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**An Comchoiste um Shlainte agus Leanai**

**An tOchtú Tuarascáil**

**Seachthorthaí Dochracha Táirgí Cógaisíochta**

**Aibreán 2007**

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**Houses of the Oireachtas**

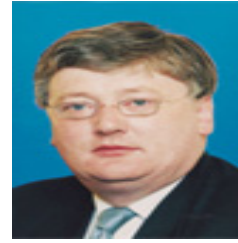
**Joint Committee on Health and Children**

**Eighth Report**

**The Adverse Side Effects of Pharmaceuticals**

**April 2007**





## **Foreword by the chairman of the Joint Committee on Health & Children, John Moloney, T.D.**

The Joint Committee on Health and Children was established in November 2002. In response to concerns expressed by professionals and members of the public, the Joint Committee agreed to establish a sub-Committee on the Adverse Side Effects of Pharmaceuticals to examine the issue in detail and report back with a series of reasonable and feasible recommendations.

The sub-Committee held its inaugural meeting in May 2006 when it decided to invite written submissions from the public followed up by oral presentations from selected witnesses.

The sub-Committee agreed to engage the services of a consultant to assist it in the preparation of a draft report.

The sub-Committee appointed Mr. Jim Dorgan, of Curtin Dorgan Associates to assist it in producing a draft Report containing a series of reasonable and feasible recommendations. A draft report was drawn up by Mr. Dorgan and agreed by the sub-Committee and referred to the Joint Committee in April 2007. The draft report was agreed.

The Joint Committee is grateful to the Members of the sub-Committee for their work on such an important issue. Members of the sub-Committee were Deputies Paudge

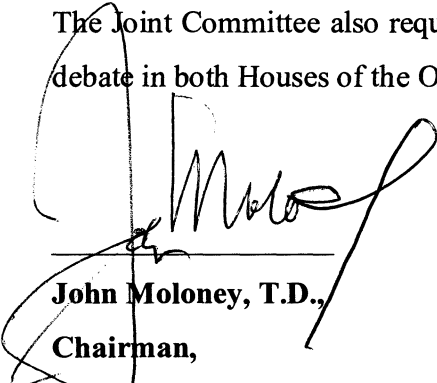
Connolly (Chairman), Dr. Jimmy Devins, Dr. Liam Twomey and Senators Camillus Glynn, Geraldine Feeney and Dr. Mary Henry.

The Joint Committee would like to thank Mr. Jim Dorgan for his assistance in the preparation of the report. The Joint Committee would also like to express its gratitude to all those who came before the Joint Committee to give evidence and to those who took the time to make written submissions.

The assistance and hospitality of the Members and staff of the Health Committee of the House of Commons in meeting Members of the sub-Committee is also acknowledged. Their wide ranging report on the Pharmaceutical Industry in the UK was of considerable assistance.

Given the importance of the issues raised in this report, the Joint Committee asks that immediate action is taken to implement the recommendations contained in this report.

The Joint Committee also requests that the issues raised in this report be the subject of a debate in both Houses of the Oireachtas.



**John Moloney, T.D.,**  
**Chairman,**  
**Joint Committee on Health & Children.**  
**April 2007.**

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## **Abbreviations**

<b>ADR</b>	<b>Adverse drug reaction</b>
<b>DTCA</b>	<b>Direct to Consumer Advertising</b>
<b>EMA</b>	<b>European Medical Evaluation Agency</b>
<b>FTIM</b>	<b>First Time in Man (Phase I clinical trials)</b>
<b>GMS</b>	<b>General Medical Services</b>
<b>HOC</b>	<b>House of Commons</b>
<b>HPU</b>	<b>Health Promotion Unit</b>
<b>HSE</b>	<b>Health Service Executive</b>
<b>IMB</b>	<b>Irish Medicines Board</b>
<b>IPHA</b>	<b>Irish Pharmaceuticals Healthcare Association</b>
<b>MIMS</b>	<b>Monthly Index of Medical Specialities</b>
<b>MAH</b>	<b>Market Authorisation Holders</b>
<b>NDAB</b>	<b>National Drugs Advisory Board</b>
<b>NPM</b>	<b>Non prescription medicine for sale in a pharmacy only</b>
<b>NHS</b>	<b>National Health Service (UK)</b>
<b>OTC</b>	<b>Over the counter (non prescription) medicine</b>
<b>OECD</b>	<b>Organisation for Economic Cooperation and Development</b>
<b>PIL</b>	<b>Patient Information Leaflet</b>
<b>POM</b>	<b>Prescription only medicine</b>
<b>PCRS</b>	<b>Primary Care Reimbursement Service</b>
<b>SPC</b>	<b>Summary of Product Characteristics</b>
<b>WHO</b>	<b>World Health Organisation</b>





## EXECUTIVE SUMMARY

1. In recent years, concern has been expressed that the role of pharmaceuticals in the health services is excessive and that some in particular have dangerous side effects which have been overlooked or ignored.
2. In response to this, the Joint Committee on Health and Children set up the Sub-Committee on Adverse Side Effects of Pharmaceuticals. The Sub-Committee received written and oral evidence from a number of organisations and individuals.
3. The purpose of this report is to review the use of pharmaceuticals and their adverse effects (referred to as Adverse Drug Reactions or ADRs) in the light of these submissions, and to make recommendations. Because of limited time and resources, the Sub-Committee's report can be regarded only as preliminary work.
4. Submissions to the Sub-Committee included a number which made specific criticisms of the use of about psychiatric pharmaceuticals. It was asserted that these medicines had dangerous, even fatal side effects, yet were prescribed extensively.
5. Other concerns expressed included:
  - i. The danger that regulatory authorities are unduly influenced by drug companies because of the latter's economic and technical resources;
  - ii. Shortcomings in the conduct of drug trials;
  - iii. Insufficient ADR reporting leading to failure to identify and cope with problematic side effects of pharmaceuticals;
  - iv. The need for improved training in pharmacology for doctors, including continuous in service training;
  - v. The 'medicalisation' or 'pill for every ill' culture, partly the result of promotion by drug companies, leading to excessive use of pharmaceuticals with attendant ADRs.
  - vi. Some types of promotional activity by drug companies targeted at doctors.

- vii. Misuse of drugs by the public through self medication, importation of non-prescribed drugs from abroad and failure to follow prescribers' instructions.
- 6. The Sub-Committee has concluded that in general, while pharmaceuticals have undoubtedly brought benefits, there is excessive reliance on them to the neglect of other forms of therapy and this contributes to high rates of adverse reactions.
- 7. Subject to a major review being undertaken, the Sub-Committee believes the following proposals should be considered
  - i) Fees for the services of the IMB should be paid by drug companies to the Department of Health and Children which should pass them to the IMB in the form of an annual grant.
  - ii) Drug trials should approximate to conditions in routine clinical settings and should include comparisons with well established medicines and non-drug approaches
  - iii) The licensing process should begin before human trials (Stage I Trials) take place
  - iv) The pharmacovigilance section of the IMB, dealing with post-marketing monitoring of pharmaceuticals, should be set up as an independent entity so as to reduce the possibility of a conflict of interest with the licensing activity of the IMB.
  - v) There is a need for large scale studies after drugs have entered circulation (Phase IV). Since drug companies invest relatively little in such studies funds should be available to the IMB to commission such studies - perhaps in collaboration with other agencies and research bodies.
  - vi) The reporting of ADRs, which occur, needs to be increased. The pharmacovigilance activity of the IMB should expand its training and promotion of ADR reporting. Patient reporting of ADRs should be encouraged. It should be possible to reports ADRs on-line. .
  - vii) There should be a coordinated approach by the Department and the Health

Promotions Unit to ensure that disease awareness material does not indirectly promote drug therapies, and to ensure that national health priorities are addressed.

viii) There is a need to expand the amount of pharmacology training for doctors within the context of Continuing Medical Education in order to ensure that they are fully informed of latest developments in this fast changing field..

ix) The Medical Council should review its rules on ethics of conflict of interest created by certain types of promotional activity by drug companies directed at medical practitioners.

x) Action needs to be taken to provide an independent and practical source of information on pharmaceuticals at national and or local level as exists in other countries such as the UK.

xi) An integrated patient record system should be created to ensure that prescribers have ready access to all relevant information on patients

xii) Records of the Primary Care Reimbursement Service should be exploited to provide information on trends in drug consumption.

xiii) Software to support drug decision making in Irish conditions should be developed and distributed to hospitals, doctors and pharmacists together with facilities to permit printing of prescriptions as a rule so as to avoid errors due to shortcomings in spelling or legibility .

xiv) The role for the pharmacist in community health should be expanded and provision made for regular medication reviews for all patients

xv) There should be an expansion of counselling and psychotherapy in the Community Health Services in order to provide alternatives to psychiatric drug therapies.

xvi) There is a need for public information campaigns to improve public attitudes to the proper use of drugs including:

- a. Advising patients that many medical problems are self limiting and they should not always demand or expect prescriptions when they visit doctors;
- b. Encouraging compliance with courses when a prescription is given;
- c. Disposing safely of unused pharmaceuticals in collaboration with pharmacists;
- d. Raising awareness of the dangers of self-prescribed medicines including counterfeit and imported drugs;
- e. Promoting awareness of ADRs among patients and of the desirability and the means of reporting them to the IMB

A Patient Safety Agency would be the appropriate body to implement many of these recommendations. The Sub-Committee recommends that such an agency be established.

# **I BACKGROUND**

## **Purpose of the Sub-Committee**

1.1 In recent years concern has been expressed about the role of pharmaceuticals in modern medicine. Critics have pointed to the rapid increase in consumption of medicines and have concluded that this is at the expense of alternative, more effective forms of therapy. There have also been criticisms of specific drugs which have had adverse effects and which, it is contended, should never have been licensed for general use. Many of these problems have been attributed to the power and influence of the drug industry which, it is argued, has led regulators and professionals to take an unduly positive view of the claims of the pharmaceutical companies about their products.

1.2 It is against this background that the Joint Committee on Health and Children decided to investigate the problem of the adverse effects of pharmaceuticals. It assigned the task to a Sub-Committee under the chairmanship of Deputy Paudge Connolly which commenced work on 9 May 2006. At that time, the Sub-Committee decided to advertise in the press for submissions from the public. Subsequently items were received from 17 individuals or organisations. Between 10 October 2006 and 7 November 2006 the Sub-Committee held public hearings at which a total of eleven individuals and organisations made oral submissions and in most cases submitted some further written material.

1.3 On 28 November 2006 the members of the Sub-Committee met members of the Health Committee of the House of Commons to discuss aspects of the report which that Committee had published in March 2005 on ‘The Influence of the Pharmaceutical Industry’.<sup>1</sup> This report examined a number of issues relevant to the mission of the Sub-Committee.

1.4 The concerns which gave rise to the formation of the Sub-Committee have complex roots. Pharmacology is an advanced science and its role in medicine is influenced by a variety of managerial, political and cultural factors as well as science. However the resources available to the Sub-Committee are limited. In compiling this

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<sup>1</sup> **House of Commons Health Committee.** *Influence of the Pharmaceutical Industry.* Fourth Report of Session 2004-5. HC 42-1, 2005 (‘HOC’).

report the Sub-Committee confined its attention to the written and oral submissions which it received and to some additional written material specifically brought to its attention, especially the report of the Health Committee of the House of Commons. The Sub-Committee recognises that this is not enough to do justice to the subject. Consequently, this report should be seen as a preliminary exploration of the problem of adverse drug reactions, their causes and consequences and proposals for reducing them.

### **Role of Pharmaceuticals in Health Care**

1.5 The amount of pharmaceuticals consumed in Ireland is not known exactly. Public expenditure on pharmaceuticals is funded from a number of sources including the Primary Care Reimbursement Service (PCRS, formerly the General Medical Services Payments Board), the hospitals and the Health Service Executive. Detailed information on expenditure, numbers and types of drugs is available from the PCRS but similar information from the hospitals and the HSE is not collated centrally. Direct data available on privately financed consumption of drugs is not available either.

1.6 However, from the available data it is clear that drugs play a large and rapidly rising role in medical treatment. In Ireland, expenditure on health services, both public and private, have risen from €3.8 billion in 1996 to about €14 billion in 2006.<sup>2</sup> Within that total expenditures on drugs of all types - prescription only medicines (POMs) and over the counter (OTC) medicines available without prescription - have risen from €400 million to €1.7 billion billion, an increase of 325%.<sup>3</sup> It should be noted that this includes estimates of private as well as publicly financed purchases. This exceeds the growth of expenditure on health generally and means that drugs have risen from 10.5% to about 12.5% of health total spending in Ireland. Nevertheless, as Table 1 shows, Irish consumption of drugs is well below the EU average. (By comparison, per capita health expenditure in Ireland is around the EU average and, like drugs, has increased rapidly in recent years.)

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<sup>2</sup> Based on OECD figures for public and private expenditure up to 2004 and assuming private expenditure has risen as fast as public expenditure in 2005-06.

<sup>3</sup> Derived from the application of OECD estimate of ratio of public and private expenditure on drugs to total health expenditure in 2004 (12.4%) to estimates of total health expenditure in 2005-06.

<b>Table 1 Per Capita Expenditure on Health: US and EU-15 Countries</b>					
<b>Per Capita Expenditure on Health</b>			<b>Per Capita Expenditure on Pharmaceuticals</b>		
	<b>Increase</b>			<b>Increase</b>	
	<b>\$</b>	<b>1994-04</b>		<b>\$</b>	<b>1994-04</b>
United States	6102	73.6	United States	752	150.7
France	3159	64.5	France	599	79.3
Austria	3124	81.8	Italy	520	66.7
Germany	3043	46.1	Spain	477	107.3
Netherlands	3041	74.8	Germany	429	58.3
Denmark	2881	57.4	Portugal	421	81.5
Sweden	2825	70.8	Austria	407	104.1
<b>Ireland</b>	<b>2596</b>	<b>131.2</b>	Greece	377	93.3
United Kingdom	2508	88.3	Finland	364	94.7
Italy	2467	60.5	Sweden	348	78.5
Finland	2235	59.6	<b>Ireland</b>	<b>321</b>	<b>169.7</b>
Greece	2162	78.1	Denmark	270	67.8
Spain	2094	88.0			
Portugal	1824	97.4			
Source: OECD Health Data 2005.					
\$ are in Purchasing Power Parities (PPPs). PPPs allow an accurate comparisons across countries					

1.7 Table 2 shows some further information on drug consumption drawn from the records of the PCRS. Public expenditure on drugs has increased by 126% since 2000.

<b>Table 2: Public Expenditure on Pharmaceuticals</b>				
<b>€ million</b>				
	<b>GMS</b>	<b>DP</b>	<b>LTI</b>	<b>Total</b>
2005	831.4	246.7	100.55	1178.7
2004	763.3	224.0	85.6	1072.9
2003	650.7	204.4	73.3	928.4
2002	550.9	192.4	61.6	804.9
2001	434.0	177.8	52.1	663.9
2000	338.8	140.6	41.7	521.1
Source:				

GMS: General Medical Service ('medical card') scheme  
DP: Direct Payments (grant for drugs exceeding a specified monthly threshold)  
LTI: Long Term Illness

## Impact of Medicines on Health Standards

1.8 It is acknowledged by health care professionals and administrators that the development of new drugs has made a big contribution to the welfare of patients in the last 50 years. This is manifest in, for example, increased life expectancy, improved quality of life, reduction of pain and more effective anaesthetics to improve outcomes of surgery. A study in the UK referred to by the Irish Pharmaceutical Healthcare Association (IPHA) in its submission to the Sub-Committee, has estimated that improved treatments in 12 areas of serious illness since the 1950s have reduced hospital bed days in the UK's NHS by the equivalent of £11 billion or £4 billion more than the cost of medicines.<sup>4</sup>

### ***Excerpt from Website of Irish Pharmaceutical Healthcare Association***

*"In the past 40 years the use of medicines has helped diminish the number of hospital admissions for 12 major diseases by half, including ulcers, mental illness and infectious diseases.*

*New treatments for Parkinsons, Alzheimers and diabetes have helped thousands of patients to lead better and more normal lives, easing the burden on care givers and delaying or avoiding costly long-term nursing care. While cholesterol-lowering medicines, at a cost of less than €3 per day can help avoid coronary by-pass surgery at around a cost of €75,000.*

*In the space of a lifetime, vaccines have virtually wiped out diseases such as diphtheria, whooping cough, measles and polio.*

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<sup>4</sup> HOC, page 13.



*By any of these measures, prescription medicines provide some of the best value healthcare. Medicines save lives, relieve pain, cure and prevent disease. Medicines help keep families together longer and improve the quality of life for patients and care-givers.”*

1.9 In the Irish environment, a concrete example of benefits in one important area of health care is given by a recently completed study of the decline in deaths attributed to coronary heart disease. This study, completed in March of 2006 by a team in the Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James Hospital concluded that 35% of the decline in deaths due to coronary heart diseases in Ireland in the period 1985-2000 was attributable to medicines (aspirin, beta blockers, ACE inhibitors, statins, and similar drugs). Another 8.5% was attributable to other forms of treatment. Most of the remainder is attributable to reduction in risk factors like smoking, cholesterol and blood pressure levels.<sup>5</sup>

### **Economic Significance of Pharmaceutical Industry**

1.10 The pharmaceutical industry is one of the most important sectors of the Irish economy. According to the IPHA it employs a total of 24,000 persons in Ireland an increase of over 100% in the last ten years. This includes employment in manufacturing, distribution and dispensing. The CSO's Census of Industrial Production tracks the size and development of the manufacturing sector – a smaller but higher value added segment. The data are summarised below and confirm the general picture of the industry from the IPHA. Employment in manufacturing has doubled while the value of output has increased nearly seven fold. Almost all of the output of the sector is exported.

<b>Table 3: Measures of Economic Significance of Irish Pharmaceuticals Industry</b>			
	Turnover	Exports	Employment
2004	5441	5294	8883

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<sup>5</sup> Bennett, Kathleen et al. *Explaining the Recent Decrease in Coronary Heart Disease Mortality Rates in Ireland, 1985-2000*. J. Epidemiol. Community Health, 2006. 60:322-327.

2003	4474	4336	8324
2002	5242	5090	8896
2001	4193	4090	8134
2000	3130	3024	7509
1999	3119		7172
1998	1850		6282
1997	1457		6012
1996	1143		5316
1995	859		4368
Source: CSO, Census of Industrial Production			

## II THE PHARMACEUTICAL INDUSTRY AND REGULATION

### Drug Development Process

2.1 The development of new drugs takes a long time and is an expensive and risky process. According to submissions to the House of Commons Health Committee, a typical drug takes 12 years to bring to market. Costs are also high.<sup>6</sup> According to the Association of the British Pharmaceutical Industry, the average cost of bringing a new drug to the market is about £750 million. For this reason, while research and testing may be contracted out, much drug development takes place in large companies. Notwithstanding their size, the success or failure of a single drug can make a substantial difference to the financial fortunes of the largest companies.<sup>7</sup>

2.2 Novelty in the drug enables the companies to enjoy ten years' patent protection from the time of licensing during which, assuming the drug is effective and has no close substitutes, the company has the chance to earn substantial profits. After the period of protection, generic copies of the drug can be produced by competitors and the price of the proprietary drug will fall, sometimes precipitously.

### Commercial Aspects of Drug Developments

2.3 Though the large drug companies are generally profitable, there is some evidence that market conditions are becoming more difficult.<sup>8</sup> It is contended that competition from generics is increasing and that health funders - governments and insurance companies - are exercising increasing downward pressure on prices. One consequence has been a certain amount of restructuring in the industry. Other developments, which may be attributed to commercial pressures, is that the number of genuinely new drugs is declining and that many new drugs in reality are not very different to preparations already on the market (i.e. 'me too' drugs).<sup>9</sup> It may also lead companies to lay greater emphasis on marketing and promotion and to put pressure on regulatory authorities to accelerate the

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<sup>6</sup> HOC, page 17

<sup>7</sup> The shares of Pfizer, the largest drug company in the world, have been in retreat since the failure of its anti cholesterol drug Torcetrapib in development, at the end of 2006.

<sup>8</sup> *Pharmaceuticals: Billion Dollar Pills*, Economist, January 27, 2007.

<sup>9</sup> HOC, page 46.

time and reduce the cost of the trial phase.

2.4 Table 4 gives details of the stages in the development of a drug.

<b>Table 4: Stages in Drug Development</b>				
Stage	Activity	Failure	Success	Duration
Selection of a promising compound for development				
Pre-clinical and non-clinical: testing in laboratory and on animals	Tests on human cells, animal tissues and whole animals.	Of 100 entering Phase I		3 years.
Phase I: First Time in Man: Tests on humans, usually healthy volunteers	Tests on 200-300 healthy volunteers.	30%	70%	10 years
Phase II: Proof of Concept: Tests in patients	Tests in hospital with cooperation of hospital doctors. Involves 200-500 patients with the condition.	37%	33%	
Phase III: Large scale studies to generate data for license application	Sample expanded to 2,000-3,000 and comparisons made with existing drugs or placebos.	8%	25%	
License application		5%	20%	
Phase IV: Post-marketing studies	Trials conducted by companies or by independent researchers to track efficacy in large scale studies and over longer term			
HOC, p18				

## Regulatory Environment: The Irish Medicines Board

2.5 In Ireland the National Drugs Advisory Board (NDAB) advised the Department of Health about drug safety matters until 1996 when it was replaced by the Irish Medicines Board (IMB) under the Irish Medicines Board Act, 1995. The members of the IMB, as also the members of Board's advisory committee on human drugs, are appointed by the Minister for Health. The IMB's department dealing with human medicines is divided into licensing and pharmacovigilance sections. The IMB has a budget of €22 million of which about 80% is derived from fees from industry (2006).

2.6 The task of the IMB is '...to ensure so far as possible, consistent with current medical and scientific knowledge, the quality, safety and efficacy of medicines available in Ireland and to participate in systems designed to do that throughout the European Union.'<sup>10</sup> Quality means that the drug conforms to specifications as to content, uniformity and stability. Safety means that the risks, which are always present in drug use, are acceptable having regard to the expected benefits. Effectiveness means that the drug is likely to be beneficial in treating the condition for which it has been developed.

Table 5: Selected Indicators of Drug Licensing Activities of the IMB				
	New Applications	Variation Applications	Renewal Applications	Clinical Trials
2005	942	15,267	1,328	119
2004	749	13,885	1,325	162
2003	683	5,407	670	116
2002	682	5,365	605	106
Source: IMB Annual Report, 2005.				

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<sup>10</sup> Gilvarry, Dr Joan, Minutes of Sub-Committee on Adverse Drug Reactions. ('Minutes'). 31 October 2006. .

## **Powers of the IMB**

2.7 The statutory powers of the IMB, and equivalent organisations in other developed countries covers the authorisation of Phase I to Phase III trials involving humans, as well as authorisation of the finished drug after Phase III (see Table 4). The IMB continues its surveillance of the drug in the post marketing phase, i.e. after it has been licensed, by examining the results of the Phase IV trials, by following the literature and by evaluating spontaneous, that is to say, voluntary reports of adverse reactions as these are reported by health care professionals, the companies themselves or patients (the pharmacovigilance activity). It should be noted that companies must report all information which may affect the licensing conditions of their drugs from whatever source.<sup>11</sup> The IMB is also responsible for ensuring quality of products in the market and of production facilities.

2.8 The powers of the IMB in relation to drugs include, most obviously, refusal to allow tests or to license a product or to order the withdrawal of a drug from the market. In the case of drugs which are licensed, the IMB has control over the statement of 'Specific Product Characteristics' (SPC) and the 'Patient Information Letter' (PIL) which drug companies must issue. The former is a statement of how the drug may and may not be used (i.e. dosages, duration, contra indications) and is primarily intended for professionals. The PIL is information for consumers. The IMB may require changes to the SPC and PIL as knowledge of the effects of the drug develops with usage.

## **EMEA**

2.9 The IMB exercises its powers within the context of EU legislation and in collaboration with the European Medicines Agency (EMA) which was set up in the EU in 1995, as a 'community agency' under the aegis of the Directorate General for Enterprise. Pharmaceutical companies have three approaches to licensing a pharmaceutical:

**National Procedure** by which the company seeks licensing from the national agency for the marketing of a drug only in that country.

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<sup>11</sup> Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use. Article 23 and Annex 1.

**Mutual Recognition** where the company obtains a license in one country and submits this with its application for licensing in other countries. This is done within the framework of the EMEA where any differences of opinion between the member agencies about the appropriateness of the original license are resolved

**Centralised Procedure** which means applications are made to the EMEA and are processed with the aid of personnel from national agencies and other experts. When adopted by the EMEA's Committee on Human Medicines and the Commission, marketing authorisation is applicable throughout the EU. The centralised procedure must be used for the licensing of certain drugs (drugs produced through biotechnology products and drugs for AIDS, cancer, neurodegenerative disease and diabetes).

2.10 The EMEA is linked with the US and Japanese agencies through the 'International Conference on Harmonisation on Technical Requirements for Registration of Pharmaceuticals' (ICH). The ICH has established standards to be observed by all members in relation to clinical trials.

2.11 The EMEA is currently implementing new legislation which will widen its responsibilities "...in particular to speed access by patients to new medicines..."<sup>12</sup> The list of drug types which must be subject to the centralised procedure is continually expanding.

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<sup>12</sup> Website of the EMEA





### III ADVERSE DRUG REACTIONS

#### Definition

3.1 ADRs is defined by the governing EU Directive as:

*A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnoses or therapy of disease or for the restoration, correction or modification of physiological function.*<sup>13</sup>

3.2 In practice, concern about adverse effects of drugs extends more widely than when they arise in ‘doses normally used in man.’<sup>14</sup>. As reflected in the submissions to the Sub-Committee, there are concerns about the reactions to excessive use of drugs in medical treatment , and to improper use of drugs as a result of failure by professionals or by patients.

#### Causes of ADRs

ADRs happen for a variety of reasons, some inevitable others, avoidable.

##### ***Inevitable:***

Inability to predict with certainty effects of drugs

All drugs have some negative effects

Information about rare events is, by definition, not likely to be available until after a drug is in extensive use

Interactions with other drugs, prescribed or unprescribed

Individual susceptibility

##### ***Preventable***

Error in diagnosis

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<sup>13</sup> Directive 2001/83/EC of the Parliament and the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use.

<sup>14</sup> Henman, Professor M. , Minutes, 7 November 2006.

Error in prescription of the drug or the dose including failure to appreciate full indications, contra indications and risks

Lack of compliance by patients with professional's or manufacturer's instructions as to timing, doses and duration of medication,

Self medication

### **Consequences of ADRs**

3.3 The consequences of ADRs are significant. In the US it has been estimated that 44,000 to 98,000 deaths occur annually as a result of medical error of which about 7,000 are attributable to ADRs<sup>15</sup>. Another US study reported that about 6.7% of patients suffer serious adverse drug effect while in hospital resulting in a fatality rate of 0.32%. In the US context that translates into 2.2 million serious ADRs in hospitals and 106,000 deaths.<sup>16</sup> Another US study reports another 350,000 serious adverse events in nursing homes. The number occurring outside the hospital system is unknown.<sup>17</sup>

Centre for Education &  
Research on Therapeutics

#### **Why Learn about Adverse Drug Reactions (ADR)?**

- Over 2 MILLION serious ADRs yearly
- 100,000 DEATHS yearly
- ADRs 4<sup>th</sup> leading cause of death ahead of pulmonary diseases, diabetes, AIDS, pneumonia, accidents and automobile deaths

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15 Committee on Quality of Health Care in America: Institute of Medicine. *To err is human: building a safer health system*. Washington, D.C.: National Academy Press; 2000.

16 Lazarou J, Pomeranz B, Corey PN. *Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies*. JAMA 1998;279:1200–1205.

17 Gurwitz JH, Field TS, Avorn J, McCormick D, Jain S, Eckler M, et al. *Incidence and preventability of adverse drug events in nursing homes*. Am J Med 2000;109(2):87–94.

- Ambulatory patients ADR rate - unknown
- Nursing home patients ADR rate – 350,000 yearly

Institute of Medicine, National 2000

Lazarou, J. et al JAMA 1998, 279 (15) 1200-1205

Gurwitz, J.H. et al Am. J. Med. 2000, 109 (2) 87-94

Source: Extract from educational module on ADRs from the FDA Centre for Education and Research on Therapeutics

3.4 Closer to home, a study in the UK of 18,820 admissions to two large general hospitals found that 6.5% of admissions were due to ADRs. About 4% of bed capacity was absorbed by these cases and the fatality rate was 0.15%. Most of the reactions were definitely or possibly avoidable.<sup>18</sup> Surveying the evidence the House of Commons report concluded that the cost of ADRs in the UK could run to £ billions per annum.

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<sup>18</sup> Pirmohamed, M. et al. Department of Pharmacology and Therapeutics, University of Liverpool. *Adverse Drug Reactions as Cause of Admission to Hospital: Prospective Analysis of 18,820 patients*. BMJ. 3 July 2004, 329(7456)

### **Excerpt from Report of Health Committee of the House of Commons**

“No figures for the economic burden of drug-induced illness yet exist, but it is feared that it could amount to several billions of pounds per year. The adverse drug reactions, which account for some 3% to 5% of all hospital admissions in the UK, cost in the order of £500 million per year. No estimates have yet been made of the presumably greater cost of adverse drug reactions which do not lead to hospital treatment at all, nor to those experienced by perhaps 15% of all hospitalised patients.”<sup>19</sup>

3.5 No studies of adverse reactions as a whole in the Irish context were brought to the Sub-Committee’s attention, though there are some studies which indicate that the situation is not likely to be much better here than elsewhere. A survey of the literature by personnel in the Pharmacoeconomics Centre in St James Hospital reported a study which identified prescribing errors of 31.1% for in patients in a Dublin teaching hospital and another, by the same authors, reported an error rate of 25% in the out patients department. The survey article also reported that two medical insurers calculated that 25% and 19% respectively of claims against GPs in Ireland were for medication errors<sup>20</sup>. A recently published survey of 600 geriatric patients by staff of the Department of Geriatric Medicine at the Cork University Hospital found that 52% were given inappropriate medicines.<sup>21</sup> The article does not quantify ADRs as such but the scale of errors suggests that the rate may be fairly high.

### **Reporting ADRs**

3.6 Reporting of ADRs by companies and professionals is essential in order to identify problems with drugs and to allow the authorities and the industry to formulate

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<sup>19</sup> HOC, page 8.

<sup>20</sup> Hughes, C., and Barry, M. National Medicines Information Centre Pharmacoeconomics Centre, St James Hospital, Dublin. *Medication Errors*, Irish Medical Journal, June 2000, Vol 95, No 4.

<sup>21</sup> Barry MB, P.J., O’Keefe MB, N., O’Connor MB, K.A. and O’Mahony MD, D.

advice or other actions to prevent these reactions or to mitigate their dangers. An important part of this process is the reporting system managed by the Pharmacovigilance section of the IMB. Under this system (colloquially referred to as the Yellow Card system from the form on which ADRs are reported), ADRs may be filed by doctors, dentists, nurses and pharmacists. This is a spontaneous reporting procedure as distinct from the mandatory procedure by which manufacturing or importing companies with licenses - Marketing Authorisation Holders or MAHs - must report ADRs to their drugs as obtained from clinical trials, post authorisation studies, and those brought to their attention by professionals. These arrangements are similar to those in use in most developed countries. At the moment there is no provision for formal reporting of ADRs to the IMB by members of the public though the public can, and frequently does, contact the IMB informally. These and all other reports are followed up by the IMB.

3.7 In Ireland the current rate of reporting of ADRs is as shown below. Reporting of ADRs has increased by about one third in the last five years. This is somewhat less than might have been expected on the basis of the increase in consumption of medicines in the same period.

Table 6: ADR Reports by Source						
	MAH <sup>1</sup>	Clinical	Doctors/	Pharma-	Nurses	Total
		Trials	Dentists <sup>2</sup>	Cists <sup>3</sup>		
2005	856	127	663	105	110	1861
2004	794	143	604	102	84	1727
2003	508	306	693	116	38	1661
2002	673	157	614	134	40	1618
2001	544 <sup>4</sup>		1604	75	59	2282
2000	NA					1407
1 Marketing Authorisation Holders						
2 General Practitioners, hospital doctors and Community Care doctors						
3 Community and hospital pharmacists						
4 Including clinical trials.						
Source: IMB Annual Reports						

## Under Reporting

3.8 In the opinions of some observers, under reporting is common and a major weakness with the pharmacovigilance process. Studies from other countries have suggested that reporting only identifies about 10% of all ADRs. There are a variety of reasons for under reporting including a tendency by prescribers to think that a given reaction will have been already noted and reported by someone else. Another factor is uncertainty of the prescriber as to whether the observed reaction is attributable to a drug or if so which one (in the case of those receiving multiple drugs).

### Excerpt from Evidence from Professor M. Henman

**Complacency** – belief that only safe drugs are authorised

**Fear** - of becoming involved in litigation

**Guilt** - because a prescribed product has caused harm to the patient

**Ambition** - to collect and publish a series of personal cases which would lead to a delay in reporting

**Ignorance** - of the requirement of reporting

**Diffidence** - about reporting suspicions that might turn out to be unfounded

**Lethargy** – lack of time, of interest, procrastination.<sup>22</sup>

3.9 Table 7 below presents an extract from training material on ADRs prepared by the FDA Centre for Research on Therapeutics which firmly rejects erring on the side of caution in the reporting of ADRs..

Table 7: REPORTING ADRS: PRESCRIBERS' PERSPECTIVE	
Misconceptions	Reality
1) All serious ADRs are documented by the time a drug is marketed;	'...rare ADRs are usually NOT documented by the time a drug is marketed.'

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<sup>22</sup> Henman, Professor M., Minutes 7 November 2006.

2) It can be hard to determine if an individual drug caused a reaction in a patient receiving multiple medications	Timing of reaction in relation to prescription and biological plausibility can be guides. 'The bottom line is, even when in doubt about whether a drug caused the reaction, report it.'
3) ADRs should only be reported if absolute certainty exists that the ADR is related to a particular drug	'A health care provider does not have to be absolutely certain that a drug caused a reaction.... 'All reports contribute to the heightening of the awareness of FDA safety scientists.'
4) One case reported by an individual physician does not contribute to medical knowledge	'One individual report CAN make a difference. Many drug withdrawals began with one clinical report that initiated further investigation.' A single complaint can gain significance in the context of results of trials and other research available to regulatory authorities.
Source: Extract from educational module on ADRs from the FDA Centre for Education and Research in Therapeutics	

3.10 In most countries, as in Ireland, ADRs are reported by health professionals, but reports from patients direct to the regulatory authorities are not systematically encouraged or processed. The reason for this is that without specific knowledge patients may not be able to distinguish between symptoms resulting from the medicine they are taking and those from their environment, lifestyle, or other causes.

3.11 It has been submitted that a problem with following up reports of ADRs in Ireland is the difficulty of tracing patients through the primary care and hospital environments without an identifying number. It would seem that several numbering systems are in use: RSI, GMS number and a number assigned by hospitals for each admission. To easily follow a report of an ADR, it is necessary to be able to identify treatment administered by doctors, pharmacies and hospitals and this would be facilitated by a common patient record system.<sup>23</sup>

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<sup>23</sup> Henman, Professor M. Minutes 7 November 2006.

3.12 There was some debate among the witnesses as to whether Ireland had a low rate of reporting. Some asserted that Irish rates were low.<sup>24</sup> But the IMB reported that the WHO had the previous year noted that the reporting rate in Ireland was among the seven highest amongst the 90 countries in the WHO's reporting system.<sup>25</sup>

### **Processing of ADR Reports**

3.13 Where an ADR is already known to the pharmacovigilance section of the IMB, the report is recorded and the origin (i.e. the professional) is contacted. If the ADR is serious and/or unexpected, the report is evaluated in the IMB and contact is made with the MAH and the EU and WHO databases are searched for evidence of similar ADRs reported elsewhere.

3.14 The practice of the IMB is to encourage professionals to make reports of ADRs. Actions which may follow include:

- Changing the SPC to include new side effects;
- Making a new contra indication (i.e. circumstance in which the medicine is not advised);
- Adding warnings;
- Restricting its use to second line use (i.e. to be used when drugs with known and milder ADRs or none have not proved successful);
- Ordering the withdrawal of the drug.

### **Communication with Prescribers**

3.15 Once evaluated, any changes resulting have to be advised to the professions. The IMB does this through:

- 'Drug Safety Newsletter', a six page newsletter published by the IMB three or four times a year and distributed to prescribers;
- Monthly articles in MIMS (Monthly Index of Medical Specialities), a

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<sup>24</sup> O'Donovan, Dr Orla, Minutes 7 November 2006

<sup>25</sup> Gilvarry, Dr Joan, Minutes 31 October 2006



pharmaceutical trade publication of the Irish Medical Times widely circulated among doctors;

- Statements to the media;
- In the event of urgent communications, the IMB uses direct mailing and emailing to contact professionals;
- The IMB may require MAH's to communicate with the professions. Such communications must be evaluated and authorised by the IMB.



## **IV SUBMISSIONS TO THE SUB-COMMITTEE**

### **Psychiatric Medicines**

4.1 As noted in paragraph 1.2 there were a total of 17 written submissions and eleven oral presentations by individuals or groups. A substantial number of these were submissions comprising reports of ADRs resulting from psychiatric medications prescribed for the witnesses themselves, their close relations or their patients. These submissions made a number of points about these drugs including that:

- their use in therapy represents unwarranted medical intervention in what are often emotional difficulties within the normal range;
- though intended for moderate to severe conditions and for relatively short periods, some medicines are prescribed for mild conditions and for extended periods;
- the drugs are often prescribed on the basis of very limited observation of the patient;
- they generate side effects which are misdiagnosed as causal, leading to further medication;
- the side effects include, behavioural disorders, physical illness, dependence, suicidal ideation and even suicide;
- the drugs in question carry inadequate warnings about these side effects;
- even where the risks of these side effects are well known they seem not be fully appreciated or are ignored by prescribers;
- even setting aside the risk of side effects, some of the drugs are of doubtful benefit.<sup>26</sup>

4.2 Most of the other submissions were from professional organizations and academics presenting their respective roles in pharmaceutical sector together with observations, analyses and recommendations. These submissions addressed the question of ADRs in general rather than in relation to specific patients or drugs.

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<sup>26</sup> O'Mahoney, Nuria and other witnesses, Minutes of 7 November 2006. Fleming, Sean written submission.

4.3 The paragraphs which follow summarise the main concerns as contained in the submissions or in the publications specifically brought to the Sub-Committee's attention.

### **Drug Trials**

4.4 There are shortcomings in the way in which drug trials are carried out and reported such that potential ADRs are not adequately identified. To some extent this is inherent in the process which is inevitably focused on small samples which cannot be wholly representative. The FDA Centre for Education and Research in Therapeutics points out that most drugs are approved on the basis of trials on subjects totaling not more than 1,500.<sup>27</sup> However, it is also contended that the form of drug trials is such that ADRs are likely to be overlooked.<sup>28</sup> Indeed, companies can structure tests with that objective in mind<sup>29</sup>. Furthermore, it is contended that drug companies are not obliged, or do not, make available all studies to regulators.<sup>30</sup>

### **Regulatory 'Capture'**

4.5 Regulatory authorities are under pressures of various kinds from drug companies by virtue of the economic size and technical resources of the latter. This may result in the authorities licensing drugs without adequate trials or accepting companies' research findings too readily or not insisting on the dissemination of all available information on potential ADRs.

4.6 Personnel of regulatory agencies are from the same professional background as the personnel in drug companies. Personnel often move between agencies and companies. There is a high level of interaction. There is always a danger that, in time, regulatory personnel may come to share some of the viewpoints of the companies. These influences are part of the process, identified originally by US political science, as 'regulatory capture'.

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<sup>27</sup> Training Modules on ADRs by FDA Centre for Education and Research in Therapeutics

<sup>28</sup> Harlan Krumholz and colleagues. *What Have We Learned from Vioxx.* BMJ 5 November 2007. page 120.

<sup>29</sup> Avorn, J. *Dangerous Deception – Hiding the Evidence of Adverse Drug Effects.* NEJM. 23 November 2006

<sup>30</sup> Avorn, J. *ibid*, HOC page 182

4.7 No evidence was submitted to the Sub-Committee that any of the foregoing specifically affected work of the IMB. However, it was noted that the establishment of the IMB was accompanied by a reorientation of priorities of which speedy approval of industry applications was an important objective.<sup>31</sup> Indeed, the reduction in the backlog of applications from drug companies is one of the first matters referred to by the Chairman in the IMB's latest annual report.<sup>32</sup> This does suggest that the tendencies at play in the larger countries such as the US and UK may be active in Ireland.

4.8 Furthermore, as outlined in Section 2 regulation is increasingly an international process and the IMB is not entirely autonomous in regulating drugs on the Irish market. In this context it was noted that the EU drugs authority, the EMEA, is under the wing of the Commission's Directorate General for Enterprise, not the Directorate General of Health and Consumer Affairs.<sup>33</sup> The Sub-Committee is uneasy about the priorities which this arrangement seems to imply.

### **Reporting ADRs**

4.9 A number of submissions emphasized underreporting of ADRs. Once drugs have been licensed and are in general circulation reporting of ADRs is essential to ensure that the manufacturer, the regulatory authorities and the professionals are informed and appropriate action is taken. Manufacturers are obliged to report ADRs but professionals are not. It is contended that there is inadequate awareness of the need for reporting and for procedures to encourage reporting. Lack of encouragement for patients to report is regarded as a particular shortcoming of the situation in Ireland.<sup>34</sup>

### **Medical Error**

4.10 Where a drug has been properly licensed and its potential ADRs identified and

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<sup>31</sup> O'Donovan, Dr Orla, Minutes, 7 November 2006

<sup>32</sup> Annual Report, 2005. IMB

<sup>33</sup> O'Donovan, Dr Orla, Minutes 7 November 2006

<sup>34</sup> O'Donovan, Dr Orla, Minutes 7 November 2006

communicated, ADRs may arise at the level of the practitioner by reason of erroneous diagnosis or prescription. Errors in diagnosis is presumably a matter of training, including in service training, and is outside the scope of this report. However, ADRs due to errors in prescribing, although with correct diagnosis, are relevant to the work of the Sub-Committee and are topical given proposals to extend prescribing authority to non doctors.

4.11 Errors in prescribing can also occur because the practitioner does not have full information on the patient by virtue of inadequate patient records. Problems also arise because of lack of communication between professionals (e.g. hospital doctors and GPs, GPs and community pharmacists).<sup>35</sup>

### **‘Medicalisation’**

4.12 ADRs may arise because practitioners have an exaggerated view of the benefit of the drugs in relation to its drawbacks. This may be partly attributable to a culture which assigns untoward confidence in drug therapies. Submissions before the Sub-Committee emphasized medicalisation of society – the ‘pill for every ill’ syndrome – which prompts practitioners to prescribe (and patients to expect) drugs rather than alternative therapies or no therapy at all.<sup>36</sup> Alternatives could include counseling in the case of psychiatric cases and life style changes in the case of cardiac care or obesity. Specific and forceful complaints on these points in relation to psychiatric drugs are noted in paragraph 2.1 above.

### **Promotion by Drug Companies**

4.13 A number of witnesses emphasized the influence of drug companies by reason of their economic size and importance, and their promotional activities. Collectively these influence the general climate in favour of drug therapies, as noted above. Promotional activity directed at practitioners also inculcates favourable attitudes to drugs in general and specific drugs in particular.<sup>37</sup>

4.14 Promotion by drug companies to the profession takes a variety of forms including:

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<sup>35</sup> Stewart, Dr Duncan, Written Submission.

<sup>36</sup> O’Mahoney, Nuria, Minutes 17 October 2006

<sup>37</sup> O’Donovan, Dr Orla, Minutes 6 November 2006

- Advertising in professional journals;
- Presentations by sales personnel to practitioners;
- Funding of research and publication by hospital and academic specialists;
- Sponsoring seminars and conferences and payment of expenses and honoraria to practitioners for lectures, presentations, and other forms of participation;
- Ghost writing articles for payment. It is asserted that in the UK 50% of journal articles reporting clinical trials are written for the authors by the drug companies.<sup>38</sup>

4.15 It should be noted that the members of the IPHA subscribe to a code of practice prescribing high standards of ethical behaviour in relations with, inter alia, the health professions.<sup>39</sup> The medical profession also has codes for its members governing conflicts of interest. But this is also true for the UK where, however, the House of Commons report noted a number of matters of concern.<sup>40</sup> The Sub-Committee has no systematic evidence of questionable practices in Ireland, though members did refer to a number of what seemed like borderline cases. Members feel that there are grounds for concern in this area.

4.16 Direct to advertising to consumers ('DTCA') is not permitted in Ireland and the members of the Sub-Committee were strongly of the view that this should not be changed as it has been in the US and New Zealand. However drug companies do sponsor health awareness events and publications. Some of these materials are for distribution in schools. These are not explicitly linked to specific drugs but in some cases at least the sponsoring company has a preparation for the illness in question. In any case, it is contended that there is narrow line between 'illness awareness' and 'disease mongering'.<sup>41</sup> Members expressed concern that the overarching effect of the association of drug companies with health messages is to confirm in the public mind the importance of drug therapy.

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<sup>38</sup> HOC, page 53

<sup>39</sup> *Code of Marketing Practice*, website of the IPHA

<sup>40</sup> HOC, page 58, page 108

<sup>41</sup> HOC, page 101

## **Reporting of ADRs by Patients**

4.17 The role of the patient in generating ADRs was also emphasized. Witnesses submitted that ADRs can arise from:

- inappropriate use of OTC drugs;
- self medication including purchase of genuine or counterfeit drugs abroad or via the internet.<sup>42</sup>
- failure to comply with dosing instructions: there are surveys which indicate that 50% of patients do not fully or at all follow the instructions on their prescriptions.<sup>43</sup>

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<sup>42</sup> Pharmaceutical Society of Ireland, written submission

<sup>43</sup> IPHA, written submission



## **V CONCLUSIONS AND RECOMMENDATIONS**

5.1 In this section the Sub-Committee presents some conclusions and a number of recommendations. As already emphasised, the Sub-Committee has not been in a position to conduct an exhaustive study of all of the concerns submitted to it about the role of pharmaceuticals in medical practice in Ireland today. Consequently, these conclusions and recommendations should be validated by a more in-depth review. But at this point the Sub-Committee believes that the conclusions and recommendations should be on the public agenda for discussion and debate.

### **CONCLUSIONS**

5.2 First, lest it be thought that the Sub-Committee is hostile to drug therapies, the valuable role which pharmaceuticals have played in the development of modern medicine should be acknowledged. That pharmaceuticals should continue to have a large contribution to medicine is not at issue.

5.3 However, the influence of the pharmaceuticals industry, and the persuasiveness of the promotion of its products is unhealthy and needs to be counterbalanced. In concluding this the Sub-Committee is not assigning malicious intent to industry personnel, but the pressures on the industry impel it to excessive promotion. The Sub-Committee believes that this contributes to a generally excessive reliance on drug therapies by the professions and the public.

5.4 The regulatory regime in Ireland conforms to high international standards and the personnel of the IMB are highly qualified and professional. However, the Sub-Committee feels that there are steps which could be taken to improve the strength, independence and transparency of drug regulation in Ireland.

5.5 Notwithstanding concerns about the regulatory process, the Sub-Committee feels that the adverse consequences of ADRs – other than those which are inevitable - are more likely to arise from erroneous use of drugs, which are otherwise safe, than from regulatory failure. This would point to the need to assign a higher priority to pharmacovigilance activities, including reporting of ADRs.

5.6 It would also, and this is the Sub-Committee's other general observation, point up

the need for improvements in pharmacological training, and information systems and more generally in the delivery of health services, which could mitigate undue reliance on drugs.

## **RECOMMENDATIONS**

### **Regulation**

#### ***Funding***

5.7 The NDAB was funded by a grant in aid from the Government. The method of funding switched to fees for services to drug companies when the IMB was established. This arrangement by-passes cumbersome budgetary procedures and ensures that funds are readily available as a function of demands placed on the Board. However, it tends to put the drug companies in the position of clients of the IMB with the inference that the IMB has a corresponding obligation to meet its ‘clients’ needs. This is not an ideal position for an agency concerned with public safety. The Sub-Committee suggests that there would be merit in the Department collecting the fees from the drug companies and consolidating the receipts into an annual grant to the Board.

#### ***Trials***

5.8 Submissions to the Sub-Committee made general references to faults in the regulation of the clinical trials process. The issue was also explored in great detail in the House of Commons report. A variety of techniques can be used by companies to show their drug in a favourable light.<sup>44</sup> The Sub-Committee has not had the time to pursue these issues in detail. However, it does endorse the recommendation of the House of Commons report that trials should approximate more closely to conditions in routine clinical settings and should include comparator drugs and non drug approaches.<sup>45</sup>

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<sup>44</sup> O’Mahoney, N. Minutes, 17 October 2006. HOC, page 50. Krumholz, *ibid*

<sup>45</sup> HOC, page 102.

5.9 Secondly, the Sub-Committee believes that the licensing process should begin before Phase I (FTIM) trials. The Sub-Committee recommends that drug companies should submit to the IMB their research programmes and results from the pre-clinical phase. These files should be sealed, to assure companies of the commercial confidentiality of their work, and only opened in the event that the companies proceed with the research to Phase I trials. This would give the IMB a more in-depth understanding of the technology when applications are received for the clinical trials.

### ***Pharmacovigilance***

5.10 It has been submitted to the Sub-Committee that an agency which licenses drugs is likely to be compromised to some degree if the drugs which it has licensed subsequently turn out to be problematic. The failure of the drug might then be seen to reflect badly on the agency's original decision and lead to some reluctance on the part of the agency to come to grips realistically with the problems. The Sub-Committee therefore suggests that there could be merit in dividing the IMB into two with one agency dealing with licensing and a second with post marketing surveillance (the pharmacovigilance function). This unit would also be involved in training and in promoting procedures in community medicine would improve reporting of ADRs.

5.11 A major and inevitable weakness of the clinical trials system is that clinical samples are much smaller than the target populations who will ultimately receive the licensed product. Phase IV studies, which follow the drug as it is dispensed through the target population are the main means of identifying problems (and efficacy) in the post marketing phase. Some studies of this type are funded by the drug companies themselves and occasionally by other – e.g. academic – bodies. But they are not systematically undertaken by regulatory authorities. The Sub-Committee recommends that the IMB (or the post marketing surveillance agency proposed above) should be in a position to fund independent Phase IV studies if it believes there is insufficient post marketing information about specific drugs.<sup>46</sup> This research could be carried out in collaboration with authorities in other countries.

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<sup>46</sup> Avorn, J. *ibid*

## ***Reporting of Adverse Drug Reactions***

5.12 The importance of increase reporting of adverse drug reactions was stressed by a number of witnesses. Reference was made, in particular, to practices in other countries such as Denmark, Netherlands and Sweden<sup>47</sup>, which encourage patients to report adverse reactions. The Sub-Committee recommends that the IMB - or the pharmacovigilance agency should there be one - should increase the volume of publicity targeted at prescribers and pharmacists and start a campaign to inform the public of the need to report ADRs. At the same time yellow cards should be widely available (e.g. in clinics, pharmacies and health centres). It should be possible also to report ADRs on line to the pharmacovigilance agency or the IMB. Training activities of the IMB in this area may also need to be stepped up, especially with the extension of prescribing powers to nurses and para medics.

## ***Disease Awareness Advertising by the Pharmaceutical Companies***

5.13 The Sub-Committee is concerned at the sponsorship of health messages by the drug companies aimed at specific clinical conditions. The Sub-Committee recognises that these messages can have positive effects in public awareness. But while it is appreciated that the companies do not promote individual products, the underlying effect may be to promote favourable attitudes of the public towards drug therapies. The Sub-Committee feels that the Department of Health, in consultation with the Health Promotion Unit (HPU), the IMB and the industry, should endeavour to ensure that these messages encompass information on non drug therapies. Also, the Department should try to ensure that taken altogether, the national health priorities are addressed by the HPU and the companies.

## **Profession**

### ***Training***

5.14 The adequacy of continuing pharmacological education for health professionals may need to be reviewed. The high incidence of prescribing errors suggests that some

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<sup>47</sup> *Patient Reporting of Adverse Reactions. Outcomes of a Seminar.* Health Action International, 26 May 2005. Document submitted by Dr Orla O'Donovan.

professionals may not be keeping up to date with fast moving developments in this field. Legislation now under consideration for doctors and pharmacists will give increased emphasis on continuing education in the future. The Sub-Committee urges that high priority be given to pharmacological training in this context.

5.15 The Sub-Committee is aware that much continuing education for doctors is funded by drug companies. The Sub-Committee would be concerned if its recommendations would lead to an increase in the prominence of the drug companies in doctors' education. At least where pharmacology is concerned, the Sub-Committee would recommend that funding be from the budget of the Community Health Services.

5.16 The House of Commons report specifically recommended that prescribers should receive training in interpretation of trial results and of material distributed by pharmaceutical companies. The Sub-Committee believes this recommendation should be considered in this country also.<sup>48</sup>

### ***Conflicts of Interest***

5.17 The Sub-Committee feels that the potential conflicts of interest created among doctors by promotion by pharmaceutical companies need to be addressed and recommends that the Medical Council review the situation. The House of Commons recommend compilation of a register of 'significant' benefits received from pharmaceutical companies by medical practitioners. This is worth consideration in Ireland.<sup>49</sup> 'Significant' should be taken to mean anything involving an overnight stay or long distance travel. Professionals writing articles or presenting lectures should be required to indicate any financial support received from commercial sources.

### ***Formularies***

5.18 Many new products are launched every year and practitioners are inundated with promotional materials and activities. Some of this material has genuine informational value. But not all. In addition, there is continuous updating of information on existing drugs. There is a need for unbiased, independent and practical information on drugs to be

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<sup>48</sup> HOC, page 107

<sup>49</sup> HOC page 108

available to hospitals and professionals in Ireland. In UK there are a number of sources at national and local levels. In Ireland the only resources are the Medicines Information Centre and the Pharmacoeconomics Centre both in St James Hospital. Both of these are operating at a small scale at the moment. Action needs to be taken to establish formularies at national or regional levels or at the level of groups of general practitioners.<sup>50</sup>

## **Health Services**

### ***Information Systems***

5.18 A number of points were made to the Sub-Committee about the availability or use of patient information for improving prescribing practices. The Sub-Committee suggest that the following should be investigated further:

- Creation of systems which enables prescribers to access information on patients from different sources such as hospitals, community medicine or pharmacists. This could be helpful in avoiding of prescribing errors or ADRs due to drug interactions. It would also be useful in facilitating follow up of reports of ADRs<sup>51</sup>
- Electronic links should be established between hospitals and practitioners and pharmacists ensuring that all sides have full information about common patients;
- Exploitation of the data base of the PCRS for macro trends in the consumption for different types of drugs;
- Creation and dissemination of computerised decision making systems capable of screening for contra indications and drug interactions when prescribers are considering drug therapies.<sup>52</sup>
- Dissemination of software, possibly linked to decision making support systems, which permit prescriptions to be printed in order to avoid mistakes caused by spelling or legibility problems.

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<sup>50</sup> Since drafting of this report commenced, an Irish Medicines Formulary produced by Meridian Ireland has commenced publication.

<sup>51</sup> Henman, Professor M. Corry, Dr Michael, written submissions

<sup>52</sup> One such system is reported under development in Cork University Hospital. Sunday Tribune, 7 January 2007, page 1

5.19 The Sub-Committee is aware that computerisation is not the panacea that some IT professionals suggest or that lay people might like to imagine. There has to be a disposition, and a capacity, on the part of all practitioners to use these systems. This should be ensured by the growing emphasis on continuing medical education. There are also formidable implementation problems and there may be ethical issues. Nor does computer supported decision making remove the need for competence on the part of the prescriber. However, when the cost of medicines and ADRs are considered, even significant investment in computerisation and associated training of professionals, would seem to be justified on cost grounds alone.

### ***Pharmacy***

5.20 The IPU and PSI made strong cases for enhancing the role of the pharmacist in community medicine.<sup>53</sup> It seems likely that the pharmacists' legislation, now under preparation, will entitle pharmacists to expand their services and responsibilities in provision of community medicine. The Sub-Committee endorses this trend and urges in particular that the practice of medication reviews, with the pharmacist as central, should be formalised.

### ***Psychological Support Services***

5.21 A point strongly made by several witnesses and by members of the Sub-Committee themselves is that psychiatric drugs may tend to be prescribed for want of an alternative. The patient presenting with symptoms expects some tangible form of treatment and the practitioner feels under pressure to respond so as, at the minimum, to send the patient away in a more confident frame of mind. It is in the absence of a full range of counselling and psychotherapy services that many medicines, intended for moderate to severe psychiatric disorders, are prescribed for minor symptoms leading in some cases to severe adverse reactions.

5.22 The Sub-Committee recommends that there should be an increase in the number of psychologists and counsellors available in the community health services. This would provide practitioners with an alternative to drug therapy in minor cases and would complement drug treatment in more serious cases.

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<sup>53</sup> Written submissions. Minutes 31 October 2006

## **The Public**

5.23 A constant theme of the submissions to the Sub-Committee, and a concern which the members share, is the excessive use of medication prescribed by health care professionals and excessive use of psychiatric drug therapies in particular. Some of the responsibility for this lies in the promotional activities of the drug companies and needs to be balanced by a programme of public education on drug use.

5.24 The role of the public, including patients, in taking responsibility for and participating actively in their own health care is widely recognised. It is the principle underlying the national Health Promotion Strategy 2000-2005 and the work of the Health Promotions Unit of the Department of Health.<sup>54</sup> Responsible attitudes to tobacco, alcohol, diet, exercise and sex are important targets of the HPU's messages. However, taking responsibility for proper use of medical drugs does not figure in the HPU's agenda. The Sub-Committee believes that establishing a balanced approach to drug therapy should be an important part of the health promotion strategy and the HPU should be mainly responsible for this change of emphasis.

5.25 Therefore, the HPU should by means of messages in the media, distribution of publicity material for health centres, pharmacies and its website;

- adopt a campaign aimed at informing the public of the appropriate use of drug therapies so as to reduce patient pressure on practitioners.
- Promote an understanding that when a course of drugs is prescribed, it is important that it should be completed

5.26 Other messages which need to be presented include

- That unused drugs should be properly discarded.<sup>55</sup> Local DUMP (Disposal of Unwanted Medicinal Products) campaigns provide the model for a national collaborative effort between the HPU and pharmacists.

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<sup>54</sup> website of the Health Promotions Unit

<sup>55</sup> Irish Pharmaceutical Union, reported that 'a total of 13 tonnes of medicines have been returned to community pharmacies in the South Western Area Health Board alone since 2003'. Written submission.



- The dangers of counterfeit drugs and self medication

5.27 The HPU should collaborate with the pharmacovigilance section of the IMB in promoting awareness of the possibility of ADRs, the need to report them and the means of doing so.

### **Patient Safety Agency**

5.28 A Patient Safety Agency would be the appropriate entity for the implementation of many of the recommendations above. The Sub-Committee therefore recommends that such an entity should be set up. It hopes that the Patient Safety Commission, set up since the Sub-Committee started its work, will come to the same conclusion.



# APPENDIX 1



## **Joint Committee on Health and Children.**

### **Order establishing a sub-Committee on the Adverse Side effects of Pharmaceuticals**

#### **1 Ordered on 12 October:-**

“That-

- a) a Sub-Committee (to be called the Sub-Committee on the Adverse Side Effects of Pharmaceuticals) be established to consider such matters as it may think fit in relation to the adverse side effects of pharmaceuticals.
- b) the Sub-Committee shall consist of 6 members of whom 3 shall be Members of Dáil Éireann and 3 shall be members of Seanad Éireann;
- c) the quorum of the sub-Committee shall be 3, of whom 1 at least shall be a Member of Dáil Éireann and 1 a Member of Seanad Éireann;
- d) in relation to the matter specifically referred to in paragraph a) above, the sub-Committee shall have those functions of the Joint Committee which are set out in paragraphs 2(a)(i) to 2(a)(iii) (Dáil) and in paragraphs 1(a)(i) to 1(a)(iii) (Seanad) of the Joint Committee’s Orders of Reference; and
- e) the Sub-Committee shall have the following powers of the Joint Committee, namely, those contained in Standing Order 81(1), (2) and (4) to (9) (Dáil) and in Standing Order 65(1), (2) and (4) to (9) (Seanad).”



# APPENDIX 2





## ORAL SUBMISSIONS

Date of Appearance Before Sub-Committee	Oganisation Represented	Witnesses
10 October 2006	Pharmaceutical Society of Ireland.	Ronan Quirke, President
		Dr Ambrose McLoughlin, Registrar
		Mr Matthew Lynch, Assistant Registrar
	Irish Pharmaceutical Healthcare Association	John McLoughlin, President Anne Nolan, Chief Executive Dr John Stinson, Medical Director Ms Leonie Clarke, Consultant
17 October 2006		Nuria O'Mahoney
		Dr Michael Corry
		Basil Miller
	Mind Freedom	John McCarthy
	Mind Freedom	Mary Maddock
		Gregory White
31 October 2006	Irish Medicine Board	Pat O'Mahoney, Chief Executive
		Dr. Joan Gilvarry, Director of Human Medicine,
		Dr Brendan Buckley, Chairman Advisory Committee for Human Health
	The Irish Pharmaceuticals Union	Liz Hoctor, Vice President
		Seamus Feely, Secretary General
		Darragh O'Loughlin, Treasurer
		Pamela Logan, Professional & Business Manager,

7 November		Dr. Orla O’Sullivan, Dept. of Applied Social Studies,UCC and Health Action International
		Martin Henman, Co. Ordinator of the Centre for the Practice of Pharmacy, Trinity College, Dublin 2

# APPENDIX 3



## **Members of the Joint Committee on Health and Children**

**Deputies:** Paudge Connolly TD (Ind)  
Beverly Flynn (Ind)  
Jimmy Devins (FF) (Vice-Chair)  
Dermot Fitzpatrick (FF)  
John Gormley (GP)  
Liz McManus (Lab)  
John Moloney (FF) (Chair)  
Dan Neville (FG)  
Charlie O'Connor (FF) (Government Convenor)  
Fiona O'Malley (PD)  
Liam Twomey (FG)

**Senators:** Fergal Browne (FG) (Opposition Convenor)  
Geraldine Feeney (FF)  
Camillus Glynn (FF)  
Mary Henry (Ind)

**Chairman:** Mr John Moloney (FF)

**Clerk:** Ms. Gina Long



**Members of the Sub-Committee on  
The Adverse Side Effects of Pharmaceuticals**

***Deputies:***                      ***Paudge Connolly (Ind)    Chairman***  
   ***Jimmy Devins (FF)***  
   **Liam Twomey (FG)**

***Senators:***                      ***Camillus Glynn (FF)***  
   ***Mary Henry (Ind)***  
   ***Geraldine Feeney (FF)***

**Clerk:**                              **Ms. Gina Long**