

Emerging Challenges and Opportunities in Drug Registration and Regulation in Developing Countries

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Abbreviations

ARV	Anti-retroviral drug
CHMP	Committee on Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
DRA	Drug Regulatory Authority
EC	European Commission
EU	European Union
EMA	European Medicines Evaluation Agency
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
GMP	Good Manufacturing Practice
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonization
IPCS	International Pharmaceutical Cooperation Scheme
MCA	Medicines Control Agency (United Kingdom)
NCE	New chemical entity
SPC	Summary of Product Characteristics
TB	Tuberculosis
TRIPs	Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization



Executive summary

The study was undertaken to meet the following aims:

- to describe current drug regulation and registration processes in selected countries, in order to understand how they affect the quality and availability of medicines in developing countries
- to develop policy recommendations as to how systems can more efficiently allow appropriate quality drugs to market
- to discuss emerging challenges and requirements posed by compulsory licensing, drugs for neglected diseases, anti-retroviral (ARV) and anti-tuberculosis (TB) drugs.

As a 'desk-based' study, the major source for the mapping of current drug regulation was the comprehensive multi-country study undertaken in 1998-1999 by the World Health Organization (WHO). The key issues identified in that study were that effective drug registration depends on appropriate legislation with adequate administrative structures, to ensure that the scientific assessment of new products (generic or innovator) can be undertaken in a rigorous and efficient fashion. Political support and financial and other resources are critical.

Since that study was carried out, the pressures on regulators in developing countries in particular have included having to respond to international political issues such as TRIPs and free trade agreements, as well as having to respond to the need for access to essential medicines for epidemics such as HIV. From the reviews and documents available, in general, many developing country regulatory systems have not been able to respond effectively. The problems include:

- lack of effective legislation to allow use of so-called 'TRIPs flexibilities' such as compulsory licensing;
- lack of adequate quality manufacturing capacity;
- lack of adequate regulatory science capacity to assess generic products that potentially meet the need for essential drugs;
- lack of adequate human resources; and
- inadequate funding for drug regulatory activities

To address these problems, it is clear that a coordinated approach at country and regional level is the only solution. Regional cooperation is needed to ensure that the scientific capacity is developed. In addition, development of regional manufacturing capacity appears to be the most likely way to simultaneously enable economic feasibility, meet adequate quality standards and comply with international trade

requirements. It is the legislative requirements and political requirements, however, that seem to be the most critical; countries need to have support to develop effective national legislation, as well as cooperating regionally to ensure that legislative variation between one country and another does not hamper access to essential medicines.

In terms of scientific capacity development, the WHO is continuing to play a major role, through its prequalification project and other activities. Given that the quality of pharmaceuticals generally is such a major issue, the WHO and other international authorities, such as developed country drug regulatory authorities, should be encouraged and supported to expand their current programmes that are designed to support developing countries. In addition, developing country capacity needs to be strengthened, not only to assess and register new products, but also to carry out the clinical trials of new drugs for neglected diseases that are necessary to establish safety and efficacy. Again, this is an activity that should be carried out at regional level. Mechanisms to retain trained personnel also need to be adequately addressed in any capacity development programme. Although outside the scope of this study, drug regulation should also be seen as encompassing the post-marketing activities and surveillance of products after marketing authorizations are issued, and mechanisms to develop effective post-marketing surveillance need to be incorporated into any drug regulatory authority (DRA).

Finally, there needs to be a reaffirmation that the purpose of drug registration is to protect the public health, not to facilitate profit of pharmaceutical manufacturers. Registration should not be seen as a detrimental hurdle to be avoided; it needs to be seen as a critical step in ensuring access to effective and safe medicines.

Recommendations for DFID

There are four key areas in which DFID's involvement and contribution would be likely to have an impact.

1. Support for the development of effective drug regulatory legislation that can also utilize the TRIPs flexibilities. This type of legislative capacity is limited in many countries and can be developed effectively at a regional level.
2. Support for structures and systems to assess available DRA capacity, as well as developing scientific capacity as required.
3. Support for the development of appropriate administrative structures and cultures to allow the effective operation of a DRA. There is no point in having scientific capacity if the administrative environment is ineffective or corrupt.
4. Development of political environments that acknowledge the need for the balance between the public health protection and industry facilitation roles of a DRA to be swung back towards the public health agenda. This is probably the key factor in increasing the capacity for DRAs to improve access to essential medicines.



1 Introduction

Drug regulation has developed over the past 50 years in response to crises in relation to pharmaceutical products. The initial regulatory standards were primarily related to ensuring the pharmaceutical quality of medicinal products and subsequent developments in the early 1960s led to the development of standards for testing efficacy and safety of new medicines as well.

Despite the existence of standards for drug regulation now for at least 50 years, there are still many problems with the safety and quality of medicines, in both developing and developed countries. As described by Rudolf and Bernstein¹ in 2002 and 2003, counterfeit epoetin and atorvastatin were identified in the United States and estimates of the total number of fake drugs available in the US were put at about 1% of the total pharmaceutical market. In many developing countries this proportion is much higher. In Cambodia, for example, studies have estimated that up to 65% of quinine may be fake² and in India, it is estimated that up to 50% of prescription medicines may be counterfeit.¹

The primary aim of drug regulation is protection of public health. Medicines are not normal 'commodities'; they meet fundamental health needs, and access to essential medicines, according to the World Health Organization, is a fundamental human right.³ Thus, medicines have additional social value. Appropriate use of medicines requires a 'learned intermediary' to prescribe them and a trained person to dispense them appropriately before the consumer takes them. The market for pharmaceuticals is therefore not a usual market in economic terms; there are major informational asymmetries and monopoly behaviours by suppliers that include patent rights and 'data exclusivity' clauses that further strengthen monopolies. In addition to the quality, safety and efficacy requirements, therefore, these are the arguments for regulating the pharmaceutical industry more generally, and controlling what it supplies.

Over the past 10 to 15 years, the balance between controlling pharmaceuticals in the interests of ensuring public health and encouraging the development of the pharmaceutical industry has shifted in favour of the innovative industry. Regulation has been seen as an 'impediment' to profits and industry development.⁴ The resulting pressure on regulators has been to approve new medicines quickly - sometimes on the basis of what can only be described as preliminary data (e.g. in the case of imatinib for acute leukaemia, there were no high quality trials completed at the time of initial approval (personal communication, Garattini)) - to remove regulatory 'bottlenecks', to carry out reviews and evaluations of data in the shortest possible time. There has also been pressure from patient groups to speed up access to new, 'breakthrough' medicines, for example in the field of HIV/AIDS.

In addition, the political climate is currently in favour of multinational companies continuing to monopolize supply through use of free trade agreements, patent legislation, political lobbying and legal pressures.⁵ It is only over the past two years that challenges to the multinational pharmaceutical industry have started to develop, and this has mainly been due to effective lobbying because of the HIV/AIDS epidemic in Africa and Asia. Strategies such as not-for-profit development of new medicines, use of compulsory licensing, and parallel importation are being considered as possible ways to improve access to essential medicines in developing countries, although they have not yet been widely used, if at all.

In this context effective drug regulation becomes increasingly important. One of the reasons for the multinational pharmaceutical industry's success is that it has become very good indeed at *developing* new medicines. The development of medicines should be distinguished from discovery of compounds; it has been suggested⁶ that many of the effective new compounds over the past 10 years have been discovered in the course of publicly funded research rather than by the industry. Trouiller et al⁷ have shown that in areas where the industry has not taken an interest, new drugs for important diseases such as malaria, or other neglected diseases have not been developed. Drug regulatory authorities and international organizations such as the WHO are having to fill this drug development gap. There are two roles: advocating or assisting in the development of needed products, and then once a dossier is prepared ensuring that new products meet adequate quality standards and that there is sufficient clinical evidence to demonstrate that the medicine is effective. One particular problem with this situation is that countries where the neglected diseases are prevalent may not have the regulatory capacity to assess safety and efficacy of new medicines. In this case, the new European Union pharmaceutical legislation may help, enabling the European Medicines Evaluation Agency (EMA) and Committee on Medicinal Products for Human Use (CHMP) to give scientific opinion to the WHO about products not necessarily meant for EU markets.

In the context of concerns about improving access to effective and safe medicines, it is clearly key to consider how drug regulation 'fits' with other policies in relation to health and medicines supply. The WHO position is that drug regulation is an essential arm of any country's national medicinal drugs policy⁸; the other parts of such a policy being a programme to ensure access, such as health insurance, a programme to ensure the best quality use of available medicines, and where appropriate, a policy to ensure a viable local pharmaceutical industry. The purpose of this study is to describe the components of effective drug regulation, define different systems to meet these requirements and to examine currently important political and scientific factors that will affect the capacity of drug regulatory authorities to ensure that only safe, effective and high quality medicines are made available to the public. The study is in part based on the WHO report, 'Effective drug regulation: A multi-country study'.⁹

The specific aims of the study are:

- to describe current drug regulation and registration processes in selected



countries, in order to understand how these processes affect the quality and availability of medicines in developing countries

- to develop policy recommendations as to how systems can more efficiently allow appropriate quality drugs to market
- to discuss emerging challenges and requirements posed by compulsory licensing, drugs for neglected diseases, ARV and anti-TB drugs.



2 Mapping the registration process and describing a normative framework

2.1 General description of registration processes

Drug regulation generally covers the following areas:

- Pre-marketing assessment and evaluation of the quality, safety and efficacy of a medicine, including compliance of manufacturing sites and processes with Good Manufacturing Practice (GMP) standards
- Assessment and inspection of all components of the pharmaceutical supply chain
- Maintenance of a register of available products, and post-marketing surveillance activities, including random sampling of registered medicines for quality control and pharmacovigilance
- Promotion, advertising and provision of medicines information.

Price control may or may not be part of drug regulatory activities (see below).

All of these activities require an appropriate legislative framework. The precise nature and scope of legislation, as well as models for drug regulatory frameworks, varies from setting to setting. Some countries model the regulatory framework on that of the US and apply controls to both food and drugs via the same legislation and administrative structures. Others control human and veterinary medicines as well as agricultural chemicals. Most arrangements are opportunistic, though sometimes availability of technical expertise determines the structure and administration.

In general terms, legislation that underpins drug regulation needs to:

- State the overall mission of drug regulation for the country (most commonly stated as ensuring the quality, safety and efficacy of medicines, but in some countries, objectives include ensuring 'rational pricing' or 'cost-effectiveness' and protection and promotion of public health)
- Define the method for keeping track of available products (e.g. a register of licensed medicines)
- Define which aspects of the pharmaceutical activities - such as manufacturing and the supply chain - are subject to controls, licensing and inspection
- Create an appropriate inspectorate and provide it with the necessary legal powers



of search and seizure

- Define acceptable quality standards for medicines
- Define the data requirements for different types of products to achieve registration
- Control the import and export of medicines
- Control advertising and promotion
- Define penalties and sanctions for breaches of the legislation and methods for implementation of the sanctions
- Delineate the administrative structures undertaking each of these activities.

Related activities that may be included are control of generic substitution, dispensing, prescribing, price controls, availability of poisons and drugs of dependence. In addition, in some countries, herbal, traditional and homeopathic medicines are also subject to controls under pharmaceutical legislation and drug regulation.

2.1.1 Key players in drug registration

Drug regulation is an interplay between law and sciences, as well as between regulators and the pharmaceutical manufacturers, with input and influences from patients and medical/health professions. In addition, a drug regulatory authority (DRA) interrelates with many other authorities active in the health sector, such as the Ministry of Health and other health protection agencies. In certain cases effective cooperation with other law enforcement agencies, such as customs and police, is necessary. Depending on the structure of the health sector, this may include interaction and/or control over medical practitioners, pharmacists and drug sellers, as well as interactions with agencies responsible for quarantine and control of imports and exports.

DRAs also need to interact with politicians; apart from anything else, politicians need to be persuaded of the importance of effective regulation in order to ensure that it is paid for at an appropriate level. Regulation is not cheap but its costs usually outweigh the potential waste on ineffective and dangerous drugs. In general terms, effective drug regulation requires effective legislation and administration, as well as a mechanism for control of the market and enforcement of penalties for breaches of legislation that applies equally to both the public and private sectors.

2.1.2 Process of drug registration: new chemical entities

In order to license/register a new chemical entity (NCE), a pharmaceutical company develops a dossier that describes the pharmaceutical quality, safety (in animals and humans) and efficacy of the product for a specified indication. An 'ideal' registration process would include:

- Evaluation and assessment of the pharmaceutical quality data, including:
 - assessing that the manufacturer(s) of all components, including that of the active pharmaceutical ingredient and the finished product, are certified as meeting the international standards for GMP that are appropriate for the component, with

- inspection of manufacturer(s)
- laboratory testing the product against the proposed specifications for content and impurities, stability data, and packaging
- evaluation of the labelling to ensure that it complies with specified standards
- Evaluation of animal (preclinical) toxicology studies in relation to acute and chronic toxicity, genetic toxicity, teratogenicity, carcinogenicity and others, including whether the studies have been carried out to international standards and whether the data and interpretation of the results are valid
- Evaluation of human clinical trials (either placebo or active comparator randomized controlled clinical trials) that have been carried out to define the dose, frequency and duration of treatment that is effective and safe, including assessing that the design and conduct of the trials meets international requirements, that the data are valid and have been interpreted correctly
- Evaluation of the product information document (called the Summary of Product Characteristics in the European Union), including the proposed indication and claims against the available data, and based on this information, the patient information leaflet/package insert.

The scientific skills that are required to carry out such a registration process are highly specialized, and generally require experts in at least the following disciplines: pharmaceutical chemistry, toxicology, statistics, and a clinical scientist in the relevant clinical field. Dossiers for NCEs typically consist of hundreds of volumes of data. The time taken to review and evaluate such dossiers is a common measure of the performance of a DRA, which unfortunately puts pressure on small authorities to keep up with international standards set by agencies such as the US Food and Drug Administration (FDA) and the EMEA.

It is difficult for small agencies (i.e. less than 20 technical staff) to undertake a full assessment. Most limit themselves to a 'partial review', concentrating on the assessment of quality and the product and patient information documents. Thus at present, the basis for a decision is generally trusting the assessment done by well-resourced and experienced agencies such as the EMEA and the FDA.

There has been debate as to whether small DRAs should review NCEs at all, or simply rely on approvals from recognised competent authorities (e.g. the US FDA or the UK Medicines Control Agency or MCA) as the basis for a local regulatory decision. The arguments for basing approval on those of major regulatory authorities are that:

- Most small authorities do not have the expertise to assess the NCE dossiers (particularly in relation to the animal studies)
- Even when the expertise is available, it is usually in short supply and would be more usefully employed in assessing generic products or problem products in the local market
- NCE dossiers are generally assessed by at least both the US and European authorities; their decisions should be an adequate basis for other countries, given



that the data in a dossier for an NCE are usually the same for every country, although the proposed indication may vary.

The arguments against such a system are:

- The only way to develop expertise is to review dossiers
- There may be country or population-specific issues that need to be taken into account, such as when the metabolic pathway for the product is influenced by race (although there are relatively few examples of this to date)
- The pattern of clinical practice varies from country to country and thus what may be a reasonable indication for a product based on the data in one country may not fit with the style of clinical practice in another
- A country needs to have access to the manufacturing information in a registration dossier for the purposes of being able to test the quality of the product available on the market
- The requirement for specific product labelling in different countries.

A key consideration should be in which areas of drug registration local authorities provide added value. One obvious area is that of validating the product and patient information as being appropriate to the local context, especially when there are language differences to consider.¹⁰ Independent drug information for doctors, pharmacists, health professionals and patients is potentially an area that could be developed in regulatory authorities in settings with limited resources.

Most drug regulatory authorities charge fees for the evaluation and registration of NCEs. Fee structures vary significantly from place to place. In some countries, fees are set arbitrarily and do not relate to the cost of providing the registration 'service'; in others, fees are scaled according to the amount of data submitted or the nature of the registration application. Whether the DRAs have direct access to the fees also varies; in some countries, the fees go directly to the DRA; in others, fees are collected by central government revenue and may or may not be returned to the agency actually undertaking the work.

The time taken to complete the assessment of an NCE is highly variable, not only from country to country, but also from product to product. If the NCE has been well developed, is chemically straightforward, and has trials that unequivocally establish efficacy and safety at the proposed dose for the proposed indication, it is possible to complete a registration review in three months if all the data is available and appropriate. This is the exception rather than the rule, as it is unusual for all of these conditions to be met. The longest reviews usually occur when the benefit of the product is uncertain – e.g. in the case of riluzole for motor neurone disease.¹¹

Many countries now have legislated maximum times allowed for review of dossiers. Current examples of target time-frames are 210 days (for major applications) in EU countries, which can be extended by 'stopping the clock' to obtain extra information from

the sponsor. The new members of the EU will be required to meet these time-frames, which may well cause problems for small regulatory authorities. Another approach is to set time-frames not by type of application (that is NCE or generic), but according to public health need: South Africa, for example, passed legislation last year setting a target of a maximum of nine months for registration of 'essential medicines' (as defined by the South Africa Essential Medicines List).

The registration of ARVs for HIV/AIDS is a useful example of the complexity of the registration processes, as well as illustrating some of the difficulties that can arise when small DRAs are required to assess NCE dossiers.

There are now five pharmacological classes of ARVs: nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors and most recently fusion inhibitors. With the exception of the second group and fusion inhibitors, there are at least three compounds generally available in each class, all of which were developed individually by different companies. In addition, there are fixed combination products available in recognition of the need for treatment to include combinations of at least three drugs of at least two classes.

Each of these products has been assessed for registration individually – there have been no 'pharmacological class' reviews. Thus for each, there has been a dossier for an NCE, and individual assessment and evaluation by DRAs. The efficacy studies for the newer ARV drugs are randomized controlled trials that measure the effects of the drugs on 'surrogate' outcomes (CD4 cell counts and viral load) rather than survival, in order to minimize the duration of time needed to show statistically that the products are effective. A typical new ARV efficacy study today compares the new product with a placebo, or with another medicine of the same pharmacological class. As there are effective treatments available, new products are nearly always studied in 'add-on' designs, in which patients continue to take a current regimen of treatment but are randomized to the new drug or placebo in addition to standard treatment. The aim of these studies is to show either that adding on the new treatment is superior to add-on placebo, or is no worse than adding on an alternative medicine from the same class.

Interpreting the results of these studies is not straightforward. Current methodological debates relate to the number of patients needed in a study to show that either the product of interest is truly better than or really equivalent to the comparator. Given the multiplicity of drug regimens that are in use, there are many different treatments available, and DRAs struggle to determine what the place of the new product really is, often based on only a limited number of trials.

In addition, the safety of the ARVs has been a major concern. The three and four-drug regimens that are needed to reduce the development of resistance are toxic and complicated to take. Normally, a dossier for a new product contains information about



safety from use in 1000-2000 patients. Although this sample of patients may be sufficiently large to detect common and severe side effects, it is not sufficient to detect less frequent events, or effects that may occur in specific sub-populations. In South Africa, for example, rightly or wrongly there have been many concerns about the side effects of ARVs. One of the challenges for the ARV roll-out there, has been establishing an acceptable post-marketing surveillance programme to identify side effects that are specific to the population. The South African DRA needed to be able to reassure both politicians and the population that the drugs were adequately effective and safe and that the authority was competent to monitor safety on an ongoing basis.¹²

Overall, the complexity of assessing NCEs is such that there is a strong argument for carrying out this assessment at regional level, rather than at country level. The current South African position, for example, may be to move towards registering NCEs on the basis of developed country authority reports, rather than repeating the evaluation locally. In practice, the sharing of evaluation work is what currently happens in the EU, where the assessment process is shared among countries, and decisions are made at EU and national level. The challenge is to establish an effective method for sharing workload amongst countries in appropriate regions. It needs to be noted that the EMEA, with its staff of approximately 300, can administer the process, but does not function as a single agency, such as the US FDA with its approximately 3000 staff.

2.1.3 Process of drug registration: generic products

The process of registration for generic products is similar to, but simpler than, the process of registration of NCEs. For a new generic product, a company develops a dossier that contains data primarily about the pharmaceutical chemistry of the product. The assumption is that an innovator product exists (usually in the same market) and that the innovator has been shown to be clinically effective and safe (although in poorly controlled markets this may not be the case). The data for the generic product is therefore designed to establish that it is clinically interchangeable with the innovator in terms of efficacy and safety. Such applications implicitly rely on the clinical data provided in the dossier for the innovator, even though there is rarely a direct comparison of the two dossiers during the evaluation. It is this implicit comparison of clinical information that may be constrained under TRIPs because of the requirements for data exclusivity, which may be interpreted as precluding reference to the clinical trials that originally established that a compound was effective and safe.

In some instances, a product can be registered on the basis of chemical and manufacturing data only (e.g. an injectable formulation for which there is a recognized pharmacopoeial standard, such as the British Pharmacopoeia, or the United States Pharmacopoeia), describing the method of synthesis and quality control for the product. For products that are for oral administration, the application will almost certainly need to include dissolution testing and limited clinical data in the form of bioequivalence and/or bioavailability studies which show that the generic product is bioequivalent to the

innovator – i.e. that it is clinically interchangeable. The most rigorous test of interchangeability is a clinical trial comparing the proposed generic with the innovator and measuring the effects of both on clinical outcomes; these trials are rarely carried out.

Examples of the use of each type of data are:

- Registering a new version of a generic product, where the major change is in the excipients – e.g. a folic acid supplement – dissolution testing would be required, but not other forms of data
- Registering a new generic for a brand product where there is an established relationship between the plasma concentration of the drug in a patient and the clinical effect – e.g. fluoxetine tablets – a bioequivalence study in healthy subjects would be necessary
- Registering a new generic version of a product where there is no established relationship between the plasma concentration and clinical effect – e.g. warfarin – a clinical trial comparing the available product with the new version would be required.

One of the current issues in relation to ARVs is what type of data would be required for a fixed-dose combination (FDC) of currently available innovator products. The EU has guidelines for the registration of FDCs in general¹³, and these indicate that usually limited clinical data (i.e. clinical trials) are required to establish that there is at least therapeutic equivalence of the FDC compared to the individual components. In the case where a combination is well established from clinical practice (e.g. use of a thiazide diuretic plus an angiotensin converting enzyme inhibitor for the treatment of hypertension, or some of the triple therapies for HIV), it might be possible to make an argument for registration on the basis of bioequivalence data alone, as was the case for Trizivir[®], an FDC containing lamivudine, stavudine and nevirapine¹⁴. Where the combinations are not clinically established, it is highly unlikely that bioequivalence data without some clinical trial data would be accepted.

For biological products, requirements are different. Biological products - for example, insulin - are not usually regarded as having 'generic' versions. It is generally accepted that bioequivalence data alone is insufficient for registration and that clinical trial data must be provided.

It is often the evaluation of bioequivalence data that presents the major challenge for small DRAs in a developing country. Firstly, not all local manufacturers in these settings are capable of carrying out bioequivalence studies. These studies require (1) access to the innovator product (note, not necessarily the innovators' dossier - a purchased batch of marketed product is adequate) (2) the capacity to carry out high standard controlled trials in humans that compare the proposed generic product with the innovator, including (3) measurement of plasma concentrations of substances using a reliable, sensitive and specific assay. For new innovator products, even if the generic company is able to



'reverse engineer' the product, there may not be a readily available standard assay method.

Secondly, if bioequivalence data is available, the comparator may not be a product available in the local market. If it is not a local product, there are two problems: lack of access to original data about the product, and difficulties arising if the proposed product turns out not to be clinically interchangeable with what is available. This is less of an issue with new products where there is only the innovator, but in the case of old medicines (e.g. diuretics) where there may be multiple small manufacturers even in a single country, clinicians need to know that different brands of the same drug have the same effect. If clinicians do not have this confidence, it undermines their acceptance of cost-control measures such as generic prescribing.

Thirdly, again assuming data is available, the evaluation of bioequivalence data requires statistical and pharmacokinetic skills that may not be readily available. For example, in Sri Lanka, product registration for generic products is carried out by five pharmacists, none of whom have had training in assessing bioequivalence studies (personal communication, Fernandopulle). However, with the increasing availability of user-friendly software and training, it should be possible for small countries to acquire the necessary skills.¹⁵

Given the sensitivity of the manufacturing data in a dossier for an innovator product, if a multinational company believes that there is a risk of such information 'leaking' to generic companies, including government-owned manufacturers in some countries, it may be an incentive for them not to submit the application for the originator product. In such circumstances, a regulatory authority would have to make a judgement about whether it would be prepared to evaluate a generic copy of the innovator on its merits using a limited dossier that provided bioequivalence data, for example, plus published clinical trials. Otherwise the access of generic medicines to the market would clearly be delayed or obstructed completely.

Registration of generic products, as for innovator products, also requires inspection and quality control of manufacturing plants. This is particularly where manufacturing standards are critical and internationally, the benchmark for manufacturing standards is defined in the International Standards for Good Manufacturing Practice (GMP). There have been anecdotal reports from many developing countries that when GMP standards were introduced, many local manufacturers could not meet the standards required under GMP for documentation, process and management controls over the production of a product. This situation has led to debate about what are the appropriate standards for good manufacturing in resource-poor settings¹⁶. In addition, local capacity to carry out GMP-standard inspections of facilities and processes is often limited, as the training and skills required to become a certified GMP inspector are significant. Training programmes have been developed, however, but need further support.¹⁵

GMP standards are often described as if they are some kind of absolute benchmark. Even amongst developed country regulatory authorities, however, such as the US FDA and the EMEA, there can be significant differences of opinion about what constitutes acceptable GMP. There are at least four international benchmark standards: the International Pharmaceutical Cooperation Scheme (IPCS), those of the US, those of the EU, and those of the WHO. The subtle differences between standards and what is acceptable even within a single standard often come down to a matter of scientific judgement, which leaves scope for the types of criticisms made by the multinational pharmaceutical industry regarding, for example, the WHO GMP standards. Although there have been many public criticisms of the WHO standards, there is no evidence that proper implementation of WHO standards can or has led to outcomes that are potentially harmful to patients. The key is in the implementation with good quality inspectors.

The time required to register a generic product varies. If it is a straightforward application with high quality data from a licensed and qualified manufacturer, then a dossier can be reviewed in 2-4 weeks. If, on the other hand, the substance is relatively poorly defined, the chemistry is complex and bioequivalence studies are needed as well as inspections of manufacturers, the process of evaluation and registration can and should take much longer. If a small DRA is registering large numbers of generic products rapidly, the quality of the evaluation and assessment of the products may well be compromised.

2.1.4 Process of registration: other aspects

A DRA may undertake a large number of other types of regulatory reviews. These include, but are not limited to, evaluating:

- changes in formulation of registered products (e.g. tablets to capsules)
- changes in excipients
- changes in dose sizes (e.g. 2mg to 4mg tablets)
- changes in labelling
- changes in product information documents
- changes in clinical aspects such as modifications to indications, safety information, interactions etc.
- licensing of manufacturers, distributors, wholesale premises, pharmacies etc
- controlling imports and exports of products
- controlling clinical trials.

Thus the workload for a DRA will depend on the scope and nature of the activities it undertakes. In the developing country context, it is probably most critical that a DRA spends adequate time and resources on controlling the products on the local market for pharmaceutical quality as well as controlling importation of products. Further recommendations in relation to this can be found below.



2.1.5 Post-marketing surveillance

Although the focus of this report is product registration, most DRAs include post-marketing surveillance in their activities. The type of activities in this group include testing 'faulty' products by quality control laboratories, testing marketed products at random and investigating reports of adverse reactions. The latter includes classical adverse reactions, as well as examining reports of inefficacy. Reports of adverse reactions can be elicited spontaneously from health professionals and pharmaceutical manufacturers, or compulsory reporting can be required, although there is no evidence to suggest that compulsory reporting is more effective than voluntary reporting.

The importance of adverse reaction reporting is that it not only can provide information about new side effects of products, it can be an immensely valuable 'signal' of quality problems. Two examples are, the problem with complementary/alternative medications manufactured by Pan Pharmaceuticals reported in Australia in 2003¹⁷, and the problem with paracetamol contamination with ethylene glycol in Bangladesh.¹⁸ In the Australian case, reports of hallucination in relation to a herbal sleeping tablet led to investigation of the company's entire range of products with the result that the company was found to have fabricated quality assurance data in contravention of GMP standards. The company was de-registered. In Bangladesh, following an epidemic of acute renal failure in children, with many deaths, once the cause was identified, it was necessary for the government to ban paracetamol syrup for a period. The total ban on the product was the only way to ensure that the toxic products were removed from the market place given the limited capacity of the drug regulatory agency to enforce quality and inspection standards.

These two examples highlight the need for post-marketing surveillance to be effectively integrated with DRA functions and also the need for countries to be able to control all aspects of their markets.

2.1.6 Control of drug promotion

In addition to the other activities, some DRAs control advertising and promotion in relation to products. There have been a number of studies showing that the approach of allowing companies to self-regulate promotion activities is ineffective, in that it results in misleading claims about, and inappropriate use of medicines.¹⁹ As a result, there are now moves away from the self-regulatory model of control of advertising material to systems of pre-approval. On the basis of current evidence, it is appropriate that regulation of advertising and promotion should increase. The trade-off is that pre-approval of advertisements also requires resources and capacity. If not done competently it is potentially as dangerous as uncontrolled advertising and it can also consume resources needed for assessment of new products. Direct-to-consumer advertising is a related topic also beyond the scope of this report, but there are a number of recent reviews available which suggest that again, it results in misuse and overuse of medicines.²⁰

2.1.7 Structural components of a drug regulatory authority- interplay with other agencies

In order to carry out these various functions, a DRA needs to contain a number of components and skills. Drug regulation is not possible without an appropriate legal framework, and therefore access to effective legal advice, particularly with regard to drafting legislation, is critical, although many DRAs do not necessarily have this expertise 'in-house'.

The second most important skill set is effective administration and management, in a civil service culture that is not corrupt. In environments where civil servants' salaries are substantially lower than their private sector peers or lower than a living wage, it is very difficult to avoid the development of a culture of bribes and fees in exchange for registration. One example of the problem of endemic corruption within an agency from the developed world was the Italian DRA in the early 1990s.²¹

Scientific skills are essential. Many developing country DRAs depend on pharmacists to carry out most of the regulatory work. Medically qualified personnel are generally expensive and hard to 'buy'. Use of expert advisory committees comprised of medical experts who provide input into the drug regulatory system on a part-time basis is one solution to the problem, but the question of potential conflicts of interest must then be considered. Toxicology and biostatistics are also essential in the context of evaluating NCEs as well as generics.

2.1.8 Cost of drug regulation

Effective drug registration and regulation generally is not cheap. In the 10-Country Study undertaken by the WHO in 1998-99⁹, country rapporteurs provided data used to estimate the cost of drug regulation and these results are shown in Table 2, Annex A. A study by Kaplan and Laing²² provides a more comprehensive overview and suggests that fees charged in developing countries are substantially lower than in developed countries. A key policy question, therefore, is who should pay for drug regulation and what should be the fee. Most countries have adopted some level of fee for service. Two 'extreme' examples of this are the US, where application fees paid by sponsors ("user fees") are balanced with assurances that decision-making will occur in time-frames that are made feasible with the increased resources, and Australia, where the entire cost of drug regulation is covered by the fees levied on applications.

The problem with a 'fee for service' approach is that it leads to the potential for regulatory capture, where the regulators may be more concerned to make decisions that will favour their 'clients' rather than decisions that are necessarily in the best interest of the public. Abraham²³ has described this problem at length and argues that the development of 'fee for services' contributes to the present drug regulatory systems being insufficiently robust. He suggests a number of strategies to overcome the problem, including public



accountability and transparency and management of the conflicts of interests of experts, such that expert advisors to regulatory agencies should be required to suspend all conflicts of interests during the time in office. In addition, Abraham proposes that DRAs should undertake some key tests of new products independently, and that the state should take responsibility for funding DRAs. Garattini²⁴ also has argued that in the EU, governments should show greater commitment to the public health priorities in regulation by funding the registration authorities to at least 50%, and this argument seems reasonable.

2.2 Mapping exercise

In 1998-99, the WHO carried out a detailed study of the drug regulatory authorities in 10 countries to establish what contributed to effective drug regulation.⁹ That study included detailed data collected from each authority, which took several months to collect. For this current report, as only a month was allocated to the study, it was not possible to undertake further primary data collection. The tables below are taken from the WHO study, and whilst the precise levels of fees etc. will undoubtedly have changed, they remain a valid illustration of the key points needed for this report. In preparing this report, we sampled information informally from Estonia, South Africa and Australia, as well as drawing on reviews of drug regulatory and reimbursement structures in Hong Kong, the Baltic States, Vietnam, and Bulgaria.

The 10 countries in the WHO study were a mix of developing and developed countries and are listed in the table below. The functions that each authority carried out are shown here and are generally representative of the range of functions carried out by most DRAs.



Regulatory functions performed by the 10 drug regulatory authorities.

(From Table 4.1, 10- Country Study)

Functions	Australia	Cuba	Cyprus	Estonia	Malaysia	Netherlands	Tunisia	Uganda	Venezuela	Zimbabwe
Licensing of manufacturing	●	●	●	●	●	●	●	●	●	●
Licensing of importation	■	■	■	●	●	●	●	●	●	■
Licensing of wholesale	■	■	■	●	●	●	●	●	●	●
Licensing of retail	■	■	●	●	●	■	●	●	●	●
Product assessment & registration	●	●	●	●	●	●	●	●	●	●
GMP inspection	●	●	●	●	●	●	●	●	●	●
Inspection of distribution channels	●	■	●	●	●	●	●	●	●	●
Import control	●*	●**	●	●	●	●**	●	●	●**	●**
Quality control of products	●	●	●	●	●	●	●	●	●	●
Control of drug promotion & advertising	●	■	●	●	●	●	●	●	●	●
Price control	■	■	●	■	■	■	●	■	■	■
Generic substitution	●	■	■	■	■	●	■	■	●	■
Control of prescribing	●	●	■	●	●	■	■	■	●	●

● = yes ■ = no

* Special permit for biological products, steroids and others.

** Permit required for investigational products and products for personal use.

2.2.1 Data requirements

One of the concerns of the pharmaceutical industry is that different countries require different data to support applications for registration of products. The argument is that different data requirements require additional work and time and money on the part of the company, as well as being unnecessary.

In the 10-Country Study, the requirements for registration of NCEs were examined. A summary of the information required for this purpose is provided in Table 1 in Annex A. In general terms, data requirements for NCEs are fairly uniform. The 10-Country Study did not address the question of dossier format, however, and it did not consider whether in some countries additional specific clinical trials might be required.

Standards for dossier format have become much less problematic since the development of the International Conference on Harmonization (ICH) Common



Technical Document (CTD) standard for trial reports and other data. This format tends to be accepted now in most countries other than the USA. Other aspects of the data that must be country specific relate to product labelling and information.

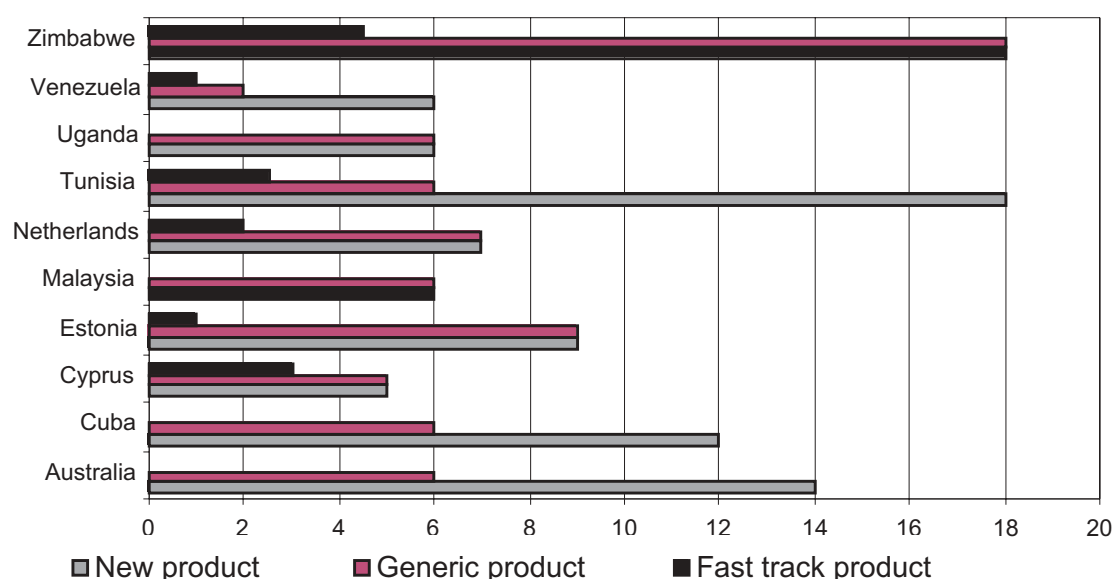
Requirements for registration of generic products were not examined in the 10-Country Study. In general terms, the data that might not be required would be clinical trials; the remainder of the information needed would be the same as for an NCE. Generic products, as noted above, can be registered on the basis of chemical comparisons alone (e.g. dissolution data), bioequivalence data or clinical trials. The requirements for generic product registration do vary from country to country, and within a country there are variations in the data required depending on the type of generic.

2.2.2 Time for product registration and fees

Average time to register products, the fees charged, and the time in relation to professional staff numbers were summarized in the 10-Country Study and the key data is reproduced below. This data does not present maximum and minimum times, however, and it tends to be these latter figures that are publicized, especially when there are complaints about delays. As noted above, legislated time-frames have been introduced in many places that mirror those of the EU.

Average time taken to register different categories of drug (months).

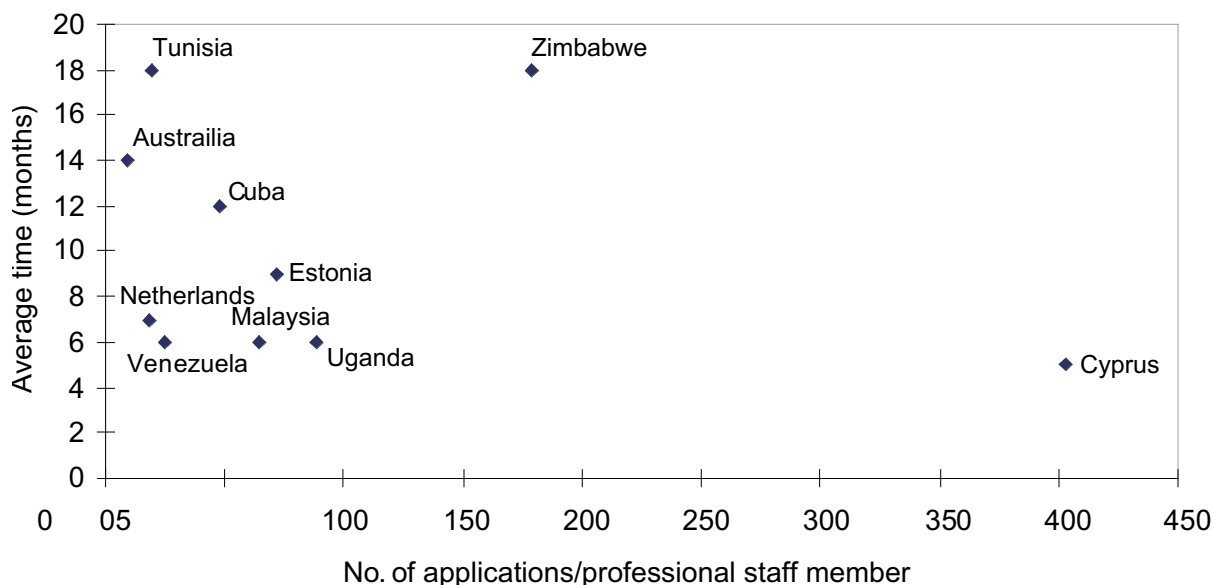
(From Figure 8.4, 10- Country Study).



Clearly, time taken relates not only to the type of application, but the number of staff available. The figure below summarises time versus available staff numbers.

Average time vs. number of applications per professional

(from Figure 8.6, 10-Country Study)



Fees and charges charged at the time of the study for the different types of regulatory activities are listed in Table 2, Annex A. Updated information has been added for Australia (see <http://www.tga.gov.au/docs/html/fees04.htm> for a complete list), Estonia, Uganda and South Africa where available. In the case of Estonia, for example, the fees and charges currently cover approximately 60% of the total cost of running the DRA.

2.2.3 Which requirements are harmonized?

In general terms, most DRAs use the same type of information to support registration applications. The differences lie in the detailed data requirements. The focus of international harmonization efforts to date has been on harmonizing these detailed data requirements for NCEs for example, in the type of animal toxicological studies required in relation to carcinogenicity. This has led to the various ICH-sponsored guidelines, described in section 3.1 below. The issues to do with harmonization at the moment are:

- whether requirements for generic product registration can, or should, be harmonized
- whether there should be country-specific requirements for particular types of pharmacokinetic or clinical safety studies
- whether it is possible to have the same wording for the indication for products
- whether the information in the product information documents (SPC) can be standardized.



2.2.4 Cost implications for a firm adapting to different requirements

The argument has been made that it is expensive and time-consuming for pharmaceutical companies to adapt to different country requirements. In the time available for this consultancy, we were not able to assemble data from a company to illustrate this point. However, there are two points to consider; for generic products, many are made by local manufacturers for local markets, and these companies may not submit applications beyond their own environment, in which problems with different data requirements do not apply. For NCEs, many of the problems in relation to different data requirements have been ameliorated by the ICH process and the tendency for most countries to use the CTD dossier format.

2.3 Proposed normative framework

The terms of reference for this study specifically request a proposed normative framework for drug registration. We have chosen to interpret this as a request to develop a proposed framework for developing competent DRAs, as drug registration clearly depends on the competency of the authority.

The key determinant of effective drug regulation is political support and political will. Political support underpins the development of effective and competent legislation as well as the development of effective methods to control the pharmaceutical market. Such controls need to be applied across all sectors of the market equally; it is not reasonable or sensible to develop a system, for example, under which government-owned factories are exempt from the requirements for private sector producers. At the present time, it is clear that one of the challenges is to develop legislation not only for effective drug regulation, but legislation more generally that includes appropriate sections regarding patents, compulsory licensing and parallel importation, in order to ensure that what little leeway exists under TRIPs for developing countries can be exercised (see below for further discussion of TRIPs and related topics). Gaining political support also needs to include determining who will pay the costs of drug regulation and guaranteeing the financial and physical resources necessary.

Once the legal framework is established, the next key requirement is capacity. As noted above, capacity development should not only include scientific skills, but it needs to include administration and management skills as well as legal capacity alluded to above. In addition, plans for effective capacity development need to take into account a strategy for retaining trained staff, whether through salary and benefits structures, contractual arrangements or service bonding systems. In countries with markedly limited capacity, judgements also need to be made about the potential for linkages with other countries in the region for skill development.

In terms of setting up drug registration, the critical first step is a system that ensures the quality of medicinal products. This therefore includes pre-market assessment evaluation

and licensing of manufacturers and processes, as well as a system of post-marketing quality control and surveillance. As drugs are registered nationally, each country needs to control its own market, including imports, and have its own capacity in relation to quality, although it is probably possible to share expertise at a regional level to a certain extent. Regional quality control laboratories would appear to be one appropriate approach. Post-market testing by itself is NOT sufficient; quality has to be manufactured into a product first.

The next step in the development of drug registration is developing the capacity to assess and register generic products. Unless products are being supplied regionally, this task should also be carried out at a national level, particularly if there are multiple local generic versions of the same chemical entity available. The expertise required for generic registration needs to include the capacity to assess bioequivalence data and possibly clinical trials.

Capacity to evaluate NCEs should only be developed once the other functions listed above are in place. The model used in most agencies that carry out this task is to have some 'in-house' expertise, but to rely heavily on external experts for advice and evaluation expertise. This can be arranged in the form of external advisory committees comprising academics and clinicians. Such arrangements need to be transparent and take into account potential conflicts of interest; often the clinicians who have the most expertise about a new product have received funding from the manufacturers for the development of it. Formal procedures for handling conflicts of interest should be developed to manage this situation; several models are available.

NCE evaluation should not necessarily be done at national level although there also needs to be a system for countries with limited capacity to evaluate medicines that meet their specific needs for treating locally prevalent diseases. Regional models based on the EMEA evaluation of an NCE for all of the EU countries need to be explored for other regions. Additional clinical studies in specific settings may be required for NCEs, but these could be carried out on a regional rather than national basis if required.

In addition to the scientific capacity, a DRA must have an effective system of tracking application assessment processes and decision-making. These systems require appropriate use of information technology. It is not simply a question of registering a product faster than any other DRA; however, measures of performance such as identification of poor quality products are much more important. Whilst there may be exceptions, for example in relation to the treatment of diseases for which there is no current effective therapy, rapid time to registration is nearly always in the interests of the manufacturer, rather than the public.

The DRA will need to ensure that it has effective interagency relationships with appropriate authorities in its own country, such as health professionals, enforcement agencies, customs and importation controls, as well as effective networks with other



DRA's. This is particularly important to ensure that the DRA has appropriate insight into its own capacity and performance.

Finally, the DRA and registration decisions must be accountable and transparent and, as noted above, there must be processes in place to avoid both actual and perceived conflicts of interest. This is a key 'defence mechanism' in response to the wide range of interest groups that try to influence DRA decisions, ranging from politicians and lobbyists to patients and clinicians. Defensible decision-making is an agency's best protection in the 'goldfish bowl' environment.



3 The role of registration harmonization

3.1 Currently existing harmonization structures

Given the major resources needed to assemble registration dossiers in multiple countries, there has always been an incentive to promote as much similarity as possible in their form and content. There are some well-established examples of harmonization of registration, and the European Union, with its reciprocal and mutual recognition procedures to enable one dossier to serve for all, is the longest established model for these. The procedures and their development are described in detail by Irs et al.²⁵ It needs to be noted that harmonization within the EU took a number of years to develop to its current status: the first European Pharmaceutical Directive (65/65/EEC) was issued in 1965, and it was not until the 1990s that effective methods for sharing regulatory processes and structures were really in place.

The International Conference on Harmonization (ICH), an effort begun in 1990 with industry and regulatory participants from the US, Europe, and Japan, has compiled documents to harmonize drug registration submissions in the 17 countries in these areas. ICH has produced many guidelines pertaining to the technical requirements for drug efficacy and safety requirements enabling the mutual acceptance of data across all ICH countries. The ICH focus was originally on NCEs and biotechnology products but the process has, over time, begun to influence requirements in non-ICH countries and for existing products including generics. These requirements, if implemented, could lead to increased demands on local manufacturers in non-ICH countries.¹⁶

It has been argued that the WHO is the more appropriate intergovernmental organization to set international standards related to pharmaceuticals, rather than a process like ICH which is limited to one stratum of countries. Non-ICH countries, which constitute 85% of the world's population, need to consider whether the cost involved in implementing ICH standards really adds to the protection of the public health in relation to pharmaceuticals, and may need to adapt the processes accordingly.

A number of other regional organizations with drug regulatory aspirations exist worldwide. In Europe, the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC) members are now officially collaborating with the EU unified procedure. In Africa, there is both the Common Market for Eastern and Southern Africa (COMESA) and the Southern African Development Community (SADC), and the latter is making progress in moving towards harmonized



guidelines for drug registration in the region. COMESA was begun in 1995 with a commitment, like that for SADC, to pursue harmonization of registration procedures with a mutual recognition process akin to that in Europe.²⁶ In Asia and the South Pacific, the Association of South-East Asian Nations (ASEAN) countries have undertaken work to attain a common approach to medicines regulations²⁶, an effort aiming at establishing a common technical document to harmonize pharmaceutical product dossiers, much like has been done with ICH.²⁷ In Latin America and the Caribbean there are similar activities in the context of the Southern Cone Common Market (MERCOSUR) and the Caribbean Community (CARICOM). Additionally, the Pan American Health Organization is aiming to establish a regional drug regulatory harmonization network and now has a working group on drug registration.²⁸

Regional cooperation efforts to deal with TRIPs flexibilities are also in progress. As reviewed by Musungu,²⁶ these efforts tend to fall into two models depending on whether the TRIPs issues are addressed in a stand-alone structure or considered more broadly in an integrated fashion with the region's other economic and development organizations. Two examples of the former are African Organization for Intellectual Property and the African Regional Intellectual Property Organization. The best example of the more integrated model is the Andean Community. Although one can imagine harmonization of drug registration would help regional cooperation on many related fronts including TRIPs flexibilities for better drug access, the published literature to date does not suggest any region has yet progressed to this stage.

3.2 How effective is harmonization?

In considering whether harmonization strategies are an effective way of improving the overall efficiency of drug registration, there are a number of issues to take into account. Firstly, the successful harmonization arrangements to date have all taken a significant amount of time and money to develop. The EU harmonization of registration requirements took years to develop, as did the ICH guidelines. Both processes required numerous meetings, technical discussions and reviews that were paid for by industry and the national governments involved. In addition, there were complex negotiations required to resolve differences of scientific opinion as well as national sovereignty issues, and these are still going on. A further example is the development of a joint medicines regulatory authority between Australia and New Zealand. The first steps in this process were taken in the early 1990s, and although it is hard to imagine two countries with more similar philosophy and backgrounds, it is only in the past two to three years that joint decision-making has really commenced. It is hardly surprising that in the developing country context, harmonization is just beginning.

Have these efforts been successful in improving the efficiency of registration? Certainly there is now a single dossier format that is generally used in EU countries, and this has also been adopted by countries such as Canada and Australia. In addition, a number of the ICH guidelines have become accepted standards. Manufacturers therefore no

longer have to prepare completely different versions of the same dossier for each authority, although there are still country-specific requirements such as the product information documents, as noted above. In addition, registration time has generally decreased,⁴ which is a prominent measure of efficiency for the industry.

It is important to note, however, that to date, most of the harmonization efforts have been mainly related to NCEs rather than generic products (although some ICH standards apply to generics as well as NCEs). Requirements for generics could be harmonized to some extent, but because local manufacturers may only supply to one or two countries, it is likely that these applications will still have to be dealt with at national level, as noted above, even if requirements can be fully harmonized.

In the EU context, a factor that has become obvious with the accession of the 10 new member states is the relationship between partners in a harmonization process. Small agencies in the accession states may feel threatened by the joint requirements, both in terms of the capacity to meet them, but also in relation to possible pressure from the 'big' countries/agencies on local decisions. A similar pattern may emerge in the sub-Saharan Africa grouping, as South Africa is seen as the 'leading agency' in that region, and therefore has the potential to have undue influence on regional decision-making. On the one hand, this may be a strength, in terms of developing capacity for drug regulation, but on the other hand, there may be a potential conflict of interest, say, if that country also hosts the largest regional manufacturer. In the latter situation, for example, one could envisage economic or political pressures on a DRA to 'prefer' or support a local product.

The 'successful' experiences of harmonization to date have hinged upon firstly developing a common scientific framework for assessing medicines, and then ensuring that legislation is enacted to support the assessments. The importance of making sure that there are sufficient resources in terms of time and money for meetings and negotiations to achieve common outcomes cannot be overstated – again, ICH was dependent on industry funding and support to drive its continuity. The importance of harmonization of legislation needs to be emphasised. If national legislation sets out registration requirements that are specific to a particular country, then clearly legislative change has to be factored into any harmonization plan.

3.3 The impact of differing registration requirements

Different registration requirements are a burden for the manufacturers, but again, they may be in the public interest. However, it is possible for manufacturers to exploit the differences to a certain extent – for example, by registering new products in countries that have minimal requirements and using these registrations as evidence to support registration in other settings. The fact that the first registering authority may not be competent may or may not be appreciated by authorities to whom the application is submitted subsequently, although many DRAs do have a list of authorities that they will



recognise. The potential advantage to the manufacturer in this situation is not only leveraging registration elsewhere; it is also an opportunity to establish a market for the product in what might be argued is a less controlled environment.

A legitimate reason for registering a new product in a small country early in the product's life may be to do with requirements for manufacturers to register products before they can be exported. In Australia, for example, any product must be registered by the DRA; a category of registration of products purely for export has therefore been developed. There is a concern currently being expressed by DRAs in developing countries that many developed countries' DRAs are not paying the same attention to product specifications if the manufacturer indicates that such a product is for export to another country, especially a developing country. This has led many of them to insist on GMP inspections of all manufacturing sites of registration applicants, whether based in a developing or developed country.



4 Emerging challenges and opportunities for drug registration

4.1 TRIPs/Doha declaration

There have been several reviews of the TRIPs agreements and related treaties in relation to access to essential medicines^{29,30,31} and this topic is still the subject of intense international debate. Another DFID paper provides a full review of the potential for use of TRIPs flexibilities in non-producing countries.³² The purpose of this current review is therefore to identify the potential impact of these agreements on drug registration requirements and to identify emerging issues for DRAs. The key assumptions are:

- Accepting that the Doha declaration implies that the TRIPs agreement does not prevent members from taking measures to protect public health
- There are a number of 'flexibilities' defined in the provisions of the agreement which provide for protecting public health, including:
 - Compulsory licensing
 - Parallel importation
 - Provisions relating to patentable subject matter
 - Provisions relating to exception to patent rights
 - Provisions relating to data protection
 - Provisions relating to abuse of rights, competition, control of anti-competitive practices.

In order to utilize the TRIPs flexibilities, a country must first have several aspects of a functional pharmaceutical sector in place: drug regulatory legislation to register a product and a regulatory authority able to administer the legislation, a quality control testing capacity, and effective control of imports and exports. Legislation in relation to patents and compulsory licences is also required, but this is not usually part of a drug regulatory law, (see for example, the WHO Model Drug Legislation³³) and DRAs generally do not deal with patents.

In addition to the requirement for appropriate drug regulatory legislation and a competent DRA, when considering TRIPs issues there is a need for a competent patents authority that is aware of the drug regulatory issues. As noted by Musungu²⁶, the capacity to develop patent legislation that is appropriately TRIPs compliant and yet at the same time takes advantages of the flexibilities has been the first stumbling block for many countries. This is aggravated by the fact that, to date, countries that do develop



such legislation have been the target of legal or other campaigns by the US and the pharmaceutical industry.³⁴

For registration of generic products, most DRAs have used the 'Bolar exception' to Article 30 of TRIPs. This permits a company to prepare a generic version of a product and submit its registration dossier for evaluation prior to the expiration of a patent. The newer bilateral free trade agreements, such as that between Australia and the USA, are now requiring amendments to drug regulatory legislation so that consideration of the patent status of a product is necessary prior to assessment of a dossier. Clearly, such amendments are likely to reduce availability of generic medicines.

4.2 Compulsory licensing

Another approach that has been advocated for improving access to essential medicines is the issuance of compulsory licensing, permitted by Article 31 of TRIPs. No permission by the patent holder is involved; thus, the term "compulsory" is used for this action. It is akin to the state's right of taking by eminent domain, and in fact such provisions were commonly used in the pre-1994 era.³⁰ The circumstances under which this may occur are left surprisingly vague in the TRIPs document, yet until early 2004 there had been no instance of such an issuance.³⁰ This would appear to be a serious indictment of TRIPs flexibilities. Some countries have successfully used the threat of issuance in trade/patent negotiations. In South Africa, for example, threat of issuance of a compulsory licence for two ARVs may have contributed to the patent holders for the originator product permitting two local companies to apply for voluntary licences (Matsoso, personal communication).

Numerous barriers to compulsory licensing are evident from the legal and administrative TRIPs procedural requirements and have been described in Baker³². In addition to meeting legal requirements, in order for a compulsory licence (if issued) to be useful, the country must have the local manufacturing capacity to produce the product. Thorpe³¹ reviewed the manufacturing capacity of countries in 2002. Out of 193 countries, 11 had a sophisticated pharmaceutical industry and research base, 17 had 'innovative capabilities' (e.g. India, China, Spain), 14 were capable of reproducing the active ingredients of products as well as the finished product (e.g. Brazil, Cuba, Romania), 91 were only capable of producing a finished product from imported ingredients and 60 had no pharmaceutical industry at all.

If a compulsory licence were to be issued successfully and a product manufactured, then presumably the product would have to undergo a standard review for purposes of registration. One approach could be that the requirements for the data to support such an application would be similar to those for a generic product i.e. data in relation to pharmaceutical chemistry and labelling information as well as bioavailability studies. The question of registration requirements for drugs with a compulsory licence has been considered in South Africa, as it is one of the few countries that have come close to

issuing a compulsory licence. The DRA position there is that the standard registration requirements would apply, and specifically that the product would need data to establish that it is of adequate quality, safety and efficacy – that is, potentially the requirements for registration of an NCE. The point was made in discussions with the head of the DRA, that any compulsory licence would be issued by the Patent Office, not the Regulatory Authority, and thus an application for registration would be considered independent of whether or not there was a compulsory licence involved. To date, however, these arguments and proposals are still theoretical.

The predicament for countries with no manufacturing capacity is worse. Their options for sourcing affordable, quality essential drugs will become even fewer because by 2005 all but the least developed countries are obligated to be TRIPs compliant. This will mean the major supplies of low- cost generics (e.g. from India) will be constrained. The consolidation of the market power of the proprietary drug industry will increase. Furthermore, compulsory licensing options under TRIPs are generally restricted to drugs for domestic use. The remaining option under the 30 August 2003 Decision is the so-called reciprocal simultaneous issuance of compulsory licensing usually in two adjacent countries, one to manufacture and the other to import. Again, there are no concrete examples of this being used successfully so far but it is hard to see that this will be a realistic possibility for countries in urgent need of a medicine to pursue.

4.3 Parallel importation

Parallel importation has been suggested as another strategy to improve access to essential medicines. Under this system, country A imports a (legally marketed) version of the product of interest from a supplier in country B, in parallel with, or instead of, the same product from the primary source, because the medicine is available there at a lower price than elsewhere. This is generally consistent with international law because the first sale (by the patent holder or his licensee to the supplier in country B) "exhausts" his exclusive rights, freeing others to commercially exploit the product. Article 6 of TRIPs and the Doha agreement, Paragraph 5(d), explicitly acknowledge the rights of countries to pursue this option. If there were an impermeable barrier between countries involved in parallel importation and those simply involved in the first importation of patented products, this arrangement could work more broadly as a differential pricing scheme. Oxfam has suggested such a two-tier system, one parallel import rule for developing countries and another for developed countries, but this suggestion has been met with the obvious practical and political resistance.

There would potentially be two approaches in relation to registration of products obtained for supply via parallel importation. If the product in question was identical to that already registered, and simply obtained from a cheaper source, then presumably there would be no additional regulatory activity – that is, Brand A from supplier A was cheaper than Brand A from supplier B. If the product in question, however, was a different brand or generic version of that registered, then presumably the requirements



for registration of a generic product would apply.

4.4 Data exclusivity and patents

Another potential barrier to improving access to essential medicines that has emerged is the issue of data exclusivity. It is addressed in TRIPs (Article 39.3) and results in a moratorium on the use of innovator dossier data on an NCE for generic applications for a period of five years in the US and from eight to eleven years in Europe³⁵ This stricture applies independent of the status of the patent and these applications cannot rely on innovator data on bioavailability or efficacy and safety (because it cannot legally be accessed). The implications of this restriction are potentially that a generic manufacturer would have to carry out clinical trials demonstrating efficacy and safety of the generic version of a product as well as bioavailability studies using the originator as a comparator. Various commentators over the last year have expressed concern that the US and Europe will increasingly use this strategy, particularly through bilateral trade agreements, to bypass the implementation of TRIPs flexibilities entirely.^{5,32}

However, this is an area where it is worth further considering alternative approaches to trial design and drug registration. For example, many of the clinical trials that are done to show efficacy and safety of a product for registration are now published fairly early after initial registration is granted and there is increasing pressure on companies to make all such trials available. If the information is in the public domain, one argument would be that a generic manufacturer would be able to use published efficacy and safety studies plus a bioequivalence study (using purchased innovator product) and manufacturing data to support registration. This approach is already accepted by the EU for registration of established products where no originator exists. There is a risk, however, that companies would stop publishing trials.

4.5 Regional markets and production

One strategy that is being proposed to improve access to high quality products is the development of regional manufacturing capacity for regional supply. Given the technological requirements for high quality product manufacturing, this appears to be a logical step. To date there are no real examples of effective regional supply, although arguably the supply by Indian and Brazilian generic manufacturers sets a sort of precedent.

4.6 Drugs for neglected diseases

4.6.1 The role of the WHO? The role of developed country authorities?

'Neglected diseases' generally have been defined as communicable, tropical diseases such as malaria, sleeping sickness, Chagas disease, and leishmaniasis, for which there is essentially no pharmaceutical research and development (R&D). This is in contrast to

the higher profile of HIV/AIDS, where there is more reliance on market-based incentives, particularly given the market for ARVs in the US. Trouiller et al⁷ have documented the absence of development of drugs for these neglected diseases, and a number of initiatives have recently developed to try to address the problem.

A political/scientific lobby group, the Drugs for Neglected Diseases Initiative (DNDi), has been formed as a partnership of Medecins Sans Frontieres, WHO/Tropical Diseases Research (TDR), Oswaldo Cruz Foundation/ Far Manguinhos (Brazil), Indian Council of Medical Research (India), Institut Pasteur (France), Ministry of Health (Malaysia), and Kenya Medical Research Institute. The goal of DNDi is to develop effective, safe, affordable and field-adapted drugs by addressing the needs of patients with these conditions. It is an independent body of international health experts constituting a 'virtual drug development initiative' to "catalyse drug R&D by enabling regional networks of researchers, health professionals, drug manufacturers, and governments, to work together."³⁶ Examples of current DNDi projects include organizing the documentation to support registration of paromomycin for visceral leishmaniasis in several African countries and India (clinical trials already exist) and moving forward two artesunate-based fixed-dose combination products for chloroquine-resistant malaria, an academic/public/private effort involving institutions in Brazil, Malaysia, Thailand, United Kingdom, Burkina Faso, France, and the WHO.

In addition to its involvement in the DNDi, the WHO has taken a prominent role in development of some products for neglected diseases, particularly malaria, through its TDR section. In the absence of commercial drug development programmes, TDR has designed much of the drug development programme for some of the fixed-dose combination products used in the treatment of malaria. However, while clinical trial design expertise is certainly available in the public sector, pharmaceutical product development is less readily available and the WHO has had to develop partnerships with individual companies to try to bring the products to market. It is not clear that this approach has been successful and there is currently major controversy about how effective it has been, particularly in relation to the artemisinin combinations (see Attaran et al³⁷ for details).

A key challenge for the future development of drugs for neglected diseases and diseases of less interest to the multinationals will be to strike a balance between stringent quality, safety, and efficacy requirements that may be technologically intensive, and a feasible public-health driven agenda. That said, there is an obvious role for regulators in developing countries to take proactive positions regarding drugs for neglected diseases. One role for DRAs is administrative facilitation through provisions such as fast-track approval. A larger issue is whether regulators should be more involved in the development programmes themselves. In developed countries this involvement is already widespread but it is strictly informal. This interaction can clearly make scientific progress more efficient, but it presents an obvious risk of conflict of interest. Can the regulators who design trials still be considered objective in the evaluation? There is a clear need for attempts to capitalize on this strategy for less



developed and least developed countries under the tutelage potentially of the WHO, with collaboration with other institutions such as DRAs from the developed countries and research institutions.

4.6.2 Fixed-dose combination products: ARVs and anti-TB treatment, anti-malarials

Fixed-dose combinations (FDCs) for HIV, TB and malaria have become a particular issue for drug development in these clinical areas. The clinical arguments in favour of FDCs in the treatment of these diseases are compelling: combination treatment is more effective, there is better compliance with treatment because one pill is easier to take than four, and there is less likelihood of microbial resistance developing. The challenge has been to define the precise combinations of medicines for each condition that are optimal and then to develop the combination as a single product.

The development poses two problems: that of chemically formulating a stable product, and then establishing that the combined formulation is equivalent to the individual components. In other therapeutic areas, such as hypertension, FDCs have been developed on the basis of small clinical trials which show that the combination product is both acceptable and effective. In the neglected disease areas, the question of what data are necessary for registration is currently being argued in relation to products such as 'Triomune', a fixed-dose combination of nevirapine, stavudine, and lamivudine that has been prequalified as an acceptable product by the WHO. To date, the private sector has had some interest in developing FDCs for the HIV market (arguably in response to lobby group pressures in the US) but limited interest in developing FDCs for malaria and TB, despite the large market for such products in developing countries. One response to this problem has been for authorities such as the WHO to try to identify a limited number of combinations that are desirable, thus almost guaranteeing a market, and then to assist private sector companies in developing the product, for example, Coartem and Novartis. There are two problems with this strategy: firstly, determining the optimum combination is not always possible based on available clinical trial data, and by committing to a single product, the possibility of competition, and thus lower prices, is reduced.

At present, given the relative lack of interest of the multinational pharmaceutical manufacturers in these essential FDCs, there is no obvious solution, if such products are to be registered widely, other than to have the WHO, developed country authorities and possibly donors contribute to the further development of data needed for registration.

4.7 WHO prequalification project

The WHO prequalification project aims to establish the quality of products that are intended for supply through a number of international agencies (e.g. UNICEF etc). Prequalification can occur at three levels: products, procurement organizations and quality control laboratories. Most of the public discussion and debate has been about the

prequalification of products. Full details of the project are readily accessible through the WHO website³⁸ and the principle is simple: for a specified list of products, interested suppliers apply for qualification and provide the specified data on a product by product basis. If they meet the standards required, which include, but are not limited to GMP, the product is recognized as 'prequalified' for purchasers to consider. Each product considered must be a legal product in its country of origin.

The focus of the project is on providing a list of high quality products for HIV/AIDS, malaria and TB. To date, the majority of products approved have been for HIV/AIDS. Applicants to the process are protected by confidentiality agreements, so it is not possible to determine whether particular applicants have applied for approval for products and been 'rejected'. The WHO view is that it does not 'reject' applications, but provides advice to applicants to assist them to bring their products up to the required standard.

There have been criticisms of the prequalification project, mainly by the US government and the multinational industry. Their arguments are mainly that the project is setting lower standards for products than those accepted by international DRAs. They also argue that by prequalifying products from 'smaller' manufacturers, there is no guarantee that the products will be available to be supplied. The WHO, however, has been prepared to approve generic versions of products that are currently still patented in the US, thus threatening the monopoly of the originator companies. Although the particulars of the decision-making process are, in the case of both the FDA and the WHO, confidential, based on each agency's published standards for assessing quality, it is highly unlikely that there are significant differences in the quality of the products being approved. There may, as noted above, be differences in scientific judgements about interpretation of aspects of the standards. WHO has announced that it will make its assessment reports public. (See <http://www.who.int/mediacentre/releases/2004/pr49/en/>, accessed Sep 3 2004).

One of the major positive effects of the prequalification project, apart from identifying good quality products, is capacity development for GMP and inspection capability and skills in assessing both innovator and generic products. Each application is assessed by at least one inspector from a developing country in combination with a person from a developed country agency, as well as regulators from developing countries working in teams. This type of shared assessment model is one that clearly should be further expanded. The WHO has already commenced a pilot project to prequalify quality control laboratories in a similar process, which is again a project that should be expanded as rapidly as possible.

Currently the rate-limiting step in the project is the number of applications from qualified applicants, particularly a problem in relation to the anti-malarial products. It is important to note, however, that the WHO has also identified a potential funding shortfall for 2003-4 for the project, particularly for product assessment work.³⁸



5 Proposals for research, monitoring and development of drug regulatory systems

The terms of reference (TORS) for this study specifically included a request for policy recommendations as to how systems can more efficiently allow appropriate quality drugs to market. The TORS also identified that there may be ‘bottlenecks’ in regulatory systems in developing countries that inhibit efficient registration. The questions are, what are these bottlenecks and what can be done about them?

In our experience, there are two key problems with regulatory systems in developing countries (and developed countries as well). The first is that DRAs are often operating in an environment with insufficient political support, resulting in inadequate legislative frameworks, inadequate financial resources, inconsistent application processes and corruption of an appropriate regulatory culture. In this type of environment, the key solution is engendering first and foremost political will and understanding of the role of a drug regulatory authority, and why a country should invest in one. If the notion of regional drug regulation can be developed, then a key role for donors such as DFID is to support the development of political support for regional authorities and the development of regional/sub-regional networks and mechanisms of sharing regulatory information to arrive at harmonized regulatory decisions.

The second problem that arises once the political will is established is lack of scientific, administrative, and legislative capacity to operate an effective system. There is no point in having scientific capacity if there is no enforcement of the law or control of the market place; likewise there is no point in trying to develop adequate scientific capacity if the incentives for scientists, once trained to work in the public sector, are insufficient. There is consistent evidence of problems with ‘brain drain’ in this field – after all, what could be more attractive to a new pharmaceutical company than to employ the country’s regulators once they have been fully trained in the requirements for product registration? DFID and other donors may be able to assist countries to develop methods for retaining staff, but the actual means of doing this, short of financial payments, is not obvious.

Bottlenecks can arise with idiosyncratic application of regulatory science, that is, where regulators take an individual view of the interpretation of data. One important mechanism to avoid this is effective networks of regulators to ensure common

understanding of scientific principles and methods. To date, most networks have been informal (apart from those mentioned in the section on harmonization) and have lacked consistent support. The main international meeting of regulators (ICDRA) is clearly a key forum for information exchange, but mechanisms for further developing regional groups and networks are key, and should be supported provided there are specific plans and targets developed (say for cooperative registration) with measurements of outcomes and achievements. One such outcome could be to measure availability of generics as a result of harmonization strategies: at the moment it can be argued that harmonization of registration requirements has made it easier for multinational corporations to access markets in different countries. What is not yet clear is whether this has also improved access to medicines, especially generics.

A further issue is the need for DRA development to be linked with other aspects of a medicinal drugs policy, such as development of effective insurance/reimbursement systems. While many countries have documents that lay out a policy that appears to meet the needs of a national medicinal drugs policy, what is much less clear is whether these are being effectively implemented. Again, this is an area where there is a need for international collaboration for research and support.

In the end, making a positive decision about a pharmaceutical product requires careful weighing up of potential benefits and harms, and the scientific complexity of such decision-making should not be underestimated. The role of donors potentially could be to support the WHO and other groups who have expertise in regulatory science to continue to undertake appropriate capacity development. Support for the prequalification programme would be one concrete example, particularly the quality control laboratory project.



6 Summary and conclusions

The complexity and challenges of drug registration should not be underestimated. It is simplistic to think that simply speeding up registration processes will improve access – this has been the industry argument that neglects to take into account issues such as market control and assurance of quality. Effective drug regulation depends on a whole melange of components, and to support a single component in isolation is unlikely to be effective. International organizations have the capacity to set a framework for registration that has as its key function the protection of the public, at the same time as improving access. Given the pressures that arise from the legitimate business interests of the multinational pharmaceutical manufacturers, there needs to be support to individual country and regional activities that is designed to ensure quality and availability of affordable essential medicines. This includes ensuring that there is adequate capacity at country level to assess and control the quality of pharmaceuticals.

It seems inevitable at present that donors will have to contribute towards drug development for drugs for neglected diseases. To do this means ensuring that organizations such as the WHO have the scientific and other resources necessary to provide the required leadership. But the most important task is to educate the politicians and governments that drug regulation is essential rather than a luxury that should be funded by the private sector. The user should certainly pay – but in this case, the real user is the taxpayer, not the pharmaceutical manufacturers.



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Annex A

Table 1 Technical information and documentation required for registration of products containing new chemical entities

(From Table 8.2, 10- Country Study)

	Australia	Cuba	Cyprus	Estonia	Malaysia	Netherlands	Tunisia	Uganda	Venezuela	Zimbabwe
Product characteristics and label	•	•	•	•	•	•	•	•	•	•
Chemical/pharmaceutical information	•	•	•	•	•	•	•	•	•	•
Clinical data	•	•	•	•	•	•	•	•	•	•
Pharmacological and toxicological data	•	•	•	•	•	•	•	•	•	•
GMP certificate	•	•	•	•	•	•	•	•	•	•
WHO-type certificate for imported products	■	•	•	■	•	■	•	•	•	•
Manufacturing process	•	•	•	•	•	•	•	•	•	•
Quality certificate for raw materials	•	•	•	■	•	•	•	•	•	•
Quality specification for containers	•	•	•	•	•	•	•	•	•	•
Bioavailability data	•	■	•	•	•	•	•	•	•	•
Stability data	•	•	•	•	•	•	•	•	•	•
Applicant information	•	•	•	•	•	•	•	•	•	•
Samples for analysis	•	•	•	•	•	•	•	•	•	•
Price information	■	■	•	■	■	■	•	■	■	■

• = Yes ■ = No

Table 2 Examples of fees and charges levied 1998-1999 (US\$)

(From Table 5.5 , 10- Country Study)

	Australia 2004	Cuba	Cyprus	Estonia 2004	Malaysia	Netherlands	Tunisia	Ugand	Venezuela	Zimbabwe	South Africa
Product registration fees	5 000 -120 000										
New product	Up to 140000	700	120	785 1200	100	15 000	1 200	1000	1 270	1 000	4300
Renewal/annual retention fee	645	350	60	571 600	100		600	300		600	80
Registration domestic product		700			100		600	200		38	
OTC/generic (imported)	2 500										
	Up to 65000	700			100	5 000		1000	215	1 000	2000
Manufacturing											
Premises licence								354-629		125	
Manufacturing licence				357	100						
Product manufacturing licence			50								
Wholesale and retail											
Wholesale dealer licence/ suitability of premises				71-357	40			228-550		38	
GMP inspection											
Licence application fee	325										
GMP inspection/other than initial	215/hr/ auditor							20-35		25	
Certificates											
Export licence/free sale certificate											
42/hr/ auditor				10						171/yr	61
GMP certificate	43/hr/ auditor										
Clinical trial fees	660-8 100				40				182		37-500