Board underwent review by the management consultancy services of Deloitte Touche and Corning Besselaar and has gradually implemented the recommendations of the consultants, which has led to considerable restructuring.

STRUCTURE AND FUNCTION OF THE BOARD

The Board consists of a Chairman and nine members appointed by the Minister for Health, who serve a term of five years. On completion of that time, they are eligible for re-appointment. The present Board has been selected to represent the interests of the medical, veterinary, and pharmaceutical professions as well as those of industry and consumers. The Board makes policy decisions and grants PAs (MAs) but it does not involve itself in details of the review process.

The Board is, by law, served by two advisory committees, one for human and one for veterinary medicines. In addition, it is entitled to set up and dissolve sub-committees to serve its functions. Currently, the sub-committee structure is as shown in Figure 1a. The Executive Board is composed of the Heads of Department; all other sub-committees are made up of external experts. The sub-committees look in detail at the assessment process, and particularly problem applications and recommendations for rejection. Figure 1b shows the internal organisation of the Board and the main functions of its various departments.

Figure 1a. The committee structure of the Board.

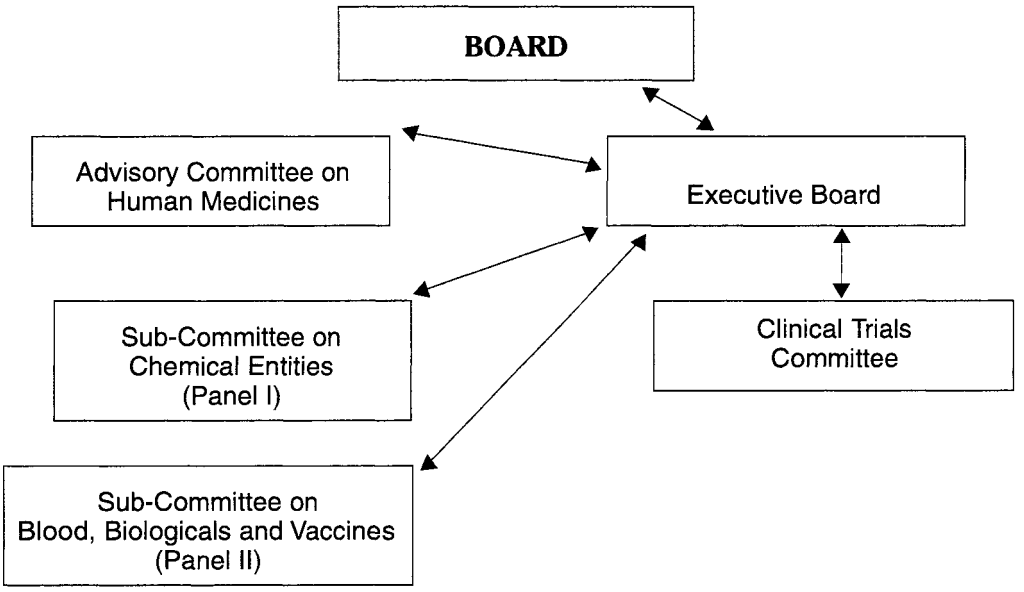
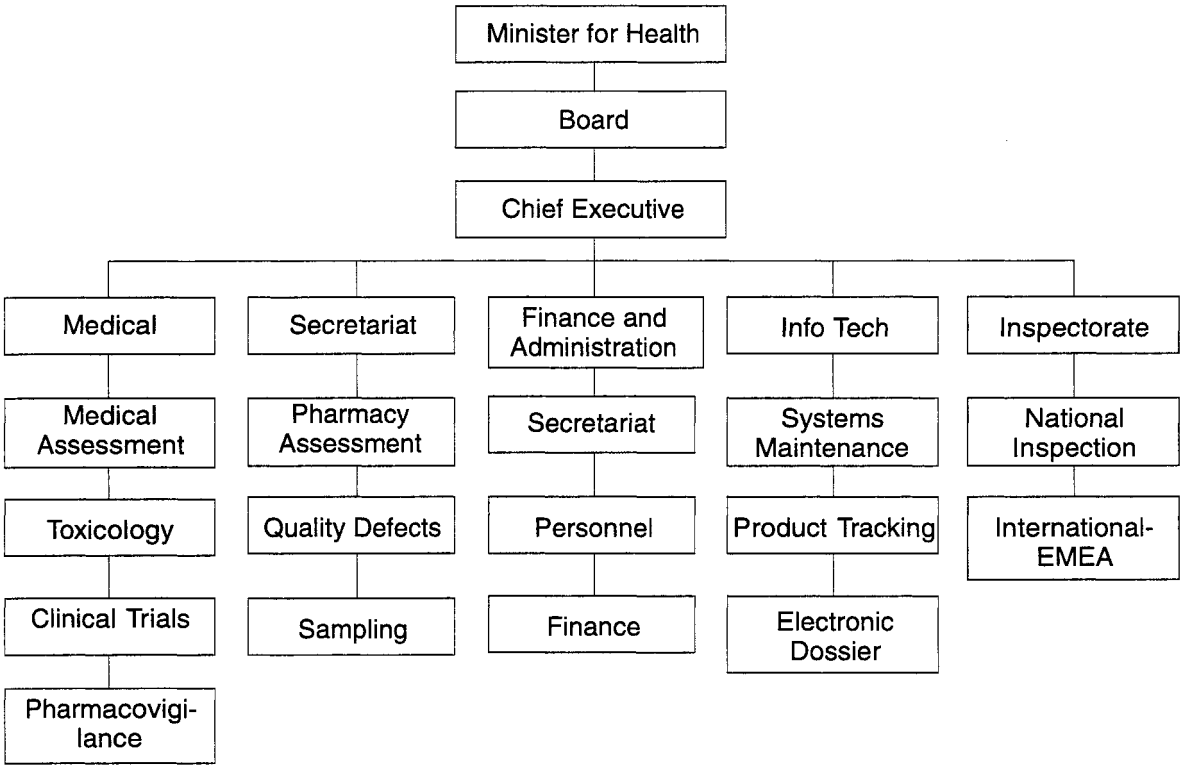


Figure 1b. The main organisational divisions of the Board and their functions.



LICENSING ACTIVITIES

For the period 1986 to 1996, there was an average of 689 applications per year for PAs. During 1995, 377 products were recommended for authorisation; this figure includes 47 novel chemical products. The median time from application to authorisation was 85 weeks (1.6 years). Sixty eight percent of products were authorised within 2 years, and 86 percent within three years. These review times are comparable to the performance of other European agencies, and are the total assessment time, including periods when questions to the applicant were being addressed. Of products under assessment at any given time, approximately 50 percent are at a stage where responses from applicants are awaited. During 1995, the Board received 1,984 requests for variations to PAs and issued 1,903.

RELATIONSHIPS WITH THE EUROPEAN MEDICINES EVALUATION AGENCY

In January 1995, Directive 75/319 of the Council of the European Communities came into force. The regulation introduced new procedures whereby a European MA may be obtained. The net effect of this has been to move work from a national to a European basis, particularly for novel chemicals. The IMB is active in both the centralized and decentralized (mutual recognition) licensing processes, having acted in the centralised process as rapporteur or co-rapporteur on 12 occasions, and having been Reference Member State (RMS) in approximately 10 decentralized applications.

MEDICAL DEVICES

The regulation of medical devices in Ireland is the responsibility of the National Standards Authority (NSA) (See Useful Addresses). Where there is an overlap, necessitating a medical opinion on a product, there is provision for cooperation between the NSA and IMB.

CLINICAL TRIALS

The Clinical Trials Act 1987 introduced stricter regulatory control of clinical trials, and made the then NDAB responsible for reviewing trial applications. A clinical trial is defined in the Act as a systematic investigation of the effects, including kinetic, of a substance. There are limited exceptions—where the substance is used in the course of routine clinical practice for the intended sole benefit of a patient, or in the course of training. In order to conduct a trial, an investigator or sponsor needs financial indemnity, ethics committee (Institutional Review Board or IRB) approval and IMB approval; the latter must be provided or refused within 12 weeks of application. Clinical trials are divided for regulatory purposes into four categories, tabulated below, according to the novelty of the investigational drug and the therapeutic indication for which it is used.

Category 1	**substance and indication both licensed**
Category 2	**substance licensed but indication not**
Category 3a	**new dosage form of a licensed product**
Category 3b	**novel chemical entity or placebo controlled study**

By a quirk of law, a placebo-controlled trial will automatically fall into Category 3b as the placebo is legally regarded as a non-authorised substance, and naturally cannot have an approved therapeutic indication.

The Board reviews 200–250 clinical trial applications each year of which Category 3 predominate, forming 70–80 percent of the total. Refusal of permission is unusual, running at two to five instances per year. Inappropriate use of placebo, leading to patients being denied a standard treatment, and inappropriate (under–qualified) investigators tend to be the most common cause of refusal. Modifications of protocols are requested in about 10 percent of applications.

ASSESSMENT AND AUTHORISATION PROCESS

An applicant for a Product Authorisation should supply a dossier as set out in *The Rules Governing Medicinal Products in Europe Volume II–Notice to Applicants*. This sets out in detail what the required elements of the dossier are.

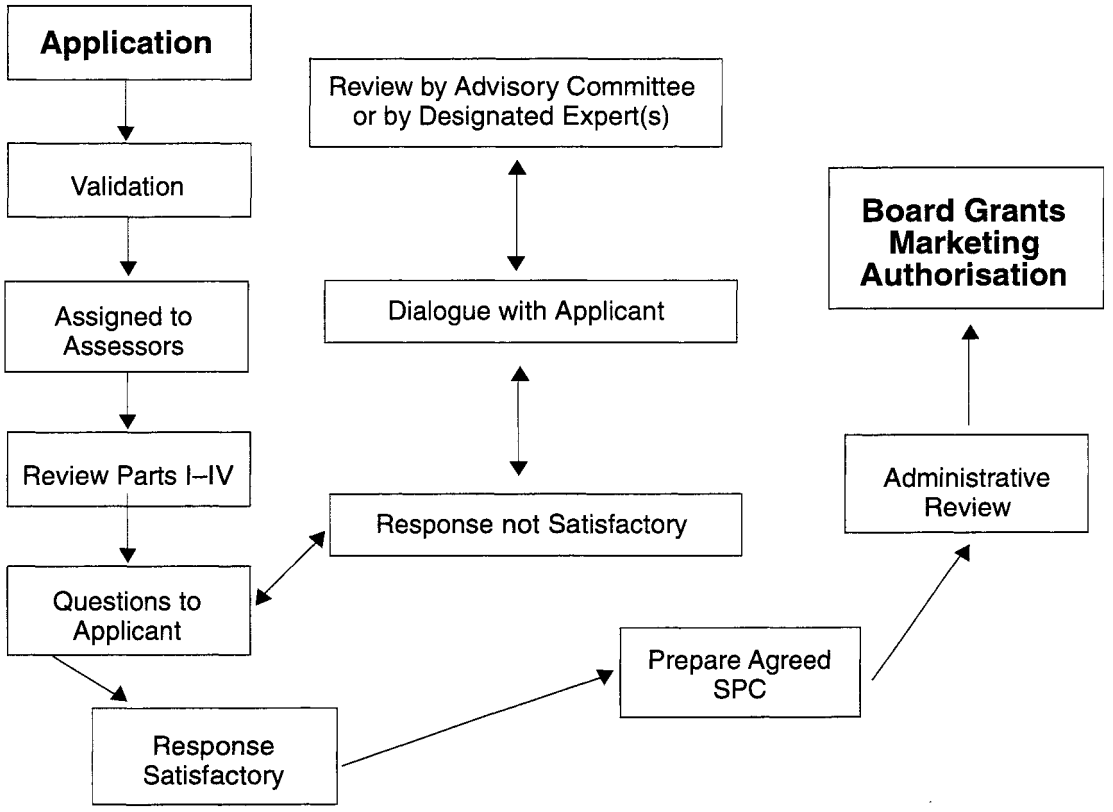
Responsibility for the safe delivery of the dossier remains with the applicant until it is received by the dossier check-in section of the Board. The dossier will be unpacked and the volumes checked against the list of contents. If one or more sections are found to be missing, the applicant will be contacted and the dossier shelved until the missing sections are supplied and the entire dossier is validated.

The assessment process starts upon successful validation (See Figure 2). The application will be assigned to pharmaceutical, toxicological, and medical assessors, who will be responsible for reviewing Parts II, III and IV respectively. In addition, they will review the relevant sections of the Summary of Product Characteristics (SPC). Sections 1–3 and Section 6 are in the area of pharmaceutical responsibility; sections 4 and 5 are medical, and sections 7–10 are administrative. The pickup time between assignment and the start of the review process is around 3 months but may be longer or shorter depending on the priority given to the application and the workload of the assessor. While the Board does not have a formal policy for prioritizing, it will be readily understood that a breakthrough new treatment for a previously untreatable disease may attract more notice than the average application.

The review process consists of two strands which run in parallel, but not necessarily at the same time. Strand I is the review of pharmaceutical quality. The reviewer will make an initial assessment and will draw up a list of comments and questions (deficiency list) which is then sent to the applicant for response.

The second strand is the preclinical and clinical review. As both elements fall within the ambit of the Medical Department, they are coordinated in time and a combined deficiency list of comments and questions on Parts III and IV of the

Figure 2. The assessment process.



dossier is sent to the applicant. In cases where there are gross deficiencies in the clinical section and the product is not thought to be licensable in the foreseeable future, the clinical assessor may, on occasion, advise his or her pharmaceutical counterpart to suspend the assessment. The two processes would then run in sequence.

Receipt of responses from the applicant triggers a second round of review. It has, historically, not been the policy of the Board to impose a time frame for the response. However, long delays on the part of applicants detract from the Board's record for the timely processing of applications. Furthermore, the imposition of a six month deadline by the EMEA and some national European agencies may lead to a change of IMB policy.

In the second phase of the assessment process the responses are gauged against the questions posed. In the event that they are not satisfactory, a fresh dialogue may ensue. This may be on the part of the applicant in the form of a request for further information. Alternatively, the advice of the Board's sub-committees or designated experts may be sought.

When satisfactory responses have been received, a draft SPC and PIL will be sent out for checking and agreement by the applicant. As with the review process, sections of the SPC dealing with Part II (pharmaceutical/quality) issues are agreed separately from sections dealing with Part III and IV issues. Upon the completion of the scientific review and the drawing up of an agreed SPC/PIL, the application is turned over to the administrative section which will check that all the processes have been completed and that the necessary documents are present and correct. The application then goes to the Board for authorisation.

In cases where the application is unsuccessful even after discussion with the applicant and the Board's committees, the applicant will be offered the opportunity to withdraw the application. In the event of refusal, the rejection procedure is initiated.

VARIATIONS

Applications to make changes to the PA should be addressed to the variations section of the IMB. In principle they are handled in the same way as applications for a PA. When the application is received it will be assigned to the most appropriate member of the professional staff, and will be subject to the same process of review as a product application. If the application is fairly routine it can be 'signed off' quickly and sent to the administrative section and the Board. In more complicated situations such as for a new therapeutic indication, it may be necessary to involve the advisory sub-committees. In the event that the variation is considered unacceptable, even after dialogue with the applicant, the same rejection procedure is invoked as for a product application.

RENEWALS

A PA is granted for a fixed period of five years after which time it must be renewed. Renewal applications should be addressed to the renewals section of the IMB. An IMB renewal form should be submitted together with additional material. Three copies of the following are required: SPC plus one electronic copy; a chronological list of variations since last renewal or authorisation; labels; PIL; and data sheet for the professions (if any). Two copies of the following should be provided: Periodic Safety Update; additional clinical or toxicity data (if any); quality defect reports; updated stability data; and updated manufacturer's authorisation.

REJECTION PROCEDURE

Article 9 of the Medical Preparations Regulations (Statutory Instrument No. 43 of 1996) describes the conditions under which the Board may refuse an application for a PA. They occur when the applicant fails to submit information, documents, samples or other materials, or when the Board is satisfied, following examination,

that there are other defects. These other defects may be as follows: the product is harmful under normal conditions of use; therapeutic efficacy is lacking; there are defects in the qualitative or quantitative composition; the labeling is not in accordance with the SPC or with the Irish Labeling and Package Leaflets Regulations (S.I No. 71 of 1993). In the IMB standard operating procedure for rejection, these defects are also considered to be reason for rejection in the case of variations to, and renewals of, PAs.

If, after discussion with the applicant, the problems have not been resolved, the assessor, after having obtained the approval of his or her Head of Department, informs the applicant that the product will be proposed for rejection. The rejection proposal is presented to the Executive Board and, if accepted, the applicant is given 30 days to comment. The response is reviewed by the Executive Board. If the matter has not been resolved, it is then referred to the Advisory Committee on Human Medicines. That Committee may conduct its own review, may refer the issue back to the Executive Board for re-evaluation or may endorse the rejection proposal, in which case it is sent to the Board. If the Board adopts the recommendation, then the applicant is notified of the rejection. Any appeal following rejection must be made to the Board.

FEE STRUCTURE

On becoming the competent authority for licensing human medicines in February 1996, the IMB set up a new fee structure with applications requiring detailed and lengthy review attracting higher fees. A full description of IMB fees is beyond the scope of this review but is available from the relevant section of the Board.

At the time of writing, the fees indicated in the following paragraphs are correct; however, they are subject to change on an annual basis and are provided here for general guidance. Before making an application, the fee should be checked with the fees section of the IMB.

Full Dossier—Complex

The full dossier—complex category applies to products containing a new chemical entity or one derived from biotechnology, including recombinant DNA technology. A fee of Irish £6,000 is payable for the first dosage form and strength of the product. Each additional dosage form, submitted at the same time attracts a subsidiary fee of Irish £2,500. Likewise, a fee of Irish £320 is payable for each additional strength. For example, product A, comprising one dosage form and two strengths, attracts a fee of Irish £6,000 + Irish £320. Product B, containing two dosage forms and two strengths per dosage form, attracts a fee of Irish £6,000 + Irish £2,500 + Irish £320 + Irish £320.

Applications, which are the subject of an MRP, result in *national* authorisations and attract national fees. However, if they are incoming from another MS they will have undergone full review in the recent past. Consequently, the assessment process is less onerous and, in recognition of this, the fee is reduced to Irish £4,200.

Conversely, in the case of an application in which it is foreseen that Ireland will act as reference MS in a subsequent mutual recognition procedure, the assessment work is greater and there is an additional administrative component: a supplementary fee of Irish £2,500 is levied. The same charges apply for additional dosage forms and strengths as for a purely national application.

Reduced Dossier—Complex

The reduced dossier—complex applies to products containing established active substances with a novel delivery system or seeking a significant new indication. A fee of Irish £4,500 is payable for the first dosage form and strength of the product. The fees for additional dosage forms and strengths are the same as for a full dossier. For incoming MRP applications, the fee is Irish £3,200; for outgoing applications, the additional fee is Irish £2,500.

Reduced Dossier—Standard

The reduced dossier—standard applies to products containing established active substances in standard pharmaceutical forms or delivery systems and for established indications. A fee of Irish £3,000 is payable for the first dosage form and strength of the product. The fees for additional dosage forms and strengths are the same as for a full dossier. For incoming MRP applications, the fee is Irish £2,100; for outgoing applications, the additional fee is Irish £1,500.

Extension Applications

Although the phrase 'line extension' is frequently used it is poorly defined, often being used to cover additional strengths, dosage forms, or therapeutic indications. The phrase has a commercial logic but not a regulatory one. For that reason there is no formal category corresponding to 'line extensions'. Applications are treated as either variations or product applications; if categorised as the latter, the fees attracted are normally those for a reduced standard dossier.

Service Items

Service items refer to items which fall into orphan categories, including the following cases: where there is very limited use and no alternative exists; unique formulations for limited circumstances of use; highly specialised formulations for special use; dose forms not available from any company; and radiopharmaceuticals. Agreement that the application falls into this category must be obtained prior to application and will be reviewed at time of renewal. The fee for a service item is Irish £300.

Variations

Changes (variations) to the PAs are grouped into complex variations and simple variations. Complex variations attract a fee of Irish £1,600 and are major changes such as a new therapeutic indication, changes to the dosage, the conditions of use, removal or addition of contraindications and warnings, and significant changes in the manufacture and/or formulation. In all, 18 categories of complex variations have been defined. All other variations are considered simple and attract a fee of Irish £240.

Variation fees are per PA (that is, per Irish PA number) and are charged for each change applied for, other than consequential. For bulk variations, the third and subsequent complex variations are charged as simple variations. The third and subsequent simple variations are charged at half rate.

To illustrate: the holder of PA XX/YY/1-2 wishes to add a new therapeutic indication, and to change the precautions and warnings section of the SPC. That would be considered as two complex variations to two PA numbers, attracting a fee of Irish £1,600 x 4 = Irish £6,400.

Other Fees

There is a yearly retention fee of Irish £290 for each product form and Irish £75 for each additional strength. Other areas attracting fees are: homeopathic registrations, wholesale and manufacturing licenses and clinical trials.

FUTURE TRENDS

Competition

The institution of the new European licensing systems (centralised and decentralilsed) in 1995 has brought about the most profound change in European pharmaceutical regulation since its inception. The scientific skills and the standards applied have undoubtedly risen, the leveling-off effect has been upwards rather than downwards. This is most evident in the new systems where the assessment reports are freely available, but it is also likely to have affected the national procedures. Skills learned in the centralised procedure will also be applied to national applications.

The new system has resulted in a diversion of work from national to European routes. In the two to three years before 1995, the IMB could expect to receive eight to ten applications for novel chemicals in addition to those going through the European procedures. In the years since 1995, that number has fallen to two to three per year. It is possible or probable that the expertise which currently exists in the national regulatory agencies will gradually shift to follow the work, that is, that staff will move for temporary periods, or permanently, to the EMEA. Whether the EMEA can or wishes to 'hire in' its expertise from national agencies on an indefinite basis as it currently does in the form of CPMP, its Working Parties and its

Experts is a moot point. At a political level the answer probably lies at a political level in the balance between federal and nation aspirations.

The decentralilsed procedure will have a similar but less predictable effect. The diversion away from national authorisation has led to increasing competition between agencies for whatever work is available. The transfer to full implementation of the MRP in January 1998 will further intensify that competition. This may lead to some agencies assuming, as their main function, local pharmacovigilance and the checking of incoming Mutual Recognition and centralised applications. This in turn is likely to prompt national governments to ask whether it is necessary to have sixteen bodies to regulate a single market.

Although the development of competition between agencies is likely to speed up the review process and reduce bureaucracy, if carried too far it may adversely affect the outcome of pharmaceutical regulation—the reason the agencies exist. Undue haste to be first to authorise, and so to have lead position as potential RMS may lead to cutting corners and to not asking questions of applicants which properly should be asked. It may also allow the pharmaceutical industry to develop undue influence. For example, a company which considered the therapeutic indication offered in MS A to be unsatisfactory could, as a bargaining point, threaten to withdraw its application and use MS B, which the company considered to be more sympathetic to a broad indication. Given the investment of time in the assessment process by MS A, and the fact that it would be forced to suspend assessment if MS B grants authorisation, the company's threat to switch can be a powerful persuasive influence.

Harmonization

It is increasingly evident through the discussions of CPMP and MRFG that many of the difficulties in drawing up an SPC acceptable to all MS are based on differences in medical practice throughout Europe. Sometimes these differences relate to external and uncontrollable circumstances. For example, the prevalence of drug resistant bacteria may make an antibiotic which is effective but has a higher than expected adverse effect profile, attractive in one MS while not in others. In other circumstances, for example, vaccination schedule differences, differences have developed through arbitrary practices in the MSs. Prior to the institution of the new regulatory systems, such differences were not legally important; differences could simply be written into the national SPC. In the new system it is very important to develop an acceptable SPC as it is legally binding. In view of the heterogeneity of reasons underlying the differences in practice, it is unlikely that any single regulatory approach will be suitable. Rather, a combination of scientific discussion, compromise, referral to CPMP, and litigation will be required. The task is not merely to harmonise a marketplace, but to harmonise an ancient and complex area of human activity, the practice of medicine. It will take at least a generation.

ABOUT THE AUTHOR

David Lyons has an MD from Trinity College Dublin and an MS in applied physiology. He trained in clinical medicine and was an MRC Research Fellow and Senior Registrar in Respiratory Medicine at Northwick Park Hospital, London, and St. James's Hospital, Dublin. Dr. Lyons joined the National Drugs Advisory Board in 1993 and has been a member of the EMEA's Committee on Proprietary Medicinal Products since 1995. He was Chairman of the Mutual Recognition Facilitation Group during the Irish presidency of the EU.

CHAPTER APPENDIX

Useful Addresses of Irish Institutions

Department of Health (government department)
Medicines Division
Hawkins House
Dublin 2
Phone: +353 1 6714711 (switchboard)
Fax: +353 1 6713164

EU Commission–Dublin Office
29 Molesworth St.
Dublin 2
Phone: +353 1 6625113

EU Parliament–Irish Office
43 Molesworth St.
Dublin 2
Phone: +353 1 6057900

Irish Medicines Board (pharmaceutical regulatory agency)
The Earlsfort Centre
Earlsfort Tce
Dublin 2
Phone: +353 1 6764971 (switchboard)
Fax: +353 1 6767836

Irish Pharmaceutical Healthcare Association (industry representative body)
Franklin House
140 Pembroke Rd.
Dublin 4
Phone: +353 1 660 3350
Fax: +353 1 668 6672

Irish Medical Organization (professional representative body)
10 Fitzwilliam Pl.
Dublin 2
Phone: +353 1 6767273

National Standards Authority of Ireland (devices regulatory agency)
Ballymun Rd Glasnevin
Dublin 9
Phone: +353 1 8073800

Pharmaceutical Society of Ireland (professional representative body)
37 Northumberland Rd.
Dublin 4
Phone: +353 1 6600699
Fax: +353 1 6681461