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Chapter 4

Ensuring Quality, Safety and Efficacy

4.1. Pre-marketing and Post-marketing Duties

At the time when modern pharmaceutical law and regulation began to emerge, they were conceived in the belief that serious problems and disappointments with medicines might largely be avoided if enough evidence of quality, safety and efficacy were provided by the manufacturer prior to their introduction. The requirements which were set for approval therefore related to the provision of such evidence, of sufficient quality and delivered in sufficient volume and good time. It was said that, had these requirements been introduced earlier in the century, some past disasters (see Chapter 3) might have been avoided, since the problems could have been predicted, for example, using studies in small rodents.

Certainly, the ability of the early organic arsenicals to damage various organ systems (Salvarsan 1922) might have been foreseen in this way, since they were broadly toxic in all species. The tragedy with diethylene-glycol as a solvent for Elixir of Sulfanilamide (Nielsen 1986, Wax 1995) could similarly have been predicted in animals, as could the toxicity of diiodoethyltin which underlay the Stalinon disaster of 1957 (H.P. 1958). However, when the hypnotic thalidomide induced phocomelia in large numbers of children in 1960–1961 the only early signs of toxicity had pointed in a rather different direction (neurotoxicity). After the tragedy, attempts to recreate the phocomelia-inducing effect using studies in pregnant animals only succeeded after much effort and then only satisfactorily in certain sub-species (Folb 1990 at pp. 1–8); this threw a serious doubt on animal tests as a predictor of unusual effects in humans. The law cannot reasonably impose on industry a duty to perform particular studies unless there is fair reason to believe that they will serve the public interest.

Similar problems arose with the belief that one could draw final conclusions on the efficacy of certain drugs before they were approved for marketing. The broad pattern of efficacy could be established in clinical trials, but once a medicine was used on a much larger scale in the field, surprises could emerge. It became clear, for example, that after a medicine had been marketed on the basis of well-conducted clinical studies and had
been used for any length of time, tolerance to it might develop, necessi-
tating an increase in the dose or a move to an alternative drug; when an antibiotic came into widespread use, microbial resistance to it might soon emerge. Efficacy apparently proven in a well-recognized disorder may or may not prove to be attainable in a closely related disorder or in certain subgroups of patients. On occasion, the dose estimated in the initial stud-
ies might ultimately prove inadequate:

From 1969 onwards, clinical studies with ibuprofen concluded that it was effec-
tive in rheumatoid arthritis in doses of 400 mg or 600 mg daily, though higher doses were tolerated. (Martindale 1977 at p. 193) Thirty years later, in 1999, com-
monly cited anti-inflammatory doses were 2000 mg to 2400 mg or more. (Felleskatalog 1999)

During hearings before the passage of the 1962 Kefauver–Harris Amendments to America’s Food, Drug and Cosmetic legislation, both sci-
centific and public representatives had stressed the need for legal and med-
ic certainty in drug regulation (Nielsen 1986); the legislation as amended required both efficacy and safety to be proven, the applicant being firmly obliged “to show whether such drug is safe for use under the conditions pre-
scribed, recommended or suggested in the proposed labelling thereof”(Art 355d). The authorities were nevertheless entitled to withdraw their approval if efficacy or safety were subsequently found not to have been established, thus introducing an element of doubt. In the meantime the pioneering legis-
lation in The Netherlands (WOG 1958) had exhibited even greater caution; the efficacy and safety were to be demonstrated “according to the judge-
ment of the reasonable man” and the judgement of the reasonable man could clearly change as time went by. What all this meant was that a firm apply-
ing successfully to market a new drug was by no means handed a guarantee of its future and permanent acceptability. The need for continued watchful-
ness on the part of the company was also apparent from the obligation to maintain records of apparent adverse reactions and report them to the FDA, but also from the requirement that the manufacturer maintain records on other matters relating to the drug, communicating new developments to the agency in the same manner. Provisions such as these, which have subse-
quently found their way into many other national laws and regulations, mean that the manufacturer or other licensee for a drug today has continuing duties with respect to the drug so long as it remains on the market.

By the time that the process of harmonising drug regulation came into swing across much of the world in 1990, the process of new drug approval had therefore been complemented by procedures to monitor both
efficacy and safety throughout the life of a product. The legal duty of the
manufacturer to maintain his commitment to the product throughout that
period was laid down clearly by the Tokyo District Court in a 1978 judg-
ment dealing with the complications caused by clioquinol:

When . . . products have already been placed on sale and put into clinical use for
humans or animals, documentation and information in medical, pharmaceutical
and other related sciences concerning such products, including homologous chem-
ical compounds, should be constantly collected. If, as a result of such activities,
there are indications that undesirable side effects exist, a comparative, quantitative
study of the reports on the clinical safety of the products available up to that time
should be concluded to determine the extent of the suspicions concerning possible
side effects. Where such suspicions do exist, the companies are required to estab-
lish as soon as possible the existence and extent of the side effects of the said prod-
ucts by conducting animal experiments or studies on the history of drug-related
symptoms and by engaging in follow-up research. In addition . . . they are
required, as part of the duty to foresee, to notify other pharmaceutical companies
that manufacture or sell similar products and to so request information from them
on both past and future side effects of the said products so as to obtain a more
defined perception of and better foresight regarding such side effects . . . .

Except for the Court’s postulate that manufacturers had a duty to report
adverse effects to each other, much of the above remains literally valid today.

The life of a drug product, during which new knowledge about it
may emerge, may be very long indeed; acetylsalicylic acid (aspirin) was
described by Felix Hoffmann on October 10, 1897 and marketed shortly
thereafter, becoming one of the most widely used medicines of all time.
Yet its probable link to Reye’s syndrome, that was seriously affecting sev-
eral hundred children yearly in America, was not propounded until 1965,
and its ability to affect favourably the prognosis for cardiovascular disease
was not made credible until the work of Elwood and Cochrane in 1974;
there is probably yet more news about aspirin, good or bad, to come.

There may even be at least a moral duty to investigate safety prob-
lems further after they have led to the withdrawal of a drug, in the hope of
finding explanations which can help to assure future drug safety in the
field concerned:

After the ICI beta-blocker practolol was withdrawn because of fibrotic complica-
tions, both the company itself and others undertook much work to determine
whether the risk was associated with particular structural characteristics and could
be avoided with other beta-blocking agents.

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1 S.M.O.N. Patients v. The State and others (1978), Judgement, at p. 322 per Kabe J.
All this means that the initial approval of a drug, however demanding the process may be, is in essence only a provisional step; it may need to be modified as time goes on and new knowledge of the product’s properties accumulates. For some drugs it may be necessary to require the originator company to undertake intensive monitoring, set up supplementary studies or perform particular tests during treatment. New Zealand was a pioneer in “intensive monitoring”, an arrangement by which a limited patient population receiving a drug is followed in great detail so that all events, wanted and unwanted, can be recorded. Now known as “monitored release” it can be required where an agency cannot take a firm decision on the future of an apparently valuable drug without more detailed information from the field. The exact duties differ from one regulatory system to another, but for all drugs, post-marketing surveillance in the form of adverse reaction monitoring and submission of new findings from other sources will be necessary. There are very few drugs about which, at the time of their introduction, there is nothing left to discover.

A concurrent problem is the fact that the standards prescribed by the law – which calls for quality, efficacy and safety – are not as exact as they appear on paper. Standards in medicine or biology are rarely as sharply defined as they can be in pharmacy or any other of the exact sciences. Some aspects of the quality of a drug can be defined in exact mathematical terms, but neither safety nor efficacy can be so rigidly circumscribed. Estimates of each inevitably vary; no drug can be expected to prove effective in 100% of the patients for whom it is prescribed, and no drug is entirely free of adverse reactions. In all three fields therefore one encounters difficulties in interpreting the law when taking decisions on particular drugs, either at the outset of their career or later.

A related problem is the interrelationship of the three basic issues. Initially, some pharmaceutical firms favoured a regulatory system in which quality, safety and efficacy, listed as separate items in the law, would also be assessed as separate matters. It soon became clear that this would not be realistic:

In 1964 the Committee on the Safety of Drugs was established by the British Health Ministers with a small staff. Strictly speaking it was authorized only to assess medicines for their safety, and some manufacturers objected to its assessing efficacy issues as well. The Committee however made it clear that one could not evaluate one without the other; whether or not a particular degree of toxicity was acceptable could depend very much on how effective and important the drug was in medicine.
In the same manner, and much though some applicants objected to comparative evaluation as falling outside the legal criteria for assessment, the acceptability of a medicine would inevitably depend on whether its efficacy/safety balance was at least comparable to that of medicines already available. The classic example cited in debate at the time was that of antimicrobial treatment. In 1930, with no antibiotics available, lobar pneumonia was commonly a fatal disease, and had a drug been created at the time that was capable of saving 30% of lives it would have been a godsend. Once penicillin had appeared a decade later and had proved capable of curing most patients, anything offering a lesser ability to cure would have been rejected out of hand.

Several striking examples of this phenomenon were seen at the time when regulation was fast developing. Until the late nineteen-fifties, patients requiring diuretics were normally treated with the highly effective organic mercury compounds despite their ability to damage various organ systems, elicit anaphylactic reactions and precipitate cardiac arrest. (Meyler 1960 at pp. 70–71) As soon as the well-tolerated thiazide diuretics became available, the mercury compounds were discarded as obsolete (Dollery 1972 at p. 313). Somewhat similarly, the highly addictive and toxic barbiturates largely lost their place during the same period to the benzodiazepines; (Shepherd 1972 at pp. 51–60; see also section 4.3. below) the dependence-producing potential of the latter became evident only much later (Medawar 1992).

On occasion, manufacturers have successfully defended their products in court precisely on the grounds of their favourable efficacy/safety balance (see Brahams 1990, cited under Section 4.3.6).

In many of the matters noted above, regulatory agencies have for all these reasons engaged in some extensive interpretation of the very general criteria listed in the law, but have as a rule done so in a consistent manner.

4.2. The Manufacturing and Quality Control of Drugs

4.2.1. The legal concept of quality

There is an apocryphal story that the prospective purchaser of a Rolls-Royce motor car who enquires as to the power of the engine merely receives the assurance “Quite sufficient, sir.”\(^2\) In a sense this is also the

\(^2\) This degree of confidentiality is no longer maintained. The 2005 Rolls-Royce Phantom develops 453 bhp.
most satisfactory answer that could be given to a purchaser asking about the quality of a medicine from a reputable supplier. There is no single, simple and universally relevant means of expressing quality or setting a quality threshold. Desmond Laurence’s admirable “Dictionary of Pharmacology and Allied Topics” does not define quality beyond ruling that “It is essential that manufactured medicines be of high and consistent quality.” (Laurence 1998 at p. 282) Even plain water has various levels of quality: alongside water approved for human consumption (aqua potabilis, aqua communis) the pharmacopoeias provide specifications and modes of preparation for both purified water (aqua purificata) which is prepared by distillation, reverse osmosis or other suitable methods and then stored in inert airtight containers, and water for injection (aqua ad injectionem) which is sterile and free of pyrogens. Physiological saline – plain salt solution – has at least five measures for quality and several standards; one must know its actual concentration, the degree to which that concentration can be allowed to vary, its degree of chemical purity and the permissible degree of contamination with bacteria, viruses or pyrogens. For a finished medicine there will be far more measures of quality and numerous matters on which experts (and regulatory agencies) may disagree regarding the necessary standards, ranging from issues of colour to stability and from disintegration time to bioavailability. If the quality standards are set too low the medicine may be ineffective or dangerous, whereas if too much is demanded the work of making the medicine and checking the quality of every batch may be so laborious as to render it unaffordable. These are not minor matters, since they have both medical and judicial consequences; the law requires in general terms that drugs be of adequate quality and imposes sanctions if they are not; there are detailed and legally established procedures for setting the standards applicable to any individual medicine and testing to these standards; finally one will be obliged to ensure that the medicine attains all those standards throughout its shelf life, and to reject or discard any medicine that fails to do so.

4.2.2. Establishment and maintenance of quality standards

Society maintains a range of complementary and legally instituted procedures to ensure the quality of medicines; standards are set, manufacturing conditions are specified, and quality is checked both at the time of drug approval and beyond.

(i) Pharmacopoeia monographs A pharmacopoeia, in the usual sense of the term, is a standard work of reference setting quality norms for
the most widely used medicines; the principal matters covered in the tech-
nical monograph for each medicine are manufacturing standards, standards
for purity, methods of assay and directions for use (with the emphasis usu-
ally on directions for handling and processing). Most significant pharma-
copoeias are state publications authorized by law; a well-equipped
laboratory is likely to have some 30 current pharmacopoeias to hand includ-
ing three regional or international volumes (the *International, European*
and *Nordic Pharmacopoeia*). Although in recent years an increasing number of
national pharmacopoeias have been assimilated in whole or in part into the
regional volumes, a number of newly independent countries are currently
preparing to institute national pharmacopoeias of their own, particularly
where there is a national (e.g. herbal) medicinal tradition.

The historical role of the pharmacopoeia was to provide the commu-
nity pharmacist with guidance on the preparation and testing of medicines,
including the identification, selection and testing of herbs, the making of
extracts and the blending of ingredients. A national pharmacopoeia would
therefore strive to list most medicines in regular use, and the differences
between national volumes largely reflected differing flora and herbal tra-
ditions from place to place. During the twentieth century, in which time
medicine has moved largely to the use of single substances (synthetic or
extracted from natural materials) the choice of medicines in daily use has
become more uniform throughout the world. The various pharmacopoeias
have therefore drawn closer together in their selection of monographs and
actual content, often sharing complete monographs. The British
Pharmacopoeia for 2003 contains, for example, 2,900 monographs, a pro-
portion of which are shared with the European Pharmacopoeia.

For new medicines developed by the pharmaceutical industry the nec-
essary quality standards are created by the originating company and assessed
for their acceptability by the Drug Regulatory Authority of each country or
region where marketing approval is sought (see below). Only in later years as
patents expire and the medicine becomes available for general manufacture
is a public pharmacopoeia monograph likely to be issued, often derived from
the manufacturer’s work and developed in collaboration with him.

Traditional pharmacopoeias provide only standards for basic medic-
inal substances and not for finished products, but the latter are now

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3 The first pharmacopoeia to gain legal recognition was that compiled by Valerius
Cordus, issued posthumously at Nuremburg in 1546. The US Pharmacopoeia was
founded in 1820 and accorded status in Federal Law under the Drug Import Act of 1848.
increasingly included in many national volumes and are finding their way into the *International Pharmacopoeia* published by WHO. Manufactured products, whether basic substances or finished medicines, that have been produced and tested to the standards listed in a particular Pharmacopoeia are authorized to be labelled as such (e.g. Propranolol Hydrochloride Injection U.S.P.).

The term “Pharmacopoeia” is also used for similar volumes produced for special purposes by health institutions or independently (Herbal Pharmacopoeia, Hospital Pharmacopoeia). *Martindale’s Extra Pharmacopoeia* is a medical/pharmaceutical reference book and dictionary with documented information on most of the medicines and medicinal substances in use in the world.

(ii) Good manufacturing practice, licensing and inspection

Although procedures to license and inspect pharmaceutical factories have existed since the nineteenth century, the standards have been much developed since the introduction of the concept of Good Manufacturing Practice (GMP).

The GMP concept arose after 1963 when the United States FDA first introduced detailed regulations setting out the practices to be followed in manufacturing, packaging and storing medicines. From 1968 onwards the World Health Organization adopted the term in a programme to upgrade and harmonise the standards imposed in its member states. Extensive GMP rules have since been developed for the European Union and in the framework of the International Conference on Harmonisation (see Chapter 3). The provisions and the prescribed arrangements for training and inspection are comprehensive. To cite only the European definition of their scope and purpose:

> Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

1. all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
2. critical steps of manufacturing processes and significant changes to the process are validated;
iii. all necessary facilities for GMP are provided including:
   a. appropriately qualified and trained personnel;
   b. adequate premises and space;
   c. suitable equipment and services;
   d. correct materials, containers and labels;
   e. approved procedures and instructions;
   f. suitable storage and transport;
iv. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
v. operators are trained to carry out procedures correctly;
vi. records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;
vii. records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
viii. the distribution (wholesaling) of the products minimises any risk to their quality.

The term GMP is not yet used consistently, since any country may regard its own manufacturing requirements as guaranteeing good practice. Increasingly, however, the term is now only applied to the highest set of standards as adopted in EU, Japan and the USA, and as a rule agreed in ICH. Factories are now in many countries both licensed and inspected according to these GMP standards, drug inspectors having been retrained to certify and control all production units. However, other manufacturing, especially in the developing world, is still carried out to a lesser standard; as noted in Chapter 8 this is commonly all that can be attained where the resources for full GMP are not available, and for many purposes a lesser standard is entirely satisfactory. Universal adoption of ICH standards regarding quality could in that respect be disastrous:

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4 Since it is not practical for every country to maintain full inspection teams, much inspection is now performed internationally under the auspices of the Pharmaceutical Inspection Co-operation Scheme (PIC/S); see http://www.picscheme.org. There are also bilateral arrangements for mutual recognition of GMP inspections between countries.
The issue was raised emphatically in July 2003 at a broadly consti-
tuted meeting convened by M.S.F. and the Drugs for Neglected Diseases
Initiative in Geneva in July 2003 which concluded that:

There are substantial fears that some ICH guidelines might have a negative impact
on access to essential medicines in developing countries. Specifically, new strin-
gent requirements for raw materials may raise drug prices without offering any
discernible public health benefit in exchange. Some medicines that are badly
needed in developing countries may not be granted regulatory approval, since
risk/benefit calculations are necessarily made differently in non-ICH and ICH
countries. In addition, the existing governance structure excludes many of the
stakeholders affected by the process, including developing countries, consumers,
and health professionals... The motivation behind extending the guidelines
beyond ICH countries is not clear. Nevertheless, it is notable that the multinational
pharmaceutical industry – far more than drug regulators – stands to benefit com-
mmercially and strategically from the globalisation of ICH guidelines, and therefore
has likely been the driving force behind it. For example, higher standards for the
quality of raw materials and drugs may allow ICH countries to protect themselves
from lower-priced (generic) imports from other markets that do not hold to ICH
quality standards, while ensuring continued access to high quality raw materials
from non-ICH countries for their domestic manufacturers. (MSH 2003)

As a regulator in Central Asia explained in 2004:

At the moment some two-thirds of our supplies come from factories, here or in
neighbouring countries, that do not have GMP certification. We are progressively
closing those that will never learn how to make drugs, but there are some which
we would simply call “clean, careful and cautious” which we can call on for sim-
ple antiacid tablets or even benzodiazepine tranquillizers, and one day we will get
them upgraded. For the moment they are not the sort of factories we will allow to
supply us with drugs having a narrow efficacy/safety margin, such as digoxin, or
any form of intravenous injection.” (Interview 38)

Many similar countries are now progressively upgrading their pro-
duction facilities so that a sufficient number of manufacturers attain GMP
within the coming years, while others are obliged to cease operations.

(iii) Drug regulatory procedures The national (and in some cases
regional) structures for drug regulation considered in Chapter 3 include
provisions to ensure the quality of products registered; as a rule there is an
associated quality control laboratory to examine both the documentation
submitted by the applicant and to analyse samples submitted at the time of
approval or taken subsequently. The Agency is as a rule closely associated
with the national drug inspectorate which can ensure that samples are
taken regularly at all levels of distribution so as to confirm that quality is
maintained. Drugs failing to meet the required standards may be recalled
or particular tainted batches removed from the market, and sanctions may be imposed.

Since a drug regulatory agency is a multidisciplinary body, differences can arise between the pharmaceutical and the medical concepts of quality:

The medical experts on the Board often pressed the view in borderline cases that the quality standard which we required for a drug should primarily depend upon the therapeutic index or margin of safety; for a product such as penicillin with a very high index a fair degree of variation in product content could be tolerated, whereas for a medicine such as lithium with a very low index the product content would be permitted to vary only within extremely narrow limits. The nature of contaminants would affect the extent to which their presence could be tolerated in the finished product. Some of the pharmacists on the other hand were prone to insist on the highest attainable standard of quality, for example with product content varying only between 99% and 101% of the norm. Discussions tended to end in a compromise in view of evidence adduced by manufacturers as to the expense of maintaining quality at an unnecessarily high level, especially once a drug was out in the field. (Interview 3)

For individual products such debates generally lead to constructive interaction between companies and regulators in order to arrive at standards which are both necessary and attainable.

(iv) Procurement agencies  In those countries – particularly in the developing world – where there is a public drug procurement system this organisation will as a rule itself maintain (or contract with) a quality control laboratory, to examine samples submitted by firms tendering for supply contracts. The need for many of these agencies to procure at low cost and thus from secondary suppliers means that a relatively high proportion of faults may be found:

When WHO examined the quality control records of experienced procurement systems in five developing countries it was found that, despite a careful pre-selection of eligible suppliers, the proportion of medicines failing to pass the necessary tests ranged from 14 to 29%.

(v) Certification schemes  Since medicines are constantly being tested at numerous institutions throughout the world there is provision for some information on their findings in order to ensure that faults found at one site do not occur at others. The current arrangements are not fully satisfactory, since some agencies hesitate in view of their confidentiality provisions to make their findings widely available, and others cannot be regarded as fully reliable sources of information. Table 4.A provides a summary of the situation.
**Table 4.A**

**Overview of International Certification Arrangements**

**WHO CERTIFICATION SCHEME (revised 1992, 1995)**
Certificate issued by a national drug regulatory agency, generally to a foreign agency or to the manufacturer concerned.
Warrants that a drug has been granted a marketing licence. Confirms that the manufacturer has passed inspection requirements.
Comments: *Is only as reliable as the issuing agency. Does not provide batch-specific information. Not verified by WHO*

**STATEMENT OF LICENSING STATUS (WHO Model 1992)**
Certificate issued by a national drug regulatory agency in an exporting country, to an importing country
Warrants only that a particular drug has been granted as national marketing licence
Comments: *Is only as reliable as the issuing agency. Does not provide batch-specific information. Not verified by WHO*

**BATCH CERTIFICATE (WHO Model)**
Certificate issued *either* by the manufacturer *or* by the national drug regulatory agency in an exporting country
Confirms that an individual numbered batch has been shown to confirm to product specifications.
Comments: *Usually requested for antibiotics or where drugs are suspect. Only as reliable as the issuer; easily falsified. Not verified by WHO*

**FREE SALE CERTIFICATE (non-WHO)**
Certificate issued by a national drug regulatory agency in an exporting country
Confirms only that a particular product is on sale nationally
Comments: *Does not confirm that the product has been evaluated for efficacy, safety or quality or has been approved.*

**GMP CERTIFICATE**
Certificate issued by a national drug regulatory agency in an exporting country
Declares that a specified plant manufactures pharmaceuticals to “GMP standard”
Comments: *Only as reliable as the issuing agency. GMP standards can vary.*

**ANALYTICAL BATCH CERTIFICATE**
Issued by a manufacturer
Copies of analytical tests and results for particular batches of a drug.
Comments: *Only as reliable as the issuing manufacturer. Easily falsified. No confirmation of national marketing licence.*
(vi) Manufacturer’s research  The fact that the above sources of standards lie with official bodies should not obscure the fact that, as mentioned above in (iii), the first well-researched proposals for the setting and testing of quality standards very commonly lie with the original or principal manufacturer of a drug who in his own field may be considerably more experienced than any outside agency in deciding what standards are necessary and realistic.

4.2.3. Packaging and distribution

The sensitive and potent nature of medicines imposes particular duties on the manufacturer regarding packaging standards and the conditions under which drugs are stored, transported and supplied so long as they remain under his control. Throughout that period it is his responsibility to ensure that they remain in good and usable condition, bearing in mind the conditions to which they are likely to be exposed.

Glyceryl trinitrate will for example sublime rapidly unless it is kept in a tightly sealed container. Many antibiotics and vaccines require supply through a refrigerated “cold chain”. Glass bottles used for blood or intravenous fluids can develop hair splits allowing infection to enter, while plastic bags may contain toxic “emulsifiers” which leak out into the contents of the bag.

When the manufacturer transfers a medicine by sale or otherwise to another party it is his duty to ensure that it comes into appropriate and authorized hands:

Each legal system has its own provisions regarding the persons or institutions entitled to handle or trade in medicines, generally limited to licensed importers and wholesalers, pharmacies, health institutions and physicians. Special provisions will apply to certain classes of drugs (e.g. controlled substances, see Chapter 9) and there may be rules regarding transport.

Manufacturers have on occasion been held liable for negligence where products (stimulants, drugs of dependence, anabolic steroids) were improperly diverted from their stocks into illegal channels.

A manufacturer has no responsibility for the fate of a medicine once he has legally transferred it to another party, but where it becomes necessary to recall a product or a specified batch he should use his best efforts to ensure that it is returned to him. He may also be required or requested by the authorities to issue warnings if particular risks become evident or precautions need to be taken, and in some instances it may be both in his
own best interest and that of the public to warn against improper use of his product.

4.2.4. **Nature and extent of quality defects**

In various parts of the world there is a considerable market in spurious and counterfeit products (see Section 2.2.4), many of these being of extremely poor quality. Setting that issue aside in the present discussion, one can reasonably conclude that quality standards in the legitimate pharmaceutical market are as a whole remarkably satisfactory. Serious defects are in many countries so rare as to be regarded as curiosities:

Sanders, writing on behalf of the pharmaceutical industry in The Netherlands, pointed to a small number of instances of serious fault reported in the course of some years in that country: in one case, infusion fluids had not been sterile; in a second, a toxic heavy metal was found in vitamin C ampoules; and in a third, digoxin tablets were contaminated with digitoxin. (Sanders 1982)

Major manufacturers have, as noted above, collaborated in the definition of high standards and have themselves respected them, and the progressive concentration of industry in larger units has made it possible to provide the staff and resources needed to maintain proper levels of quality. Where defects have occurred they have generally been attributable to human error. In one calendar year, despite the intensive controls of quality in the US drug market, only 354 drug recalls were ordered by the FDA, many relating only to individual batches (Picariello 2005). An analysis for the year 2000 of the ten principal reasons for such recalls (CDER 2001) showed that these comprised:

- Lack of assurance of sterility in production or testing of sterile drug products
- Deviations from current good manufacturing practices
- Subpotency
- Microbial contamination of non-sterile products
- Chemical contamination
- Penicillin cross-contamination of other products
- Failure of validation of the manufacturing processes or inability to validate it
- Drug product marketed without an approved new or generic application
- Failure of drug to dissolve properly
- Product found to exceed limits set for impurities or degradation.
Detailed data on drug recalls because of quality defects are published promptly on the internet by the authorities in the United States, Britain and a number of other countries. While some agencies have been reticent to follow the example, fearing libel proceedings in the event of error, much wider dissemination of such information could be helpful in eliminating this source of inefficacy and risk.

4.2.5. Liability for quality defects

While many civil actions are brought against manufacturers for alleged safety defects (see Section 4.3) relatively few are brought for quality defects; the latter are more usually the source of measures taken by the national drug inspectorates, resulting as a rule in the withdrawal of a tainted batch of a drug and occasionally in criminal charges under the medicines legislation.

A prominent civil case, already briefly referred to in Chapter 2, related to an alleged manufacturing defect involving a hepatitis vaccine on sale in Britain:\(^5\) It merits citation in that the defendant manufacturer raised a number of arguments in his defence which could be relevant in other cases though they did not avail him in this instance:

The claimants had been infected with Hepatitis C virus through blood transfusions which had used blood or blood products obtained from infected donors. They brought actions for damages against the defendants, the authorities responsible for the production of blood and blood products. During the period when most of the claimants were infected, the risk of such infection through blood transfusions, though known to the medical profession, was impossible to avoid, either because the virus itself had not yet been discovered or because there was no way of testing for its presence in blood. Accordingly, the claims were brought not in negligence, but under the Consumer Protection Act 1987 which implemented the European Product Liability Directive of 1985 under which a product was defective when it did not provide the safety which a person was entitled to expect, taking all circumstances into account, including the presentation of the product, the use to which it could reasonably be expected that the product would be put and the time when the product was put into circulation. Article 7(e)b of the Act provided the producer with a defence if he could establish that the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable ‘the existence of the defect’ to be discovered. In the trial of the six lead cases, the defendants accepted that a producer’s liability under art 6 of the Act was irrespective of fault. They nevertheless contended that, in assessing whether the infected blood was defective, the unavoidability of the risk was a circumstance to be taken into account, and that the

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\(^5\) A and others v National Blood Authority and another [2001] 3 All ER 289. High Court, Queen’s Bench Division, London. Judgement of March 26, 2001 per Burton J.
most that the public was entitled to expect was that all reasonably available precau-
tions had been carried out, not that the blood would be 100% clean. In so contend-
ing, the defendants submitted that the infected blood was to be regarded as an
inherently risky standard product (i.e. one which performed as the producer
intended) rather than a non-standard product (i.e. a product which was deficient or
inferior in terms of safety from the standard product, and whose harmful character-
istic, not present in the standard product, had caused the material injury or damage).
They also relied on the fact that they were obliged to produce blood and had no alter-
native but to supply it to hospitals and patients, as a service to society. Alternatively,
the defendants sought to rely on the art 7(e) defence, contending that an unavoidable
risk qualified for protection under it if the producer was unable to discover, by
means of accessible information, the defect in a particular product.

Giving judgement, Mr Justice Burton held that:

(1) Avoidability was not one of the circumstances to be taken into account under art
6, even in respect of a harmful characteristic in a standard product. In that provision,
‘all circumstances’ meant all relevant circumstances. Avoidability was not a relevant
circumstance since it fell outside the purpose of the directive, which was intended
to eliminate proof of fault or negligence. That was not simply a legal consequence.
It was also intended to make it easier for claimants to prove their case, such that not
only would a consumer not have to prove that the producer had not taken reasonable
steps, or all reasonable steps, to comply with his duty of care, but also that the pro-
ducer had not taken all legitimately expectable steps either. Even without the full
panoply of allegations of negligence, the adoption of tests of avoidability or of legit-
imately expectable safety precautions would inevitably involve a substantial investi-
gation. If it had been intended that avoidability would be included as a derogation
from, or a palliation of, the directive’s purpose, it would have been mentioned. It
would have been an important circumstance, and it was intended that the most sig-
nificant circumstances were those listed. In the case of a non-standard product, the
circumstances specified in art 6 might obviously be relevant, as well as the circum-
cstances of the supply. However, the primary issue might be whether the public at
large accepted the non-standard nature of the product, i.e. whether they accepted that
a proportion of the products was defective. That was not the end of the matter,
because the question was one of legitimate expectation, and the court might con-
clude that the expectation of the public was too high or too low. Questions such as
warnings and presentations would be in the forefront, but the avoidability of the
harmful characteristic, the impractability, cost or difficulty of precautionary mea-
ures, and the benefit to society or the utility of the product (except in the context of
whether, with full information and proper knowledge, the public had and should
have accepted the risk) were not relevant. In the instant case, the infected blood
products were non-standard products since they were different from the norm which
the producer intended for use by the public. They were defective within art 6 because
the public at large was entitled to expect that the blood transfused to them would be
free from infection. There had been no warnings and no material publicity. The
knowledge of the medical profession, not materially or at all shared with the con-
umer, was of no relevance. Nor was it material to consider whether any further steps
could have been taken to avoid or palliate the risk that the blood would be infected.
(2) The defence in art 7(e) of the directive did not apply where the existence of the
generic defect was known or should have been known in the context of accessible
information. Once the existence of the defect was known, there was the risk of that
defect materialising in any particular product, and it was immaterial that the known
risk was unavoidable in the particular product. It would be inconsistent with the
purpose of the directive if a producer, in the case of a known risk, continued to sup-
ply products simply because, and despite the fact, that he was unable to identify in
which of his products that defect would occur or recur, or, more relevantly in a case
where the producer was obliged to supply, he continued to supply without accept-
ing the responsibility for any injuries resulting, by insurance or otherwise. Such a
conclusion did not mean that non-standard products were incapable of coming
within art 7(e). Such products might qualify once, i.e. if the problem which led to
an occasional defective product was not known. However, once the problem was
known by virtue of accessible information, the non-standard product would no
longer qualify for protection under art 7(e). Accordingly, in the instant case, art 7(e)
was of no avail to the defendants, and the claimants were therefore entitled to
recover against them.

(3) If, contrary to the court’s primary conclusion, the issues of avoidability or dis-
coverability of the defect in the particular donation of blood had arisen, precau-
tions to prevent or make a material reduction in the transfer of transmitted
infection through infected blood were available and not taken. From 1 March 1989
the blood was defective in all the circumstances and from 1 March 1990 the defect
in the donations was discoverable.

(4) The damages recoverable by the claimants could include, dependent upon the
facts, provisional or final damages in respect of invasive or debilitating treat-
ments, handicap in respect of employment and insurability, and the provision of
gratuitous services.

Alongside this, a single example of a regulatory measure taken in
the light of industrial failure as regards quality must be cited here at sim-
ilar length. It is intended, not in order to cast any aspersions on a particu-
lar corporation, but to show how even a well-reputed firm with extensive
procedures for quality assurance and control may on occasion fall foul of
a watchful agency charged with maintaining strict standards in this
demanding field, especially if the firm fails to respond adequately and
immediately when the agency expresses concern. It also illustrates the fact
that firm measures can and will be taken against a firm merely because the
quality standards have been contravened, and not because there was nec-
essarily any risk to patients:

FDA News, March 4th 2005. In a response to ongoing concerns about manufac-
turing quality, the Food and Drug Administration (FDA) and the Department of
Justice today initiated seizures of Paxil CR and Avandamet tablets manufactured
by GlaxoSmithKline, Inc. (GSK). Manufacturing practices for the two drugs,
approved to treat depression and panic disorder (Paxil CR) and Type II Diabetes (Avandamet), failed to meet the standards laid out by FDA that ensure product safety, strength, quality and purity.

“FDA and the Department of Justice will not allow drug manufacturers to ignore our high public health standards for drug manufacturing,” said John M. Taylor, FDA Associate Commissioner for Regulatory Affairs. “Once we discover a company is not following the standards, which were created to ensure safety and quality, we expect them to correct the deficiencies in an expedited manner. American consumers deserve the best health care products on the market today, and companies that are not adhering to these standards cannot assure FDA and American consumers of the quality of their products.”

FDA is not aware of any harm to consumers by the products subject to this seizure and it does not believe that these products pose a significant health hazard to consumers. Consequently, FDA urges patients who use these two drugs to continue taking their tablets and to talk with their health care provider about possible alternative products for use until the manufacturing problems have been corrected. FDA has determined that neither product is medically necessary and that alternative products are available for consumer use.

The agency is concerned that GSK’s violation of manufacturing standards may have resulted in the production of poor quality drug products that could potentially pose risks to consumers. Among the violations noted during FDA’s latest inspection was the finding that the Paxil CR tablets could split apart and patients could receive a portion of the tablets that lacks any active ingredient, or alternatively a portion that contains active ingredient and does not have the intended controlled-release effect. Additionally, FDA found that some Avandamet tablets did not have an accurate dose of rosiglitazone, an active ingredient in this product.

The seizures follow warrants issued by the U.S. District Courts for the District of Puerto Rico and the Eastern District of Tennessee. The seizures were executed today by the U.S. Marshals Service at GSK’s Cidra, Puerto Rico manufacturing facility, its Knoxville, Tennessee distribution facility, and a Puerto Rico distribution facility. GSK has voluntarily recalled some of the affected lots of Paxil CR and Avandamet; however, it has failed to recall all affected lots of these products. This failure on the part of GSK resulted in today’s seizures by federal authorities.

4.3. Establishing the Safety of Drugs

4.3.1. The legal concept of safety

Section 2.2.3 referred to a case in the English High Court regarding thromboembolic injury suffered by women using the third-generation oral contraceptives. That case turned on the question as to whether these products
possessed the degree of safety which “persons generally” were under European Product Liability Law entitled to expect, and it was clear that this expectation was in turn based on past experience with the widely used second-generation products. The latter had attained a degree of safety that the community had come to regard as acceptable, as reflected in their widespread use, and “persons generally” had a right to expect that a subsequent product would not be significantly less safe. Safety, as noted in Section 4.1, is not an absolute concept where drugs are concerned since all have adverse effects, and in considering whether a product is acceptably safe one must have some basis for comparison with what already exists, while the degree of risk which may exist must often be weighed against the benefit that the medicine can provide. Many subtle cases are on record and they can give rise to lengthy disputes:

The analgesic dipyrone (metamizole), introduced early in the twentieth century and very widely used by the public in some parts of the world, was found to induce blood dyscrasias in some patients. Because it was widely used without medical prescription and was especially popular in countries without sophisticated systems for adverse reaction reporting, the incidence of dyscrasia could not be estimated with any accuracy. An “international agranulocytosis study” sponsored by the manufacturer, which suggested that the risk was very low, was both attacked (Offerhaus 1987) and as vigorously defended (Levi and Shapiro 1987). In most industrialised countries the drug was restricted or removed from the market but elsewhere it remained popular. In the critical view the essential reason to reject the drug, irrespective of the statistics, was the fact that other simple analgesics were as effective without exposing the user to these risks at all.

In such cases the manufacturer may be better placed than most to gather and examine the evidence of risk, and withdraw the drug from the market if it is verified. It is equally obvious, however, that where a drug remains highly profitable after a long period he may be hardly motivated to do so, especially as long as statisticians can be recruited who are willing to defend the product. In such an instance, and if there is no public health interest in retaining the drug on the market, unusual forms of pressure may be applied on the part of the health authorities in order to ensure that action is taken:

An early but illustrative case is that of the disinfectant clioquinol which over a period of more than forty years enjoyed massive and worldwide popularity as an oral remedy and prophylactic for non-specific (“tourist”) diarrhoea. Evidence of efficacy with internal use was little more than anecdotal. There was indeed some reason to believe that in long-term use clioquinol might actually induce diarrhoea, thus setting in motion a vicious circle, but the problems were not widely known
and drug regulation was still at an early phase of development. From 1960 onwards however, a neurological condition known as Subacute Myelo-opticoneuropathy (SMON) became frequent in Japan, proceeding to paralysis, blindness and sometimes death. An official enquiry into the cause of the disease led to the discovery of a clioquinol metabolite in the urine of the victims, and a close correlation was subsequently found between use of the drug (which in Japan was unusually heavy) and the occurrence of the disease; cases were also reported in other countries. (Soda 1980, Dukes 1981) The drug was rapidly prohibited or withdrawn in Japan and in many western industrialized countries, but continued to be produced on a large scale for use elsewhere. Ultimately, prolonged pressure by officials of the World Health Organization appears to have led to corporate reassessment of the situation and the manufacture was after a number of years discontinued. (Dunne 1993)

Where a drug is shown, rapidly and convincingly, to bring with it disproportionate risks, a manufacturer will commonly withdraw it without protest and even at his own initiative, believing this to be in the common interest. Serious conflicts between the public and the commercial interest can however arise where the business interests at stake are large and long-standing, and especially where the proof of injury is less than absolute. The legal and other mechanisms which might provide a basis for global public action are still not in place, although much-publicized restrictive actions in one major country or region are often emulated in another.

As discussed in Section 2.2.3, the legal basis for a manufacturer’s liability to a user for a defect in his product (including the ability to injure) has to some extent shifted in recent years. Traditionally, he might be found liable in negligence, such as failure to detect the risks associated with his drug, failure to correct them or to warn of them. That is still the case in much of the world. In the European Union, however, he may be found liable if his product does not possess the degree of safety which persons generally are entitled to expect. In either situation it is clear that the manufacturer has a duty to examine the safety of his product and to act according to his findings. Where medicines are concerned that duty is also specifically imposed by drug legislation and has been amply confirmed by the courts.

Periodically, there is discussion as to the legal situation arising when a drug is dispensed for a purpose other than that approved by the regulatory authorities. Use for such a “non-approved indication” is generally regarded as being at the physician’s discretion and is not prohibited by drug law. However, if a serious adverse reaction results, the patient will probably not be able to bring a case against the manufacturer alleging that his drug is defective; according to some older American case law, such a departure from the official standards of safe and effective drug use may be
held to constitute prima facie evidence of negligence. The issue has been discussed in legal, medical and political circles without being clearly resolved. A relevant question for a Court will clearly be whether occurrence of the injury was attributable to the drug’s use in a particular non-approved indication or not. If so, the patient might be able to bring a case against the prescriber rather than the manufacturer of the drug, e.g. if the prescribing was ill-considered. Cautious pharmaceutical firms, for their part, have sometimes distanced themselves, with good reason, from all non-approved uses of their drugs.

Many major drug manufacturers have furnished prescribers and pharmacists alike with letters of indemnity undertaking to defend against and pay any claims resulting from the use of their drugs. A careful reading of these letters limits the liability of the manufacturer to the approved use of the drug. (Nielsen 1986 at p. 20)

**4.3.2. Physical, social and mental injury**

Before considering further the issue of duty as regards adverse reactions it is helpful to make a distinction between two main manifestations of drug injury since the problems with each have proved to be somewhat different. The most concrete and readily recognized form of drug injury is **physical**. Even though there may be doubt as to causation, the fact of the injury – be it liver damage, gastric perforation or thrombosis – is as a rule incontrovertible. Methods for the detection of adverse reactions are also heavily attuned to detecting physical damage. Where on the other hand a medicine causes some change in **social or mental functioning** or induces some form of **dependence or addition**, this may be more difficult to recognize, especially where the drug has itself been given as a treatment for some mental or behavioural condition. The problem has come strongly to the fore in the last half century, first with the benzodiazepine tranquillizers and more recently with the SSRI antidepressants.

Medawar and Hardon\(^7\) have briefly summarised a century and a half of problems in this field:

\[
\text{“Between the 1860s and 1960s, doctors treated mental distress by prescribing alcohol and opium, then morphine, heroin and cocaine. Later came chloral,}
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6 Mulder v. Parke-Davis & Co., 181 N.W. 2nd 882 (1970).
7 I am grateful to Charles Medawar and Anita Hardon for much of the material in this subsection.
bromides, barbiturates and many similar drugs. Bar alcohol, each of these
drugs was also used to treat addiction – and later found to cause it too.”
(Medawar 2004 at p. 11).

The barbiturate sedatives were widely used from 1905 until about 1970. As late as
1941, standard medical texts declared that addiction to these drugs probably did not
occur (Goodman Gilman 1941), but by 1950 addiction to high doses had been
proven and by 1958 “chronic barbiturate addiction” had been demonstrated. In
1957 Hoffmann La Roche introduced the first benzodiazepine tranquillizer, chlor-
diazepoxide (Librium) and many benzodiazepines followed either as daytime seda-
tives or nighttime hypnotics (Medawar 1992). The belief was widely propagated
that these drugs did not produce dependence and they largely replaced the barbitu-
rates for this reason. In fact addiction had been demonstrated from 1961 onwards
but was dismissed by investigators associated with the company as occurring only
with excessive doses or in addiction-prone personalities. By 1973 the Third US
District Court of Appeals in Philadelphia, considering a move to have two benzo-
diazepines listed as controlled drugs, noted that they produced euphoria, tolerance,
withdrawal reactions and paradoxical rage and had a substantial potential for abuse;
(Pekkanen 1973) nevertheless, by 1979 benzodiazepine use in Britain alone peaked
at 30 million prescriptions yearly. The Roche company long continued, through its
associated experts, to deny any significant dependence risk (Marks 1978); the dan-
gers however became increasingly clear with the introduction of short-acting ben-
zodiazepines where the withdrawal reactions appeared earlier and were more
violent. Agitation, amnesia and psychotic reactions, including murderous and sui-
cidal behaviour, were documented. There has since been massive litigation against
the manufacturers of the benzodiazepines. Though some cases have been side-
tracked (notably by the withdrawal of legal aid to 12,000 litigants in Britain) very
large sums have been paid out in damages. The injuries concerned were matters
which could to a large extent have been recognized, acknowledged, and publicized
many years earlier and thereby largely avoided. However, many millions of patients
have for much of their lives become accustomed to a tranquillized state in which
they are cocooned from worry and stress and concerned about the effects of with-
drawing the drugs; so long as their physician is willing to continue to prescribe ben-
zodiazepines they have therefore seen no reason to complain.

The history of the SSRI antidepressants, which is still ongoing, is
interwoven with that of the benzodiazepines:

It had long been clear that physicians were confused between “anxiety” and
“depression”, particularly since they could co-exist and the clinical picture varied.
During the period of ascendancy of the tranquillizers they had been used for “anx-
iety” while depression had been treated mainly with the “tricyclic antidepressants”
which were effective but somewhat toxic; both types of drug were often given
together. In 1989 the first of a new class of drugs – termed by their makers “select-
ive serotonin reuptake inhibitors” (SSRI) was introduced to treat depression.
Fluoxetine (Prozac) was followed by others including paroxetine (Paxil) and ser-
traline (Zoloft). There has been criticism both of the literature claiming to prove
efficacy and of the hypothesis that depression is linked to serotonin levels. Since it is well known that the majority of cases of true depression recover spontaneously, the true indications for treatment are limited, but sales of the various SSRI inhibitors have attained levels similar to those reach by the benzodiazepines at the peak of their popularity. Popular books, the mass media and some advertising have portrayed the SSRI inhibitors as being suitable for the relief of various forms of unhappiness and worry and have disseminated the notion that these constitute depression; there is also a wide public impression that the products induce a marked form of euphoria ("the happiness pill.") However Medawar (2004) and others have collated the considerable evidence that this type of product in fact induces a serious form of dependence; there have been numerous reports of severe withdrawal reactions and suicides (including children) and as of April 2004 GSK was facing 1500 single multidistrict cases in California alone relating to alleged withdrawal reactions with paroxetine (Paxil). (Scrip 2004c,d).

The above histories illustrate the fact that the study of drug safety is by no means a simple question of collating and reporting unpleasant physical symptoms. The unwanted effects on an individual, especially when they concern states of mind, can be extraordinarily difficult to recognize as such; they may even be mistaken for welcome effects and underlie a demand for the product concerned, a demand that can all too easily be further stimulated.

4.3.3. Initial evidence of safety

At the present day the initial evidence as to the degree of safety or risk presented by a new drug is based primarily on the study conducted by or under auspices of the manufacturer prior to its introduction. The principal elements of experimental proof in safety matters of safety, as embodied in present-day regulatory requirements, are briefly summarized in Table 4.B, alongside the types of evidence which may demonstrate efficacy.

At the time when the marketing decision has to be taken, either by the manufacturer or the regulatory agency, the difficulty of extrapolating from the available data to the future patent population is only one of the problems to be faced. One difficulty concerns the scientific dependability of the findings; particularly for the regulatory agency it may be impossible to assess the trustworthiness of an investigator with whom it has no contact, or of the report which has been written on the basis of his work. Another arises because much of the experimental material pertains to animals, and the range of patients to whom the drug has been administered is never fully representative of the patient group who will use it in the field. A third problem is however to decide what degree of risk would be acceptable, even if one could calculate it reliably. For a nasal spray providing mild relief for the
Table 4.B
Elements Contributing to Proof of Efficacy and Safety

| Animals | Human Subjects |
|---------|----------------|
| **Pharmacology** | **Phase 1: Clinical Pharmacology** |
| Action relevant to proposed therapeutic use | 20/50 subjects |
| Other actions on main systems | Healthy volunteers (or patients) |
| Interactions with selected drugs | Pharmacokinetics |
| Pharmacokinetics | Pharmacodynamics |
| **Toxicology** | **Phase 2: Clinical Investigation** |
| Single dose (acute toxicity, various doses) | 50–300 subjects |
| Repeated dose (from subacute to long-term) | Patients |
| **General** | Pharmacokinetics |
| • Subacute, intermediate, long-term | Pharmacodynamics |
| • Two or more mammalian species | Rising dose studies (Efficacy/Safety) |
| • Nature of effects at post-mortem | **Phase 3: Formal Therapeutic Trials** |
| • Duration proportional to proposed use | Randomised controlled design |
| • Human dose level. toxic level, | 250–1,000 or more subjects |
| **Intermediate** | Patients |
| **Special toxicology** | Efficacy studies on a large scale |
| • Mutagenicity | Safety |
| • Carcinogenicity | Comparisons with other drugs |
| • Reproduction studies | **Phase 4: Post-marketing studies** |
| **Notes:** | 2,000–10,000 or more subjects |
| a. The use of human subjects or animals in studies is only ethically justified if the study serves a serious purpose and is sufficiently well designed and performed to achieve that purpose. General ethical aspects are considered in Sections 9.1 and 9.1 |
| b. For some purposes a study will only be of value if statistically analysed. |
| c. Long-term recording of clinical observations must be arranged for patients who cannot be included in formal studies but who may incidentally be exposed to the drug (such as pregnant and lactating women, children, patients with serious organic disease) |
| d. For fixed combinations, the mixture should if possible be tested in special studies against its components |
| e. Bioequivalence and bioavailability studies may be performed to examine the effect of changes in pharmaceutical formulation or to compare two similar formulations |
| f. If the drug is likely to be used in special conditions which could affect its performance or introduce risk, it should undergo supplementary testing in these conditions (e.g. tropical climate, genetically distinct population) |
common cold, one fatality in ten thousand patients will presumably be unacceptable, whereas for a cytostatic capable of inducing marked remissions in ovarian cancer one fatality in ten may have to be accepted.

The acceptability of the risks which the sale of a drug entails is dependent on the seriousness of the disease or disorder which it is intended to cure or to combat. The more serious the illness, the greater the risk one is justified in taking. Insomnia is not a serious disorder; a sleeping tablet must not present more than negligible risks.8

These non-statistical expressions of risk will also come to the fore again if at a later date the medicine is the subject of product liability claims in court. In most cases the estimate will have to be verbal (“frequent”, “rare”, “occasional”) rather than statistical because nothing more is feasible.

The duty to investigate adverse effects certainly comprises more than mere literal conformity with such official standards, which cannot provide for every possible future situation; it also involves an obligation to perform those studies which seem indicated in view of all that is known as to the characteristics of the product, the purposes for which it is to be used, and the population groups most likely to be treated with it. This will mean for example that:

a. any indication of risk which is obtained in routine studies should be followed up with specific investigations to confirm or exclude the risk. Once evidence emerged, for example, that beta-blockers could seriously aggravate asthma it became incumbent upon any firm developing or marketing a beta-blocker to quantify this risk for its own product
b. a drug which is chemically or pharmacologically closely related to one already known to cause a major risk must be carefully evaluated on this score; any new non-steroidal anti-inflammatory drug might, for example, be expected to cause gastric complications, and a new neuroleptic must be expected to cause tardive dyskinesia, until or unless the contrary is proven
c. a drug which is likely to be used in a particular risk group of the population must be studied in that group. An anti-rheumatic drug

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8 Legal commentary on the Netherlands Halcion cases in *Ned. Juristenblad*, 9 February 1990, No. 6; pp. 225–229. (In Dutch).
is for example likely to be used predominantly in the middle-aged and elderly, and it is insufficient to study it in young subjects (WHO/EURO 1988); failure to live up this standard perhaps explained the severe problems with the anti-rheumatic drug benoxaprofen in 1982 (Dukes 1984). Similar special standards will apply if a drug is intended for use in pregnant or lactating women or in children (see Section 4.3.7)

It is clear that if any evidence of fault or negligence is recognized during a clinical trial or subsequently, it will be the sponsor’s duty to take whatever action is necessary to protect the participants or to prevent incorrect information from the study being passed on. Exceptionally the error may be such as to play a role in subsequent withdrawal of the drug:

In March 2001 Johnson & Johnson and Organon voluntarily withdrew the surgical muscular relaxant Raplon (rapacuronium) from the US market. An element in the decision was “… a strong probability that the pharmaceutical company Organon was negligent in the performance of Phase III clinical trials of the drug and post-marketing surveillance. Patients who died or suffered brain damage from surgery in which Raplon was administered from August 1999 until April 2001 or physicians who administered the drug to such patients have a strong scientific and medical basis for complaint against the company”. (Drugintel 2001)

4.3.4. Adverse reaction monitoring systems

Up to the time of the thalidomide disaster in 1960–1961 there had been no systematic means of collecting information on adverse effects produced by medicines which had already come into use. Individual practitioners observing unexpected and unwanted effects might report them in a journal letter, and an occasional study might be performed and published of an unwelcome phenomenon, but that was all. Within companies one might find a “complaints register” in which reports of apparent problems of all types were collected, but again unsystematically. From 1964 onwards however a series of countries established national adverse reaction monitoring centres and invited practitioners to report suspected adverse reactions for evaluation. As a rule such a centre would also communicate the reports in outline, without identifying names, to the companies concerned and seek their comments. In the United States the FDA considered it appropriate for physicians to hand their reports to the company’s travelling representative and the firms themselves were obliged to pass these reports to the FDA; physicians however also had a right to
report to the FDA directly if they so wished, though only a minority did so. The World Health Organization established an International Centre (in Geneva, later in Uppsala, Sweden) where the reports from the national centres could be collated and examined; as of 2004, 55 countries were contributing to the system. The European Union has its own centre (EUDRA Vigi- lance), processing reports from national agencies. More recently, following successful experience in Sweden with direct reporting of adverse reactions by patients, agencies have begun to establish contacts with the public in both directions, both receiving reports and making Drug Analysis Prints publicly available. (Yellowcard 2005)

The legal framework for pharmacovigilance of medicinal products for human use in the Community is given in Council Regulation (EEC) No 2309/93 and Council Directive 2001/83/EC and is based primarily on ICH guidelines. Both the marketing authorisation holder (MAH) and the competent authorities are obliged to maintain pharmacovigilance systems and all relevant information should be shared between them, as well as with other EU and EEA member states. The marketing authorisation holder must ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary. The marketing authorisation holder should have permanently and continuously at its disposal in the European Economic Area (EEA), a “qualified person” responsible for pharmacovigilance who if not medically qualified should report to, or have access to a medically qualified person. National regulations in some Member States require in addition a nominated individual in that country who has specific legal obligations in respect of pharmacovigilance at a national level. The qualified person is responsible for the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the marketing authorisation holder, including medical representatives, is collected and collated in order to be accessible at least at one point within the Community for the preparation for competent authorities of the Member States, where the medicinal product is authorised, of the adverse drug reaction (ADR) reports, Periodic Safety Update Reports (PSURs) and company sponsored post-authorisation study reports. Ongoing pharmacovigilance evaluation ensures provision of information requested by the authorities in the countries where the product is marketed, including figures on sales and prescriptions if required. The marketing authorisation holder is responsible for reporting suspected adverse reactions to the authorities of the Member States and the European Agency. For medicinal products authorised through centralised or national procedures, including through mutual recognition, suspected adverse reactions received from health-care professionals should be reported. Spontaneously reported suspected adverse reactions, suspected adverse reactions from post-authorisation studies and those reported in the world-wide literature are included. A reaction is suspected if either the reporting health-care professional or the marketing authorisation holder believes there is a possible causal relationship.
between it and the drug in question. Spontaneous reports of suspected adverse drug reactions received from health-care professionals should be reported even if the marketing authorisation holder does not agree with the reporter’s assessment of a possible causal association, or if the reporter has not provided a causal assessment. Adverse events which are not suspected of being product related by the health-care professional attending the patient should not be reported unless the marketing authorisation holder has reason to believe that a causal relationship is possible. If the marketing authorisation holder is aware that a health-care professional has reported a reaction to one of its products directly to the authority of a member state, the marketing authorisation holder should still report the reaction, informing the authority that the report is likely to be a duplicate of a previous report. In this situation it is essential for the marketing authorisation holder to provide all the available details including any registration number provided to the reporting health-care professional by the authority, in order to aid identification of the duplicate. Marketing authorisation holders are expected to validate and follow up all serious reactions reported by them to the authorities. All available clinical information relevant to the evaluation of the reaction should be provided.

All expedited reports should be reported immediately and in no case later than 15 calendar days from receipt. The marketing authorisation holder should report, on an expedited basis, all serious suspected adverse reactions, occurring within the European Union and brought to its attention by a health-care professional to the competent authority in the member state in whose territory the incident occurred. For mutually recognised products or products which have been the subject of a referral, these should additionally be reported to the Reference Member State, in accordance with Article 104 of Council Directive 2001/83/EC. The marketing authorisation holder should report, on an expedited basis, all suspected serious unexpected adverse reactions occurring in the territory of a non-EU country and brought to the marketing authorisation holder’s attention by a health-care professional in such a way as to be available to the Agency and to all Member States where the medicinal product is authorised. All other ADR reports do not need to be reported on an expedited basis, but should be reported on request or as line listings according to the section on periodic safety update reports. Reports from the worldwide literature in accordance with the provisions of section 1.2.1 are considered to be reports of which the marketing authorisation holder can reasonably be expected to be aware and have knowledge. The marketing authorisation holder is expected to screen the world-wide scientific literature (see section 1.2.2) and report promptly published suspected serious adverse reactions associated with the use of the active substances(s) of its medicinal products, as relevant to the categories identified in Section 1.2.2.1 i. and ii. above. A copy of the relevant published article should be provided in a language acceptable to the member state. The MAH is therefore required to report all serious adverse reactions which have occurred within the EEA to the Member or EFTA State in whose territory the incident occurred and all serious unexpected reactions from outside the EEA to all Member States where the product is authorised and to the Agency. As with other reports from outside the EEA, these reports should be provided electronically to the Agency making use of the data-processing network foreseen in Article 105 of Directive 2001/83/EC.
Reporting forms acceptable to the competent authorities of the Member States, and to the Agency for centrally authorised products, should be used. In exceptional cases, when a reported ADR impacts significantly on the established safety profile of the product, the marketing authorisation holder should indicate this in the report.

Reports on medicines registered in EU/EFTA member states are accessible to the companies holding marketing authorizations through the EMEA’s central computer database Eudra Vigilance.

There has been criticism of an EU provision that a firm having new information on a safety issue need to only inform the national agency where the drug was first assessed for the Union, leaving this agency to inform others. It could be advisable for a firm experiencing a serious problem to inform all agencies at the same time to avoid delay (Tuffs 2001).

Further experience will show to what extent these extensive provisions in the European Union, with the major involvement both of national centres and of industry, will succeed in improving the performance of adverse reaction monitoring without proving excessively burdensome on the parties.

4.3.5. **Role and duties of industry in ADR monitoring**

Within companies there was for many years a very variable level of activity as regards the monitoring and reporting of adverse reactions; some firms remained with the traditional “complaints register” unless or until a regulatory agency required them to play a more active role. America’s FDA was the first to require active industrial participation, to the extent that the majority of field reports arriving from practitioners in the new adverse reaction monitoring system set up by the agency in the mid-1960s (later termed “MedWatch”) were expected to be delivered by doctors through company detailmen; in Europe on the other hand most reports from the field were submitted to the national agency directly.

For a long time there was to the outside observer no evident difference in the results delivered by the two systems, though both were characterized by very considerable under-reporting. Both had the fatal weakness that one never knew the degree of under-reporting or the turnover of the drug, so that the frequency of an adverse effect could not be calculated. Both systems produced a useful but very small cross section of the adverse effects actually occurring. Each had some notable achievements in identifying new adverse reactions early, but each clearly missed a great deal. Witnesses in litigation who gained access to company records were able to
report in a limited circle to what extent companies had failed to pass on adverse reaction reports to the FDA after discarding a proportion for reasons of varying validity, but this did not become general knowledge.

Only towards the turn of the century and thereafter was the reliability of industry’s input into the post-marketing surveillance of adverse reactions seriously questioned. The doubts arose not primarily from the formal monitoring systems but from (initially anecdotal) evidence that major firms had withheld vital negative data on a series of important drugs. To cite a selection of the events which became public knowledge:

In 1959, Messrs Wallace and Tiernan had marketed a tranquillizer (Dornwal) in the U.S. despite warnings from staff experts that it could cause serious and possibly fatal liver damage; the company failed to report the risk to the F.D.A. The firm was subsequently found guilty on criminal charges. (Silverman and Lee 1974)

In 1991-2 a Federal inquiry in the US confirmed earlier evidence that Upjohn had suppressed in its internal archives early data on the ability of its record-selling hypnotic Halcion to induce psychotic reactions. (FDA 1992)

Prior to 2000, as later evidence showed, Warner-Lambert had failed to reveal what it knew about liver toxicity caused by Rezulin, which led to the drug’s withdrawal from the market (Chernavsky 2005)

From 1980 onwards, a number of companies had, as noted above, been less than open as regards the risks of their benzodiazepines (Medawar 1992, Revill 2004; see also sub-section 4.3.2. above).

In 2004 it appeared that Merck had delayed by four years the release of its information on the cardiovascular effects of Vioxx (rofecoxib) (Jüni et al. 2004, Horton 2004)

In 2004 there was a public call on the FDA for a criminal investigation of AstraZeneca for allegedly delaying the submission of reports of serious reactions to Crestor (rosuvastatin) (HRG 2004)

In 2004, again, the media reported that Lilly had long been aware of the potential of Prozac (fluoxetine) to precipitate suicide (CNN 2005).

Three expert witnesses involved in drug injury litigation and interviewed for the present volume had between 1995 and 2001 the opportunity to examine internal U.S. company records of relevant adverse reaction reports received from physicians; all had observed that a high proportion of these were discarded for trivial reasons and were therefore not submitted to the FDA (Interviews 24, 25, 26).

It is primarily against this background that a serious demand has arisen for a rethinking of the entire system of adverse reaction monitoring
and the duties accorded to industry in that system. Were the system inher-
ently strong and capable it might be able to withstand a degree of abuse. An
authoritative paper in the JAMA late in 2004, however, set the sponta-
neous reporting system alongside the other forms of post-marketing sur-
veillance and industry’s role in them and found a bleak picture:

The inadequacies of the postmarketing surveillance system (i.e. FDA’s MedWatch
program with passive collection of spontaneous reports of adverse drug reactions)
for ensuring safety are well known and include: reliance on voluntary reporting of
adverse events by physicians and other health care professionals; poor quality of
submitted reports, often with inadequate documentation and detail; under-report-
ing of adverse outcomes with capture of only a small fraction of adverse events
that actually occur; difficulty in calculating rates of adverse events because of
incomplete numerator data on events, together with unreliable denominator data
on exposure; limited ability for spontaneous reports to establish causal relation-
ships; and difficulty in determining whether the adverse event resulted from the
drug or the disease it was intended to treat.

The major problem with the current system for ensuring the safety of medications
is that drug manufacturers are largely responsible for collecting, evaluating, and
reporting data from post-marketing studies of their own products. This approach
has many inherent problems. For instance, it appears that fewer than half of the
post-marketing studies that manufacturers have made commitments to undertake
as a condition of approval have been completed and many have not even been ini-
tiated. Moreover, despite the mandatory adverse event reporting system for com-
panies subject to the FDA’s post-marketing safety reporting regulations, drug
manufacturers may be tempted to conceal available data that may signal the pos-
sibility of major risks. In some cases, the FDA and drug manufacturers may fail
to act on that information and fail to conduct appropriate studies to examine a
potential risk rigorously and promptly.” (Fontanarosa 2004)

In the same issue of the same Journal, Psaty and co-authors, from their own expe-
rience with a major adverse reaction problem leading to withdrawal of a drug,
express similar concern. Summarizing the changes in recent years in the U.S. drug
regulatory environment aimed at more rapid approval of new drugs, they conclude
that that this approach “relied increasingly on the pharmaceutical industry to con-
duct its own post-marketing safety evaluation.” They raise the concern that “a
pharmaceutical company’s appraisal of suspected ADRs may be influenced by
economic considerations,” and call for legislation to “mandate and provide ade-
quate support for independent reviews and analysis of post-marketing data.”
(Psyt et al. 2004)

In the light of such concerns and evidence of practice to date, one is
bound to ask how dependable the industrial input from some companies into
the new European network and central register (EUDRA 2004) can be made.
In the US, a thorough re-examination of the process is now being undertaken
with a view to improve both its input and its central authority. It could be that the output of that re-examination could be of value in other countries as well, and helpful to the industry in putting its own house in order.

4.3.6. Safety in overdose

In some cases it can be relevant for a company to demonstrate that a product is relatively safe (i.e. as compared with other drugs) when given in excessive dosage, and this can outweigh certain disadvantages which the drug may possess:

In 1990 Britain’s Licensing Authority took restrictive action against the antidepressant mianserin because of adverse effects involving the blood. The Organon company challenged the restriction in court since it could be shown that, as compared with other antidepressant drugs, mianserin was notably safe in overdose; it was argued that this element should be taken into account when assessing the product’s overall safety. Both the Divisional Court and subsequently the Court of Appeal found for the company: the latter considered that under Section 28 of the Medicines Act the Licensing Authority had discretion to make comparisons with other drugs in forming its judgement, and that such comparisons could relate to safety in overdose where this was relevant. (Brahams 1990)

This particular case is exceptional to the extent that antidepressant drugs pose a special problem; many older antidepressants are dangerous in overdose, yet they have to be employed in patients who because of their depression are prone to commit suicide by taking the product in excessive doses; it is not clear that overdose is equally relevant when assessing the overall safety of drugs in other classes.

4.3.7. Pregnancy, lactation and beyond

Although thalidomide was the most notorious drug disaster involving pregnancy and the unborn child it was not the only one. In the years following, the “hormonal pregnancy tests” in use at the time were accused of disrupting some pregnancies by inducing uterine bleeding despite the presence of a foetus. The anti-nausea combination Bendectin (also known in modified form as Debendox), specifically intended to relieve nausea of

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9 For a fuller coverage of the issue of the manufacturer’s liability for second-generation injury see Dukes MNG, Mildred M and Swartz B (1998): Responsibility for Drug-Induced Injury, IOS Press, Amsterdam, Berlin and Oxford, at Chapter 12.
pregnancy, was withdrawn on suspicion (probably incorrect) of being a mild teratogen. (Bryan 1980) The most serious of the dramas was that involving diethylstilbestrol (DES) and it illustrates both the medical and legal problems which can surround drug-based teratogenicity: (Noller 1990, Anon. 2003)

Diethylstilbestrol was developed in the United Kingdom prior to 1940 as an effective low-cost oestrogenic hormone. For altruistic reasons the inventor left it unpatented and the drug was therefore soon marketed by many companies. Two U.S. physicians intensively propagated its use in pregnancy for treating threatened abortion or preventing habitual abortion. Few clinical trials were ever performed and the reasons for thinking that it might be useful in pregnancy were mainly theoretical; it is doubtful whether it had any useful effect whatsoever. However, some 12–15 years after the peak of its use had passed it was found that female children of these pregnancies tended to develop vaginal changes when reaching adolescence or adulthood and that these could become cancerous; there was also a high incidence of fertility disturbances among these daughters. Analogous changes were found in some male offspring. The scale of the DES disaster apparently much exceeds that of thalidomide, since the drug was used in many hundreds of thousands of pregnancies, with a particularly high incidence in the U.S.A. and The Netherlands (Buitendijk 1984). Some thousands of cases have been brought to court, most directed against former manufacturers but some against the U.S. FDA. Problems in dealing with liability arise mainly because of the very late manifestation of the injury (making it difficult to prove that the drug was taken) and the multiplicity of former producers. As with the thalidomide case, however, an important element in determining causality is the characteristic nature of the defect. Though the material is not homogeneous and strict statistical analysis of some of the epidemiological data inevitably points to shortcomings, there is overwhelming evidence of a cause-and-effect relationship. There is also increasing evidence that some defects can appear in the third generation, i.e. the grandchildren of the original users (Lynch et al. 1990).

In 1991 claims were prepared by some 100 “DES-granddaughters” in the U.S.A.; they alleged that maternal uterine hyperplasia, cervical stenosis and/or endometriosis caused by their mothers’ exposure to DES in foetal life were responsible for their own disorders. The first such claim to be heard, brought by a girl of 9 with cerebral palsy, was rejected by a majority of 6-1 in the New York Court of Appeals in February 1991. The majority judgement was not based on failure to prove causation but on grounds of practicality. To cite Chief Judge Sol Wachtler: “For all we know, the rippling effects of DES exposure may extend for generations. It is our duty to confine liability within manageable limits. Limiting liability to those who ingested the drug or who were exposed to it in utero serves this purpose. Judge Hancock, dissenting, considered the conclusion inequitable.  

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10 Enright v. Eli Lilly & Co., no. 19, N.Y. Court of Appeals, February 19th 1991.
The most obvious problem with ensuring safety in this field is that one cannot ethically perform studies in human pregnancy and that no dependable animal model for human teratogenicity has been found. The problems are compounded if the possibility exists of adverse effects in the third or later generations; not only is one without an experimental model, but the problems of proof and of identification of a defendant can be almost insuperable; the defects may be uncharacteristic, and both the drug and the manufacturer may by that time have been largely consigned to history, as was the case with DES.

At the present time, one can do little more than require the manufacturer to gather, wherever possible, reports of any case in which a new drug is – accidentally, negligently or because of a vital indication – administered to a pregnant woman, and record the outcome of the pregnancy. Until or unless certainty is ultimately gained that the drug is harmless in pregnancy, strict warnings must be given. The problems of the third and later generations, should they arise, will hopefully be covered by non-confrontational compensation schemes (see Chapter 12).

Similar considerations arise with respect to the use of drugs in lactation, but it could be valuable to know the extent to which the drug passes into the milk during breast-feeding; animal models would here be relevant, though they might not deliver helpful data on the effect of the medicine on the offspring.

4.3.8. Relevance of regulatory approval to civil liability for injury

For a period, pharmaceutical companies faced with claims for injury caused by their medicines sought to argue that, since their drugs had been approved by a national regulatory authority, they must be considered acceptably safe by a civil court. This view was indeed accepted in 1966 in US litigation regarding injury by MER-29 (triparanol):

...a drug, properly tested, labelled with appropriate warnings and approved by the Food and Drug Administration, and marketed properly under federal regulation, is, as a matter of law, a reasonably safe product. Accordingly, a person claiming to have suffered adverse effects from using such a drug, unless he can prove an impurity or an inadequacy in labeling, may not recover against the seller for breach of warranty...\(^{11}\)

\(^{11}\) Lewis v. Baker, 413 P.2d 400, 404 (Or. 1966) (en banc).
This view has been followed in a number of other American cases in later years\(^{12}\) but in others judges have exercised their discretion to allow the question of the safety or the benefit/risk ratio of the drug to be reconsidered by the jury as a question of fact. Some defendants have been hesitant to rely on the “prior approval” defence since they have not been entirely open with the FDA – as indeed Merrell itself had not (see Section 2.2.5). Plaintiffs, for their part, have sought evidence that defendants had not complied with statute law or FDA regulations, e.g. that the New Drug Application or subsequent data submitted to the FDA had been untruthful or incomplete:

In one American case, an action was brought on behalf of a small girl who had suffered irreversible brain damage as a result of convulsions induced by lidocaine. The Astra company had received earlier reports of such effects but on formal grounds had not passed on information concerning these effects to the F.D.A. as required by regulation. Though the jury concluded that the manufacturer had warned physicians, it found that Astra’s failure to report adverse reactions to the F.D.A. was a “substantial factor” in causing the plaintiff’s injury. The U.S. Court of Appeals in fact ordered a retrial because the jury had clearly reached a compromise verdict, but the Court fully accepted the argument that if the F.D.A. had been allowed to perform its statutory duty, the risks associated with the drug would have been better understood and more widely appreciated.\(^{13}\)

As Willig and Ruger have put it: “...failure to follow the law can make an important contribution to a product liability case” (Willis and Ruger 1994), though one should add that the statutory offence has not always been of great relevance to the injury complained of.

Authorities in other countries have pointed out that compliance with statute law and regulations does not exclude a drug manufacturer’s liability in civil law, since written law is only one source of a manufacturer’s duties. In particular, the general obligation to work according to the current state of the art may create duties which go beyond those officially imposed, especially where the drug licence or the regulations under which it was issued were not of recent date. The latter point was made judicially, though in *obiter dicta*, by the Arnhem District Court in The Netherlands in 1984 in one of the cases relating to alleged injury by the hypnotic drug Halcion:

The fact that Halcion had been registered by The Netherlands Committee for the Evaluation of Medicines and corresponding bodies abroad was regarded as one of

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12 Brown v. Superior Court, 245 Cal. Rptr. 412 (1988).
13 Stanton v. Astra Pharmaceutical Products (1983). US Court of Appeals, 3rd Circ. Nos 82-3364 and 82-3380.
the elements leading its conclusion that the drug was not disproportionately dan-
gerous. On the other hand, in the Court’s words, “. . . The control exercised by the
government authorities relates to the minimum standards which a pharmaceutical
must attain, and not the totality of prudence which is the duty of the party pro-
posing to market the drug. The fact that the Committee for the Evaluation of
Medicines had advanced no objections to the text of the introductory folder and
the package insert does not therefore mean that the Upjohn company cannot have
failed in its duty of care”\textsuperscript{14}

In a subsequent judgement on the same matter, the higher Court at Arnhem con-
cluded, despite the fact of registration by the authorities, that the manufacturer had
indeed committed a tort against users of the drug by causing it to be registered and
marketed without sufficiently warning the users or physicians respectively of the
dangerous and unpleasant adverse effects.\textsuperscript{15}

In dealing finally with the same matter, the Supreme Court of the Netherlands
explicitly stated that registration of a drug by the authorities does not abolish the
liability of the manufacturer at civil law.\textsuperscript{16}

In England the situation regarding pharmaceuticals is likely to be
influenced by several general legal principles derived from case-law
involving other sectors. As a general rule of English law, the fact that a
defendant has adhered to standards demanded by statute\textsuperscript{17} is not decisive
in cases where negligence is at issue. The limited pharmaceutical case law
seems to show that a court will in a civil case be prone to regard the
Licensing Authority’s approval of a drug as a preliminary finding of fact
which it will be “reluctant to criticize”,\textsuperscript{18} i.e. it is likely to prove influen-
tial in the proceedings, even if it is not determinative.

In summary, despite discrepancies between national systems, evi-
dence that a pharmaceutical company has conformed to its statutory obli-
gations regarding drug registration is likely to have persuasive effect in
cases where civil actions for negligence are brought against it, but it will
not determine the issue. Conversely, its failure to meet its obligations

\begin{footnotesize}
\begin{itemize}
\item[\textsuperscript{14}] Rechtbank Arnhem (Court of Arnhem), 28 juni 1984. Reported in \textit{Tijdschr v. Consumentenr.}, 1985, pp. 82–89 and \textit{Tijdschr v. Gezondheidsr.} 1985, pp. 109–114).
\item[\textsuperscript{15}] Hof Arnhem, 7 July 1987; reported in Tijdschr. Consumentenr., 1987, pp. 272–282 with
editorial annotation and in Tijdschr. Gezondheidsr., 1988, pp. 324–329); see also Ten
Hoopen M.M. and Rijken G.J., \textit{Ned. Juristenbl.}, 18 February 1988, Nr. 7), pp. 217–224.
\item[\textsuperscript{16}] Reported in \textit{Ned. Jur. Bl.}, 9 February 1990, afl. 6; pp. 225–229.
\item[\textsuperscript{17}] \textit{Bux v. Slough Metals Ltd.} [1974] 1 All E.R. 262.
\item[\textsuperscript{18}] \textit{Smith, Kline and French Laboratories Ltd. v. Licensing Authority}, [1989] 1 All E.R. 578.
\end{itemize}
\end{footnotesize}
under statute or regulation will undoubtedly cause a court to consider carefully whether there is a link between this breach of duty and the injury complained of, and it may discredit the defendant in the view of a jury.

4.4. Establishing the Efficacy of Drugs

4.4.1. The legal concept of efficacy

The law and the regulations require that the manufacturer shall demonstrate the efficacy of his drug; but for all the reasons defined above, the legislator is very reticent about defining what he means by it. The Netherlands lawgiver of 1958, already cited for his common-sense approach, required that a drug should have been shown to have the effect claimed for it “according to the standards of a reasonable man.” That comes remarkably close to the thinking of the European Product Liability Directive and the Statutes derived from it which two decades later (Chapter 2) declared that a product should have that decree of safety “which persons generally are entitled to expect.”

Continuing in this vein, one might expect the “reasonable man” to hope that a medicine will exert its effect on his illness to a useful extent – either curing him or alleviating his symptoms so that they are much less troublesome, and continuing to be effective for a long time when he uses it according to the instructions. He might also feel entitled to an effect that entirely outweighs whatever adverse effects the product may exert. These are reasonable demands from the user's point of view, yet they have led to difficult exchanges between some industrial applicants and regulatory authorities:

This applicant came with a non-steroidal anti-inflammatory drug that he wanted to register for use in rheumatoid arthritis. His longest clinical study to demonstrate efficacy was positive, but it had lasted only four weeks. The Chairman pointed out that that rheumatoid arthritis was a chronic condition and that patients would need it much longer; one would need to be sure that in the longer run it remained effective and well-tolerated. The applicant then suggested that as an alternative we register it for the indication “treatment of rheumatoid arthritis for up to four weeks”. The Commission considered this unrealistic. (Interview 16)

We had met this representative before when he presented a new drug for accelerating wound healing; his firm had tested it against an old product XX that was also supposed to heal wounds and they found it just as effective. The trouble was that

19 The late Mr C.J. Goudsmit.
we had no reason to believe that the old drug XX was itself effective so we stressed the need for him to do a trial against a dummy. We never heard any more of it. Then this time he came back with an application for a kale derivative to stop asthma attacks, and proudly showed us that his people had tested it against a dummy, proving that it was more effective. The difficulty this time was the difference was really very slight, and if the drug was effective at all then it was much less effective than the products we already had, like corticoid sprays and betamimetics and cromoglycate, so this time we asked him to produce a comparison with them. He got quite upset and brought a statistician to show that there really was a difference from the dummy, which got us into a discussion on differentiating between statistical significance and clinical significance. In the end they took us to Court, claiming that effectiveness as compared with a dummy was effectiveness in law. Happily, the Court saw sense and upheld us. (Interview 8)

It was a product to relieve intermittent claudication – helping old people who couldn’t walk very far without getting pain in their legs. After I had gone through all the statistics with him we agreed that the drug probably increased the mean walking distance for a while from 50 metres to 53 metres. But, said our medical colleagues, that’s not enough to be useful to a patient. The man from the firm was a smart cookie; “Well,” he said, “what if the poor chap lives 52 metres from the nearest letterbox? (Interview 23).

A product should clearly have the type of pharmacological effect and the potency which it is claimed, explicitly or by obvious implication, to possess; a product sold as an antibiotic or a corticosteroid must possess these properties to a clinically significant degree. Similarly, a product must have the therapeutic effect claimed for it, i.e. it must be generally effective in the disorders for which its use is recommended. These standards are set specifically by medicines legislation but they also flow from general commercial law (Chapter 2). If a drug does not attain these standards, and a patient can be shown to have suffered injury as a direct result of this fundamental shortcoming of the product (e.g. because of failure to recover from an acute and life-threatening condition), there will be a basis for claiming damages. If, for example, a patient in severe shock is treated with injections of a corticosteroid and his failure to respond can be traced to the fact that the substance in the ampoules administered, though described as a corticosteroid, had little or no such activity, there will be liability.

4.4.2. Warranties and guarantees

As noted in Section 4.4.1, efficacy is not an absolute quality and a drug will not produce the desired effect in every patient. A manufacturer cannot therefore be held liable for failure of treatment in an individual patient unless
it can be shown to be attributable to total inefficacy of the drug, or unless he has been so reckless as to claim or imply universal efficacy.

In the past it did happen that guarantees of efficacy were rashly provided. In the nineteenth century a British manufacturer offered the Carbolic Smoke Ball, which emitted aromatic vapours to prevent and relieve upper respiratory congestion; in an advertisement he offered £100 to any individual who, after exposure to the vapours, contracted influenza. A Mr Carlill suffered this experience and claimed the sum to which he was entitled, bringing an action for breach of warranty when the manufacturer refused to pay. The producer argued that there was no contractual relationship between him and the claimant. The Court of Appeal, however, found for the appellant on the ground that an offer had been circulated to the general public which ripened into a contractual relationship when a particular section of the general public had met the conditions attaching to the offer.20

Such offers are rare today, but one still encounters them in some parts of the world, though apparently in situations where the risk of the guarantee being taken up is remote:

In May 2003, the Hong-Kong based firm CK Life Sciences released Vitagain, a drug based on yeast technology that was claimed to strengthen the immune system sufficiently to protect individuals against severe acute respiratory syndrome (SARS). The company chairman issued a declaration that should a client successfully complete the 90-day treatment period and then contract SARS the company would make a compensatory payment from a “health maintenance fund” of 200,000 Hong Kong dollars (US$ 25,641). (PD 2003)

Bona fide firms have on some occasions offered more modest money-back guarantees in the event of failure of treatment:

In 1994 Merck Inc. offered to refund the cost of treatment with its anti-androgen finasteride for prostatic hyperplasia. The cost would be refunded if the drug failed to improve symptoms within six months or if the patient needed prostatic surgery within two years. A urologist commented that most cases of prostatic hyperplasia indeed reacted well to antiandrogen therapy, though a significant minority failed to improve at all. However, since most patients were only being treated for their symptoms, any subsequent assessment of benefit was bound to be largely subjective. A company spokesman noted that patients “had to comply with treatment at least three quarters of the time for the offer to hold”. (BMJ 1994)

There is some advertising for pharmaceutical products which carries with it such emphatic implied promises that an analogous situation could

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20 Carlill v. Carbolic Smoke Ball Co. (1893), 1 Q.B., 256.
on occasion arise\(^{21}\) and it is common in US litigation for statements of claim to allege that the defendant manufacturer has breached “express and implied warranties of merchantability and fitness for a particular purpose”\(^{22}\) which can rely heavily upon texts which appear to constitute a warranty. A relevant issue in this connection could be the custom of many manufacturers, noted above, to use extremely emphatic printed advertising texts and visual messages, while approved textual material from the data sheet is appended only in much smaller print. While a strictly formalistic approach would lead to the view that the small print counterbalances the exuberance of the main message, a court might more realistically look to the promises made or implied in those parts of the promotional effort which the physician or patient is most likely (and is indeed intended) to assimilate.\(^{23}\) It is indeed notable that courts in the United States, where “warranty” plays a more prominent role than elsewhere, have been willing to interpret various forms of promotional text as implying warranties. In the case of vaccines (see Chapter 9) the implied promise of efficacy is particularly strong.

The oral contraceptives constitute a special case, largely because their degree of efficacy is commonly claimed (and correctly assumed) to approach 100%.

Whether incidental failure of an oral contraceptive to have the desired effect could today in most systems of law result in a successful claim for damages (e.g., for “wrongful birth”) seems dubious, though it was a question which greatly exercised the minds of manufacturers of such products when a number of such actions were attempted unsuccessfully in the 1960s. In fact, no manufacturer ever seems to have claimed 100% efficacy for this type of product in so many words, and even though the chance of unwanted pregnancy is with most hormonal contraceptives very small indeed, any physician and patient is today likely to realise that it exists. It is of course clear that if the failure were demonstrably due to a manufacturing defect – e.g., if it could be shown that a manufacturer had in error released a batch of an oral contraceptive in which the active substance was missing – a different situation would arise.

\(^{21}\) See Dommering-Van Rongen L. (1982): *De patient/konsument en de produktaansprakelijkheid (The patient/consumer and product liability)*. Paper presented to the NIA symposium in Product Liability, 18 September. (*In Dutch*).

\(^{22}\) See for example Reeves v. Geigy Pharmaceutical, Eli Lilly and Gerald B. Moress: Court of Appeals of Utah, November 10th 1988.

\(^{23}\) Cf. McEwen v. Ortho Pharmaceutical Co. (1975), op. cit.
Firms selling drugs or health products outside the normal regulatory system tend to make extreme claims of efficacy but to complement these with reservations which are likely to exclude claims for liability;

Nebulised “Colloidal Silver”, claimed to be effective in treating respiratory disorders, is classified by the U.S. FDA as “not generally recognised as safe and effective”. It is nevertheless stated by the manufacturer in promotional material that “results have ranged from excellent to ‘near miraculous’”. However the explicit warranty is limited to product quality and “Use and/or results for any application are not guaranteed and no claims are made, other than that to state that “Col-Sil” “Supports and Helps Maintain a Healthy Immune System” as approved by the USFDA.” (CS 2005)

Products in the field of “alternative medicine” now frequently issue explicit medical disclaimers:

X is a recent development in the alternative health market, and thus most studies which could be a basis for inference are not double blind controlled studies, but instead anecdotal observations of benefits. As a result, medical claims cannot be asserted until more intensive studies are completed. Our products are believed by the manufacturer to provide significant user satisfaction based on testimonials and anecdotal reports from users. Accordingly, we must by law issue the following disclaimer: The firm does not make or imply any medical claims for products we manufacture. These products are not medicines/medical devices and cannot be relied on to supply medical benefits and are not a substitute for proper medical care. Thirty-day Money Back Guarantee on All Products! (based on Norso 2000)

4.4.3. Efficacy of “old” drugs

Doubts as to the stringency of efficacy requirements commonly arise when a regulatory agency sets out to assess an old drug that has been on the market for generations and has never been tested under modern clinical conditions, yet may have a placebo effect because of its long reputation. Agencies have generally shown some tolerance to such products, assuming that they will at a given moment die a natural death. Section 4.4.5 on “efficacy and compassion” is also in some cases relevant.

A further contested point, noted earlier in this volume, is whether a new drug should only be considered acceptable if it is as effective as (or more effective than) an existing product of the same type, or has some other unique virtue, for example, in terms of safety. For a time, as noted in Section 4.4.1, firms tended to argue that any product that was more active than placebo must be considered acceptable under the law. At the
other extreme was the argument that it was undesirable to accept any new drug unless it had clear advantages over those already on the market. In course of time, both extremes have been largely abandoned; as a rule a drug will be considered “effective” in terms of the law if it is clinically and genuinely useful – to an extent that the reasonable man will appreciate.

4.4.4. Proof of efficacy

The law demands that a drug be efficacious, yet there is very little litigation in which lack of efficacy is alleged; since a drug cannot be guaranteed to have the desired effect in every user this is understandable. On the other hand, regulatory agencies have repeatedly refused or withdrawn licences on the grounds of lack of proven efficacy; between a quarter and a third of applications are withdrawn for this reason, and some of these items appear on the market later as “health products” or “natural products” for which no proof of efficacy is demanded.

The fact, noted above, that field experience may make it necessary to revise one’s view of a drug’s efficacy (just as is the case with its safety margin) is poorly reflected in the law. As Britain’s House of Commons study of the industry has pointed out:

Drug companies may conduct their own Phase IV studies, comparing the efficacy of their drugs to others, but there is no mandatory requirement for the industry to investigate the long-term effects of their medicines in the community. (HoC 2005 at, para. 63)

This does not appear to presage any coming obligation to conduct Phase IV studies with all drugs; the duties imposed both by current European and American regulations to provide ongoing information to the agencies after marketing are likely to be considered sufficient, with formal post-marketing studies only being required where there is a special reason to carry them out.

The public’s belief in the efficacy of drugs in general and in the industry that produces them has wavered and varied. Despite the basic desire of a patient to believe that a medicine will be effective, there has at times been considerable public scepticism regarding the drug trade. For a long period it was engendered by the fact that the most visible and audible makers of drugs were the charlatans whom Daniel Defoe had encountered in the eighteenth century and the British Medical Association so vigorously condemned in the twentieth (Chapter 3). The patient’s understanding
of illness and of medicines has grown in the course of the years, but the totality of knowledge has grown at the same time, leaving him still very much dependent upon the good faith of others, and all too aware that he can be deceived. Trust in the industry and its products was probably at its highest in the brief era of the wonder drugs between 1940 and 1960 when penicillin, cortisone, poliomyelitis vaccine and the “pill” seemed to change the face of medicine forever. But then came thalidomide and the flimsy promises of the “feminine forever” oestrogens; perhaps not everything was as trustworthy as it had seemed.

Law and regulation function best when they provide judges with firm measures by which to judge real events, and clinical science is not always willing to provide those firm measures. To see Mr Justice May wrestling in London’s High Court with a pack of bickering statisticians unable to agree on clinical truth about oral contraceptives and thrombosis leaves one despairing about science but with a sneaking admiration for judicial common sense. And when a prestigious author notes in 2004 that the sponsor of an SSSI inhibitor is perfectly content to deposit it in the therapeutic arena if a mere two out of six trials point to its having some effect, then one can only wish for much judicial – and regulatory – common sense in the coming years.

This is not the place for detailed presentation of the technicalities of clinical-pharmacological proof. They are massively documented and widely agreed. Only when dealing with an individual medicine will one be able to decide precisely which clinical-experimental model and which degree of certainty will suffice if one is to conclude that this medicine is truly effective. Reasonable certainty that a drug is truly effective can only emerge from a complex of studies that have to be considered together; they complement each other and in some instances one may override another; in some situations particular studies may be superfluous, and in others additional work may be required. Table 4.B provides no more than an ultrasummary, for the present purpose, of the elements of proof likely to be needed to satisfy those implementing current legislation and regulation that a drug is effective.

4.4.5. Publication bias

A series of workers have examined the question as to whether clinical studies which have been conducted and published under the sponsorship of the pharmaceutical industry show bias in favour of the company product concerned. A systematic review of this work, conducted in 2003
by Lexchin et al. points strongly towards publication bias in sponsored studies:

... Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98–5.51; 18 comparisons). (Lexchin et al. 2003)

Various of those who have examined the matter find documented explanations for publication bias. Companies may select investigators who are known to favour particular drugs or therapies, comparator drugs with a lesser degree of efficacy may be chosen, parameters selected may be those most likely to favour the sponsor’s product, and unfavourable studies may be suspended or remain unpublished.

Whatever the explanation in any particular case, the issue is a serious one since the regulatory view on the efficacy (and safety) of medicines is so heavily dependent upon clinical investigations that have been conducted in this way, especially at the outset of a drug’s career. A company’s obvious duty to conduct and present its work in a balanced manner to the professions and to society generally has hitherto been regarded primarily as an ethical issue, but it is closely linked to its duties in law regarding the submission of evidence to the regulatory authorities. Current moves to ensure that all clinical trials are registered at the outset, (DeAngelis et al. 2005) so that they cannot subsequently disappear from the record, reflects the extent of concern on this matter. To judge from ongoing legal consultations it would seem extremely likely that in the near future the issue of liability for the deliberate distortion of evidence will be increasingly raised with the courts.

4.4.6. Efficacy and compassion

An ethical issue which does not yet appear to have reached the courts but is now actively in discussion relates to the situation of drugs which may have only a minimal therapeutic effect yet deserve to be available on compassionate grounds where no more active product exists. The issue has long been in debate in regulatory circles as regards products intended for the relief of symptoms related to senility and atherosclerosis:

Our Committee faced the problem years ago when we set out to assess an old “grandfather clause” drug, namely dihydroergotoxin, which they also called Hydergine or ergoloid mesylates. It had been sold for years to relieve mental symptoms in the elderly. The serious books didn’t mention it and the clinical work was pathetic, but the geriatric homes used it by the cartload. We were all set to
cancel the licence of right until we saw that the FDA in America had registered it. When we talked to Dr Crout, who headed the Bureau of Drugs at the time and was an eminently sensible man he agreed that Hydergine wouldn’t pass a real efficacy screen of the usual type, but it wasn’t inactive. When people who had been going downhill mentally, and knew it, suddenly found that they could tie their shoelaces again it gave them a boost. That was the sort of thing it seemed to do. So we registered it, and to my knowledge it’s still there. (Interview 5)

Prof. Søren Holm in Wales has raised much the same issue following a preliminary recommendation by Britain’s National Institute for Clinical Excellence (NICE) that a number of drugs currently used in Alzheimer’s disease are not sufficiently cost-effective to justify their continued use in the National Health Service. He comments:

Alzheimer’s Disease is not a nice disease to have for most patients, and caring for someone with Alzheimer’s is not easy. It is frightening to literally lose one’s mind, and it is a cause of great sorrow to see this happen in a spouse, partner or parent…

…NICE seems to have forgotten one of the central values in health care, the value of compassion. Among the many patient groups that suffer and die, only a few could make a stronger claim on our compassion than those who suffer and die from Alzheimer’s. Or, to put it in simpler terms, NICE has forgotten that it is not enough to be effective, one also needs to be compassionate and nice. (Holm 2005)

Compassion should indeed be an element both of medicine and of law.