

# United States



Harvey L Kaplan and John C Vaglio, Shook, Hardy & Bacon LLP

[www.practicallaw.com/2-383-9797](http://www.practicallaw.com/2-383-9797)

## REGULATORY OVERVIEW

1. Please give a brief overview of the regulatory framework for medicinal products/pharmaceutical products/drugs (as they are called in your jurisdiction), including the key legislation and regulatory authorities.

The United States Food and Drug Administration (FDA) (see box, *The regulatory authorities*) is responsible for protecting the public health by assuring the safety, efficacy and security of:

- Human and veterinary drugs.
- Biological products.
- Medical devices.
- Food.
- Cosmetics.
- Products that emit radiation.

While the FDA does not develop, manufacture or test drugs, it requires evidence of a new drug's safety and efficacy demonstrated through clinical trials of the drug on human volunteers (see Question 7) before it will approve a drug for marketing. Drug manufacturers submit reports of these drug studies so that the FDA can:

- Evaluate its data.
- Assess the benefit-to-risk relationship.
- Determine if a drug will be approved.

Within the FDA, the Center for Drug Evaluation and Research (CDER) oversees the research, development, manufacturing and marketing of drugs. Also within the FDA, the Center for Biologics Evaluation and Research (CBER) regulates all biologic products (see box, *The regulatory authorities*).

While the FDA enforces many statutes and rules that govern the regulation of pharmaceutical products, the primary legislation governing the FDA is the Federal Food, Drug and Cosmetic Act (FDCA) (21 USC § 301, et seq). A list of laws enforced by the FDA and related statutes is available at [www.fda.gov/opacom/laws/](http://www.fda.gov/opacom/laws/).

## PRICING AND STATE FUNDING

2. Please give a brief overview of the structure and funding of the national healthcare system.

There is no national healthcare system that covers all citizens. Most Americans have medical insurance through private insurance companies, which pays a percentage of healthcare costs. Employers may provide or subsidise the cost of medical insurance premiums. There are two government programmes, Medicare and Medicaid, which cover or assist with medical costs for the elderly, poor and disabled.

3. In what circumstances are the prices of medicinal products regulated?

Pharmaceutical companies are free to set their own prices within market demands. Anti-trust regulations overseen by the Federal Trade Commission (FTC) (see box, *The regulatory authorities*) apply to the marketing of pharmaceuticals. Generally, manufacturers and wholesalers negotiate with Health Maintenance Organisations (HMOs), large chain pharmacies and smaller independent pharmacies to set prices. There is also indirect influence through government control of drug reimbursements in Medicare and Medicaid programmes.

4. When is the cost of a medicinal product funded or reimbursed by the state? Please briefly outline the procedure and pricing for state funding or reimbursement (for example, is the reimbursement paid to the producer, pharmacist or end-user)?

Medicaid is a joint federal and state programme that provides medical assistance (including prescription drugs) for low income individuals who meet certain criteria. Under the federal Medicaid Drug Rebate Program, drug manufacturers must grant discounts on prescription drugs to state Medicaid programmes if they want to be eligible for Medicaid reimbursements. No federal funds are reimbursed to drug manufacturers although there is indirect governmental influence (see Question 3).

In January 2006, Medicare prescription drug plans were implemented. These prescription drug plans are available to all individuals with Medicare. Insurance companies and other private companies work with Medicare to offer these drug plans and prices. Like other insurance, Medicare prescription drug plans require payment of monthly premiums, deductibles and part of

the prescription cost. Assistance with payments associated with the Medicare prescription drug plans is available for individuals with limited resources.

## MANUFACTURING

### 5. Please give an overview of the authorisation process to manufacture medicinal products. In particular:

- To which authority must the application be made?
- What conditions must be met to obtain authorisation?
- Are there specific restrictions on foreign applicants?
- What are the key stages and timing?
- What fee must be paid?
- How long does authorisation last and what is the renewal procedure?

#### Application

Companies that manufacture drugs and human biological products are required to register their establishment(s) and submit to the FDA a listing of every product in commercial distribution (*section 510, FDCA (21 USC § 360)*).

#### Conditions

FDA Form 2656 is used for registration of a drug establishment. FDA Form 2657 is used for drug product listings. FDA forms are available at [www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html](http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html).

#### Restrictions on foreign applicants

All foreign drug establishments involved in the manufacturing, preparation, compounding, or processing of drugs or devices for importation into the US must register with the FDA (*21 USC § 360(i)(1)*). There are specific procedures set out for the registration of foreign drug establishments (*21 Code of Federal Regulations (CFR) § 207.40*).

#### Key stages and timing

A manufacturer must register with the FDA as a drug establishment using FDA Form 2656 within five days of beginning the manufacturing, preparation, compounding, or processing of a drug or biological product (*21 CFR § 207.20-21*). The registration must list every drug that is in commercial distribution by the establishment. The drug listing can also be submitted by the distributor of a drug manufactured or processed by a registered establishment.

#### Fee

An annual fee is allocated to each prescription drug establishment named in a New Drug Application (NDA) (*21 USC § 379h(a)(2)(A)*). Annual fees are available at [www.fda.gov/oc/pdufa/default.htm](http://www.fda.gov/oc/pdufa/default.htm).

### Period of authorisation and renewals

Each drug establishment must renew its registration annually (*21 CFR § 207.21(a)*). Drug listing information must be updated every June and December (*21 CFR § 207.21(b)*). Any changes in the manufacturing of drugs and their packaging are reviewed by the FDA. Manufacturers must notify the FDA in advance of these changes by filing a manufacturing supplement to a new or generic drug application.

### 6. What powers does the regulator have to:

- Monitor compliance with manufacturing authorisations?
- Impose penalties for a breach of a manufacturing authorisation?

The FDA has enforcement powers to ensure product safety, effectiveness and compliance with current good manufacturing practices (CGMPs). The FDA has statutory authority to:

- Seize any drug that is adulterated or misbranded when initially introduced into the market, while in interstate commerce or while held for sale (*21 USC § 334*).
- Enter any factory, warehouse or establishment in which food, drugs, devices or cosmetics are manufactured, processed, packed or held for introduction into interstate commerce, or to enter any vehicle being used to transport or hold such products (*21 USC § 374(a)(1)*).
- Inspect at reasonable times, within reasonable limits and in a reasonable manner, that facility or vehicle (*see bullet point above*) and all relevant equipment, finished and unfinished materials, containers and labelling (*21 USC § 374(a)(1)*).
- Collect samples of drug products (*21 USC § 372(b)*).
- Inspect records, files, papers, processes, controls and facilities related to drug products (*21 USC § 374(a)(1)*).

FDA inspections, procedures and policies are described in the FDA's Investigations Operations Manual (*see www.fda.gov/ora/inspect\_ref/iom/*) and also the FDA Enforcement Manual.

If a company fails to comply with CGMPs, the FDA can:

- Issue a warning letter.
- Initiate regulatory actions.
- Impose fines after an administrative hearing (*21 CFR § 17.1*).
- Suspend, revoke or fail to approve an application to market a drug.

## CLINICAL TRIALS

7. Please give an overview of the regulation of clinical trials. In particular:

- Which legislation and regulatory authorities regulate clinical trials?
- What authorisations are required and how is authorisation obtained?
- What consent is required from trial subjects and how must it be obtained?
- What other conditions must be met before the trial can start (for example, the requirement for a sponsor and insurance cover)?
- What are the procedural requirements for the conduct of the trial (for example, using certain medical practices and reporting requirements)?

Before beginning a clinical investigation of a new drug in human subjects, a study sponsor must:

- Submit an Investigational New Drug Application (IND) using FDA Form 1571 (available at [www.fda.gov/cder/regulatory/applications/Forms.htm](http://www.fda.gov/cder/regulatory/applications/Forms.htm)).
- Obtain FDA approval (*21 CFR §§ 312.2(a), 312.20, 312.21(a)(1) and 312.50*). An investigator cannot participate in a clinical trial until it provides the sponsor with specific information, including a completed, signed statement of investigation (FDA Form 1572) (*21 CFR § 312.53(c)*).

The investigator must agree to conduct the study according to the protocol, report any adverse experiences, and maintain adequate and accurate records. In addition, informed consent must be obtained from each study subject who will be administered the investigational drug (*21 CFR § 312.60*). An Institutional Review Board (IRB) must also review and approve all clinical studies before an investigator begins conducting research.

After submission of an IND, pre-approval clinical testing on human subjects consists of (*21 CFR § 312.21*):

- **Phase I.** Small studies of 20 to 80 patients to determine toxicity and pharmacological information.
- **Phase II.** Small studies of several hundred patients to determine safety and efficacy.
- **Phase III.** Large studies of several hundred to several thousand patients to determine safety, efficacy and adequacy of labelling.

After the FDA has approved a drug, Phase IV post-marketing studies can be conducted to collect additional information about the risks, benefits and optimal use of a particular drug (*21 CFR § 312.85*).

## MARKETING

8. Please give an overview of the authorisation process to market medicinal products. In particular:

- To which authority must the application be made?
- What conditions must be met to obtain authorisation?
- What are the key stages and timing?
- What fee must be paid?
- How long does authorisation last and what is the renewal procedure?

### Application

Manufacturers must obtain FDA approval of an NDA (FDA Form 356h) before marketing a drug. The application must include the information mentioned in *21 CFR § 314.50*. After an NDA is approved, there are ongoing requirements for the reporting of post-marketing adverse drug experiences (*21 CFR § 314.80*). Annual reports must also be filed (*21 CFR § 314.81(b)(2)*). FDA Form 356h can be found at [www.fda.gov/cder/regulatory/applications/Forms.htm](http://www.fda.gov/cder/regulatory/applications/Forms.htm).

### Conditions

The FDA will approve an NDA after it is satisfied that the drug meets the statutory standards for:

- Safety and effectiveness.
- Manufacturing and controls.
- Labelling.
- Bioequivalence (where applicable).

The FDA must use its judgement in determining the kind and quality of the data and information necessary for approval (*21 CFR § 314.105(c)*).

### Key stages and timing

The two main stages are:

- **IND review.** New drugs are tested for toxicity and efficacy on laboratory animals (for flowcharts of the new drug development and review process, see [www.fda.gov/cder/handbook/](http://www.fda.gov/cder/handbook/)). If the tests indicate that a drug may be effective and that it is reasonable to test it on humans, the manufacturer must first obtain the FDA's approval (*21 CFR §§ 312.2(a), 312.20*) by submitting an IND application (see *Question 7*) to the FDA (*21 CFR § 312.23*) (for a flowchart on IND Review Process, see [www.fda.gov/cder/handbook/ind.htm](http://www.fda.gov/cder/handbook/ind.htm)). The FDA must review IND applications within 30 days of submission and take appropriate action (*21 CFR § 312.40(b)*). If the FDA responds negatively, the IND does not take effect. If the FDA responds favourably or does not respond, the manufacturer can proceed with clinical testing on human subjects.

- **NDA review.** Once adequate safety and efficacy information is developed for a drug, the manufacturer must obtain FDA approval by submitting an NDA (see above, *Application*). Drug companies can submit their NDAs electronically. The FDA has 180 days to respond after an NDA is filed (21 CFR § 314.100(a)). The FDA interprets filed to mean when it is considered approvable by the FDA rather than when it was initially submitted by the manufacturer. The time from product conception to approval can range from a few years to 20 years.

### Fee

Fees are set by the FDA Prescription Drug User Fee Act. For fee information, see [www.fda.gov/oc/pdufa/default.htm](http://www.fda.gov/oc/pdufa/default.htm).

### Period of authorisation and renewals

Authorisation to market a drug continues unless and until it is withdrawn from the market, either voluntarily by the manufacturer or by the FDA, or the FDA withdraws its approval of an NDA.

## 9. Please briefly outline the abridged procedure for obtaining marketing authorisations for medicinal products. In particular:

- Which medicinal products can benefit from the abridged procedure (for example, generics)?
- What conditions must be met?
- What procedure applies and what information can the applicant rely on?

The following may apply:

- **Treatment IND.** This allows physicians to prescribe experimental drugs before approval under certain circumstances (21 CFR § 312.34(a)). Drugs may be available for use after Phase II testing is complete (see *Question 7*).
- **Fast track programmes (21 CFR § 312.80, et seq).** Fast Track designation is intended to expedite the FDA review of drugs designed to treat serious or life threatening conditions and which show potential to address unmet medical needs. This is accomplished through increased interaction between the manufacturer and the FDA. Fast Track designation provides for meetings with the FDA for its input, the ability to submit an NDA in sections, and possible evaluation of studies using surrogate endpoints for Accelerated Approval (see below, *Accelerated Approval (Subpart H)*). Additionally, Fast Track designation is independent of Priority Review and Accelerated Approval. Manufacturers can request Fast Track designation at the time of the original submission of the IND or any time afterwards, before approval.
- **Priority Review.** The FDA designates each application as either Standard Review or Priority Review. A drug is given Priority Review if it offers major advances in treatment, or provides a treatment option where adequate therapy is not currently available. The FDA attempts to review Priority drugs within a six-month timeframe. While the review time for Priority drugs is shortened, the process is essentially the same, with the same supporting data required for safety and efficacy as drugs

classified as Standard. Products submitted for Fast Track approval are typically designated for Priority Review. All non-priority drugs are considered Standard applications.

- **Accelerated Approval (Subpart H).** Accelerated approval is intended to make promising products for life threatening diseases available on the market as a result of preliminary evidence. This preliminary evidence is usually based on a surrogate endpoint (a substitute measurement for the clinical measurement, such as prolongation of survival or symptom improvement) that is considered likely to predict patient benefit. Accelerated approval is also appropriate when it is determined that safe use of the promising product is based on restriction of the product's distribution or use. Accelerated approval is provisional and a written commitment to complete clinical studies to formally demonstrate patient benefit is required.
- **Parallel track approval.** Under this FDA policy, AIDS patients who cannot participate in clinical trials due to their condition receive investigational drugs that show promise in preliminary studies.
- **New or expanded use review.** Applications for a new or expanded use of an existing drug are received as efficacy supplements to the original NDA. The FDA's goal is to review standard supplements in ten months and priority supplement in six months or less.
- **Listed drugs versus generic drugs.** Manufacturers of drugs that are identical, similar or related to listed drugs (that is, FDA approved drugs) can circumvent the extensive NDA approval process and file an Abbreviated New Drug Application (21 CFR § 314.92, et seq.). This is the procedure followed for generic drugs.

## 10. Are foreign marketing authorisations recognised in your jurisdiction? If so, please briefly outline the recognition procedure.

Foreign marketing authorisations of medicinal products are not recognised in the US.

## 11. What powers does the regulator have to:

- Monitor compliance with marketing authorisations?
- Impose penalties for a breach of a marketing authorisation?

The FDA monitors compliance with NDA approval by requiring that adverse event reports, and other post-marketing reports, be filed by the respective manufacturer (21 CFR §§ 314.80-81). This ensures that drugs remain safe and effective.

If the FDA no longer believes that the data supports the safety and efficacy of an approved drug, it can:

- Issue a written notice or warning.
- Suspend or revoke the NDA's approval.
- Seize or recall the drug.

In addition, violation of the FDCA can result in both civil and criminal penalties.

**12. Are parallel imports of medicinal products into your jurisdiction allowed? If so, please briefly outline what conditions must be met by the parallel importer. Can intellectual property rights be used to oppose parallel imports?**

The FDCA (*21 USC §§ 331(d) and 355(a)*) currently prohibits interstate shipment of any unapproved new drugs. This also includes foreign-made versions of US approved drugs that have not received FDA approval. Importers must show that any drugs offered for importation have been approved by the FDA.

**13. Please briefly outline the restrictions on marketing practices such as gifts or “incentive schemes” for healthcare establishments or individual medical practitioners.**

Federal anti-kickback statutes regulate the remuneration that can be provided. Offering any type of remuneration, directly or indirectly, to any person or entity in a position to purchase, lease, order or prescribe (or influence such) a service or item reimbursed by a federal healthcare programme could violate the federal Anti-Kickback Statute (*42 USC §1320a-7b(b)*), if the purpose of the payment or gift to the healthcare professional is to induce federal healthcare programme business. Pharmaceutical manufacturers must, therefore, carefully scrutinise sales and marketing practices involving gifts, donations or other forms of remuneration that may be given to medical professionals and/or facilities.

Generally, no gift can be given to healthcare providers in exchange for prescribing products or a promise to continue prescribing products. Gifts provided to physicians should primarily be for the benefit of the patient. In July 2008, the Pharmaceutical Research and Manufacturers of America (PhRMA) announced a revised Code on Interactions with Healthcare Professionals. This revision, which takes effect in January 2009, prohibits non-educational gifts of any value, including pens, mugs, and medical equipment. The revised Code allows for the distribution of materials of minor value (that is, less than US\$100 (about EUR70)) which are intended for the education of patients or healthcare personnel. The revised Code also allows for occasional modest meals to be provided to doctors in conjunction with an educational presentation, but only in the office or hospital setting.

The American Medical Association (AMA) provides guidance to physicians as to the gifts it considers acceptable in its *Gifts to Physicians from Industry (Council on Ethical and Judicial Affairs, Opinion 8.061)*. Similar to the PhRMA's revised Code, the AMA's Opinion sets out the guiding principles that gifts given to physicians should primarily benefit the patient, not be of substantial value, and not influence the physician. The AMA indicates that gifts of minor value which serve an educational purpose are appropriate, including textbooks and modest meals. The AMA finds that a physician can receive modest meals at educational functions, but does not set location limitations similar to the PhRMA Code. Unlike the PhRMA, the AMA allows for physicians to receive gifts of minimal value related to their work (for example, pens and notepads) and also medical equipment of non-substantial value. Both the PhRMA

and AMA agree that items intended for the personal benefit of the physician, including cash or cash equivalents, are considered inappropriate (except as compensation for bona fide services).

Under the FDCA, representatives of drug manufacturers have traditionally been banned from promoting the use of medications for uses that have not been approved by the FDA (known as off-label use). The Food and Drug Administration Modernization Act (FDAMA), which amended the FDCA, provides specific conditions under which manufacturers can lawfully distribute material regarding off-label use (*Pub. L. No. 105-115, 111 Stat. 2296 (1997)*) (see Question 15).

The FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) advises the pharmaceutical industry on proposed advertising and promotional labelling (*21 CFR § 202.1(j)(4)*). The DDMAC has requested that launch campaigns be submitted voluntarily to the DDMAC for comment before dissemination. Companies can request an advisory opinion on non-launch promotional pieces before they use them (*21 CFR § 10.85*).

**14. Please briefly outline the restrictions on marketing medicinal products on the internet, by e-mail and by mail order.**

Pharmaceutical products can be marketed and sold over the internet. However, a patient must have a prescription from a physician to purchase a prescription drug. Given the difficulties of regulating the internet and uncertainty over who exactly has the authority to regulate it, many people may be purchasing prescription drugs without prescriptions.

Some states have attempted to regulate the prescription of drugs on the internet by enacting laws that make it illegal for a doctor to prescribe a drug without an examination. The AMA has stated that it is an ethical violation to sell drugs without a face-to-face consultation. For further information, see [www.fda.gov/oc/buyonline/default.htm](http://www.fda.gov/oc/buyonline/default.htm).

## ADVERTISING

**15. Please briefly outline the restrictions on advertising medicinal products. In particular:**

- Which legislation applies and which regulatory authority enforces it?
- What types of medicinal product cannot be advertised?
- What restrictions apply to advertising that is allowed?

FDA regulations concerning prescription drug advertising are designed, in part, to ensure that claims are supported by credible scientific evidence (*21 CFR § 202.1*). A prescription drug is considered “misbranded” if an advertisement fails to satisfy the requirements of the FDCA and FDA regulations (*21 USC § 352*). Generally, prescription drug advertisements do not require prior FDA approval (*21 USC § 352(n)*). In the case of accelerated approval products, however, all promotional materials intended for dissemination within 120 days of approval must be submitted to the FDA during the pre-approval period (*21 CFR § 314.550*). Advertisement pre-approval may also be required, in special circumstances, as part of an enforcement action.

All advertisements must be submitted to the DDMAC when the advertisement is initially published (21 CFR § 314.81(b)(3)(i)). The DDMAC also offers comments on any adverts submitted before publication (21 CFR § 202.1(j)(4)).

The Lanham Act (15 USC § 1051, *et seq.*) permits lawsuits based on claims of false advertising. Competitors of the defendant can sue to challenge advertising as false or misleading (§ 43(a), *Lanham Act*, 15 USC § 1125(a)(1)(B)).

Regulations involving direct advertising to consumers are extensive. The manufacturer must present a fair balance between the information relating to efficacy and the information regarding side effects and contraindications (21 CFR § 202.1). There are exemptions to these regulations (see 21 CFR §§ 200.200 and 202.1). Drug manufacturers must also distribute patient labelling or medication guides when the FDA determines that a prescription drug or biological product poses a serious and significant public health concern (21 CFR § 208.1).

The FDAMA abolished the prohibition on dissemination by manufacturers of information about off-label uses (use of an FDA-approved drug for an indication other than that for which it was approved) of drugs and medical devices. The FDAMA allows manufacturers to disseminate peer-reviewed journal articles about off-label use of a product to healthcare providers. Specifically, they can provide information concerning the safety and efficacy of a drug for a use not included in FDA-approved labelling (21 USC § 360aaa *et seq.*).

## PACKAGING AND LABELLING

### 16. Please briefly outline the regulation of packaging and labelling of medicinal products. In particular:

- Which legislation applies and which regulatory authority enforces it?
- What information must the packaging and/or labelling contain?
- What other conditions must be met (for example, information being stated in the language of your jurisdiction)?

#### General labelling provisions

The FDA requires that specific requirements be met for drug labelling to be approved. The general labelling provisions are applicable to all drug labels and a variety of information must be included (21 CFR Part 201). Information included on drug labels must be prominent and conspicuous. In nearly all circumstances, the label must be in English (21 CFR § 201.15). There must be no misleading statements on a drug label with regard to another drug, device, food or cosmetic (21 CFR § 201.6). A drug label must clearly bear the name and place of business of the manufacturer, packer or distributor (21 CFR § 201.1). Directions for use must be included and provide the following information (21 CFR § 201.5):

- Statements of all conditions, purposes or uses for which the drug is intended.
- Quantity of doses for different age groups.
- Frequency and duration of administration.

- Time of administration in relation to meals or other time factors.
- Method of administration and preparation for use.

#### Labelling requirements for prescription drugs

A prescription drug label must bear the established name of the drug as one of its principal features (21 CFR § 201.50) and include the net quantity of the content (21 CFR § 201.51). It must also contain a summary of the essential scientific information needed for the safe and effective use of the drug. This information should be based on data derived from human experience whenever possible (21 CFR § 201.56(a)(3)).

In an effort to provide healthcare professionals with clear and concise prescribing information, the required format and content of the label for prescription drugs have been revised. (See 21 CFR §§ 201.56, 201.57.) The revised labelling requirements require these drug labels to include three overarching sections:

- Highlights of Prescription Information.
- Full Prescribing Information: Contents.
- Full Prescribing Information.

The information that must be included under each of the above sections is also mandated by the FDA (21 CFR § 201.57).

For some prescription medicines, the FDA approves special patient materials and medication guides to instruct patients about the safe use of product. (See 21 CFR 208). These patient package materials may be given to patients by their healthcare provider or pharmacist, and are considered part of FDA-regulated product labelling. The FDA may require distribution of medication guides to consumers for selected prescription drugs that pose a serious public health concern.

#### Labelling requirements for OTC drugs

As OTC drugs are used without the supervision of a physician, additional labelling requirements apply (21 CFR Part 201). The FDA has issued regulations to provide easy-to-understand labelling for OTC drugs (21 CFR § 201.66). These regulations require use of a standardised format which clearly show a drug's ingredients and warnings, and make it easier for consumers to understand information about a drug's benefits and risks, as well as its proper use.

#### Specific labelling requirements

Certain drugs have specific labelling requirements and all relevant regulations must be consulted concerning these drugs (21 CFR §§ 201.300-325).

## TRADITIONAL HERBAL MEDICINES

### 17. Please briefly outline the regulation of the manufacture and marketing of traditional herbal medicinal products in your jurisdiction.

Homeopathic drugs must meet the standards for strength, quality and purity established by the Homeopathic Pharmacopeia of the United States (HPUS). If a homeopathic remedy is offered for the

cure, mitigation, prevention or treatment of disease symptoms, it is classified as a drug and subject to regulation by the FDA.

Although homeopathic drugs fall under the authority of the FDA, they are regulated differently from other drugs. For example:

- Manufacturers of such drugs are not required to submit NDAs.
- They do not have to undergo finished product testing for identity and strength because they contain little or no active ingredients.
- There are no toxicity or poison-control issues.
- They can contain more than 10% alcohol.

Companies that manufacture, prepare, propagate, compound or otherwise process homeopathic drugs must register as drug establishments and conform to CGMPs.

A further regulation is that homeopathic drugs that claim to treat a serious disease can only be sold by prescription. No prescription is required for homeopathic drugs that are used to treat minor health problems, such as colds or headaches.

## PATENTS

### 18. What types of medicinal products and related substances and processes can be protected by patents and what types cannot be patent protected? What are the legal criteria to obtain a patent? Which legislation applies?

Generally, patent laws are codified in Title 35 of the US Code. Pharmaceutical and medicinal products generally fall within the scope of patentable subject matter. Provided that they satisfy requirements such as novelty, non-obviousness, and utility, they can be patented (as long as the other requirements in Title 35 are also satisfied). Novelty and non-obviousness are assessed based on the prior art at the time of filing a patent application, and the level of skill of ordinary skilled artisans.

### 19. How is a patent obtained? In particular:

- To which authority must the application be made?
- What fee must be paid?
- What are the key stages and timing?

#### The authority

Patent applications can be filed electronically with the US Patent and Trademark Office (USPTO) through the Electronic Filing System (EFS-Web) at [www.uspto.gov/efc/efs\\_help.html](http://www.uspto.gov/efc/efs_help.html).

#### Fee

For complete fee schedules for 2008 and 2009, see [www.uspto.gov/go/fees/index.html](http://www.uspto.gov/go/fees/index.html).

#### Process and timing

The timetable for the issue of a patent can vary a great deal, from about 24 months to multiple years. The USPTO will answer an applicant's enquiries regarding the status of the application. If an applicant is represented by a lawyer or agent, all comments concerning the application should be addressed through them. Rejected applications can be appealed to the Board of Appeals and Inferences, and even to the courts (for further details of the application process, see *35 USC §§ 111 and 112*).

### 20. How long does patent protection last? How is a patent renewed or patent protection extended?

Generally, a patent's term is 20 years from the date of original filing (*35 USC § 154(a)(2)*). Drug manufacturers receive five years of exclusivity for new chemical entities and three years of exclusivity for new indications. In some cases where delay is due to actions of the USPTO, a patent's term can be extended to offset prosecution delays.

### 21. In what circumstances can a patent be revoked?

Three main ways in which patent protection can cease include that the:

- Patent can be held unenforceable.
- Patent can be held invalid.
- Owner might not comply with required post-allowance activities.

A patent can be held unenforceable if those who sought and participated in its prosecution are found to have engaged in inequitable conduct before the patent office. Invalidity might stem from a post-issuance showing (to a court or even the patent office by way of re-examination) of lack of novelty, obviousness, lack of enablement, or lack of written description (which means that the patent lacks sufficient disclosure to conclude that the inventors had possession of their invention at the time of filing).

If an owner does not pay its required maintenance fees, or fails to respond to a re-examination request, the patent might go abandoned. Laches can also prevent patent-rights enforcement, such as when a patent owner knows about infringing activity but waits a long period of time to enforce its rights.

### 22. When is a patent infringed? How is a claim for patent infringement made and what remedies are available?

A patent is infringed on the unauthorised making, using, importing into the US, offering for sale, or selling of any patented invention during the term of the patent. If a patent is infringed, the patent holder can sue in federal court for damages and also seek an injunction to stop the infringing activity (for the patent infringement and remedy process, see *35 USC §§ 271-297*).

## TRADE MARKS

### 23. Can a medicinal product brand be registered as a trade mark? What are the legal criteria to obtain a trade mark? Which legislation applies?

While trade mark law is governed by both federal and state law, federal law provides the primary source of trade mark law. (See *37 CFR Part 2 and 15 USC § 1051, et seq.*) Trade mark law generally applies to pharmaceutical and medicinal products in the same way it does to other products.

A trade mark must be capable of distinguishing goods or services from those of another and it must be in use (and in interstate commerce for federal protection). A trade mark application can be submitted in three situations:

- Where the applicant has already begun using a mark in commerce.
- Where the applicant has not yet used the mark but intends (in good faith) to use it in commerce.
- Where there is a foreign applicant who has an application or registration in another country (under certain international agreements).

### 24. How is a trade mark registered? In particular:

- To which authority must the application be made?
- What fee is payable?
- What are the key stages and timing?

#### The authority

Trade mark applications can be filed electronically with the USPTO through the Trademark Electronic Application System (TEAS) at [www.uspto.gov/teas/index.html](http://www.uspto.gov/teas/index.html).

#### Fee

For complete fee schedules for 2008 and 2009, see [www.uspto.gov/go/fees/index.html](http://www.uspto.gov/go/fees/index.html).

#### Process and timing

The applicant should receive an initial response from the USPTO within six to seven months from filing the application. The total time for an application to be processed can vary from one year to several years. The application timing depends on the basis for filing and the legal issues which may arise. Current status information on trade mark applications is available through the Trademark Applications and Registrations Retrieval (TARR) database at <http://tarr.uspto.gov/>.

### 25. How long does trade mark protection last? How is a trade mark renewed?

The initial and extendable duration of a trade mark registration is ten years. A trade mark can last indefinitely provided the owner continues to use the trade mark in connection with all of the goods or services identified in its application, renews its registration, and pays the applicable fees (*15 USC §§ 1058-59*).

### 26. In what circumstances can a trade mark be revoked?

A trade mark's registration can be cancelled in any of the following circumstances (*15 USC § 1064*):

- The trade mark becomes a generic name for the goods or services.
- The trade mark has been abandoned.
- Registration was obtained fraudulently.
- The trade mark is used to misrepresent the source of the goods or services with which it is connected.
- A trade mark is cancelled by an adversary (subject to a quasi-judicial cancellation proceeding administered by the USPTO).

### 27. When is a registered trade mark infringed? How is a claim for trade mark infringement made and what remedies are available?

The use of a registered trade mark in connection with the sale of goods constitutes infringement if it is likely to cause consumer confusion as to the source of those goods or as to the sponsorship or approval of such goods. In deciding whether consumers are likely to be confused, the courts typically look to a number of factors, including the:

- Strength of the mark.
- Proximity of the goods.
- Similarity of the marks.
- Evidence of actual confusion.
- Similarity of marketing channels used.
- Degree of caution exercised by the typical purchaser.
- Defendant's intent.

Enforcement is achieved by bringing an action for trade mark infringement. The action can be based on a registered trade mark or on common law rights in a trade mark.



## 28. Is your jurisdiction party to international conventions on patent and trade mark protection?

The US is party to international conventions on patent and trade mark protection, a few of which include:

- The Patent Cooperation Treaty.
- The WIPO Paris Convention for the Protection of Industrial Property 1883.
- The WIPO Protocol Relating to the Madrid Agreement Concerning the International Registration of Marks 1989.

## PRODUCT LIABILITY

### 29. Please give an overview of medicinal product liability law, in particular:

- **Under what laws can liability arise (for example, contract, tort or statute)?**
- **What is the substantive test for liability?**
- **Who is potentially liable for a defective product?**

#### Legal provisions

Actions against drug manufacturers for producing or marketing a product with either a defective design or inadequate warning primarily lie in tort (negligence or strict liability) and breach of warranty claims (quasi-contractual in nature).

#### Substantive test

The tort law applicable in product liability cases involving drugs varies from jurisdiction to jurisdiction. The Restatement (Third) of Torts, drafted by the American Law Institute, provides the basis for tort law in product liability cases in many jurisdictions (see [www.ali.org](http://www.ali.org)). The Restatement (Third) establishes separate tests for manufacturing defects, design defects and defects in warnings. Strict liability applies only to manufacturing defects.

Under the Restatement (Third), design defects claims require a foreseeable risk of harm posed by the product which could have been reduced or avoided by the adoption of a reasonable alternative design. Design defect liability for prescription drugs and medical devices is limited (see § 6, *Restatement (Third) of Torts*). A design defect only exists if the risk of harm from the drug or device is so great when compared with the therapeutic benefits that doctors would not prescribe the drug for any class of patients. Drug and medical device manufacturer liability is essentially limited to defects in manufacturing and failure to warn. The risks about which manufacturers must warn are “foreseeable risks” (*Restatement (Third) of Torts: Products Liability § 6(d)(1) (1998)*). A breach of warranty is a strict form of liability, but it is limited by the contractual concepts of disclaimer and notice. Warranty theories are governed by the Uniform Commercial Code (UCC), which has been adopted in some form by each state.

The UCC recognises various warranties, including:

- Express.
- The implied warranty of merchantability.
- The implied warranty of fitness for a particular purpose.

#### Liability

The pharmaceutical manufacturer is usually liable in civil actions, but all parties involved in the business of selling or distributing a product are subject to liability for harm caused by a defect in that product. The claimant can also sue its physician for malpractice in the same lawsuit.

### 30. What are the limitation periods for bringing product liability claims?

The limitation period varies from state to state and can range from one year to six years. The time generally begins to run from the date of injury. It can be extended where the claimant had no reason to know of his injury or that the drug may have caused it (the discovery rule).

Although state laws vary, there is a general four-year limitation period on actions for breach of contract arising out of the sale of goods (*UCC 2-725(1)*). This period begins to run when delivery is tendered (*UCC 2-725(2)*). The discovery of a latent defect sometime after delivery would not affect the limitation period.

### 31. What defences are available to product liability claims?

Like the product liability claims themselves, defences are a matter of state law and, therefore, vary from jurisdiction to jurisdiction. Available defences include:

- **Statutes of limitation.** For personal injury claims, statutes of limitation can range from one year to six years. Many states employ the discovery rule (see *Question 30*) to determine when the statute of limitations begins to run.
- **Statutes of repose.** This requires a claimant to bring a claim within a certain period of time after the product is manufactured or sold. While statutes of repose are usually longer than statutes of limitation, they are not subject to the discovery rule and represent an absolute bar to a product liability claim.
- **The learned intermediary doctrine.** This doctrine provides that a prescription drug manufacturer discharges its duty by adequately warning the claimant's prescribing physician (the manufacturer has no duty to warn the consumer directly). The physician, therefore, acts as the learned intermediary between the patient and the manufacturer.
- **Intervening/superseding cause.** If a claimant's injury is caused by the intervening conduct of another and such conduct is also a superseding cause, a defendant may avoid liability in most

jurisdictions. An intervening act is a superseding cause when a manufacturer could not reasonably be expected to protect against it, and includes such things as criminal acts, use of a product in an unforeseeable manner, alteration of the product, negligent use and failure to properly maintain a product.

- **Contributory negligence/comparative fault.** According to the theory of contributory negligence, a claimant is barred from recovery if its own negligence caused or contributed to its injury. Most jurisdictions, however, have abandoned contributory negligence in favour of comparative fault. Under comparative fault, a claimant's recovery is reduced if its own negligence (or fault) contributed to his injury.
- **Assumption of the risk.** In some jurisdictions, a claimant can also be barred from recovery if he is aware of a product defect and the accompanying dangers, but proceeds to use the product anyway. Therefore, this defence is based on what the claimant actually knew, not what a reasonable person would know.
- **Preemption.** When governmental statutes, rules and regulations control certain aspects of product safety, some jurisdictions have held that product liability claims imposing different or additional requirements on manufacturers are pre-empted. This attempts to prevent manufacturers from being subjected to different and conflicting standards. The preemptive effect of a statute or regulation can be expressly stated or implied from the comprehensive nature of the enactment.

The FDA promulgated a rule in January 2006 in an effort to simplify drug labelling (see *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed Reg 3,922 (24 January 2006)). The preamble of the rule states that FDA approval of drug labelling, "preempts conflicting or contrary state law," including tort law (*Id at 3934*). The preamble strengthens the position that the FDA previously set out in amicus curiae briefs - that its regulation of prescription drug labelling preempts common-law failure-to-warn claims. The FDA also published a final rule in August 2008 entitled Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices (73 Fed Reg 49,603 (22 August 2008)) which reiterates its views mentioned above on preemption and arguably provides additional support for preemption claims. Courts are divided as to whether to apply the FDA's preemption defence, and this issue remains unsettled. (See *Question 34* for further developments regarding preemption.)

- **State of the art.** If a manufacturer can establish that a product was manufactured according to the scientific and technical achievement in the relevant field (the state of the art), such evidence can be used to show the manufacturer acted with due care.

### 32. What remedies are available to the claimant?

Various remedies, including monetary damages and equitable remedies, are available to a claimant in a product liability claim.

## THE REGULATORY AUTHORITIES

### US Food and Drug Administration (FDA)

**T** +1 888 463 6332  
**F** N/A  
**E** Contact through the FDA website at [www.fda.gov/comments.html](http://www.fda.gov/comments.html)  
**W** [www.fda.gov](http://www.fda.gov)

**Main areas of responsibility.** The FDA regulates the safety of food, and safety and efficacy of human drugs, veterinary drugs, biological products, medical devices, cosmetics and electronic products that emit radiation. The FDA administers the statutes and rules that govern the regulation of pharmaceutical products (*Federal Food, Drug and Cosmetic Act (FDCA) 21 USC § 301, et seq.*).

### Center for Drug Evaluation and Research (CDER)

**T** +1 888 463 6332  
 +1 301 827 4573  
**F** N/A  
**E** Questions and comments for the CDER can be sent via the internet at [www.fda.gov/cder/comment.htm](http://www.fda.gov/cder/comment.htm). E-mails for the Division of Drug Information can be sent to [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov).  
**W** [www.fda.gov/cder/](http://www.fda.gov/cder/)

**Main areas of responsibility.** The CDER has regulatory responsibility for the safety and efficacy of drugs, including prescription, generic, and over-the-counter drugs.

### Center for Biologics Evaluation and Research (CBER)

**T** +1 301 827 1800  
 +1 800 835 4709  
**F** N/A  
**E** Consumer questions: [octma@cber.fda.gov](mailto:octma@cber.fda.gov).  
 Manufacturers assistance questions: [matt@cber.fda.gov](mailto:matt@cber.fda.gov).  
**W** [www.fda.gov/cber/](http://www.fda.gov/cber/)

**Main areas of responsibility.** The CBER has regulatory responsibility for biological and related products.

### Federal Trade Commission (FTC)

**T** +1 202 326 2222  
**F** N/A  
**E** Consumer complaint forms available at [www.ftccomplaintassistant.gov/](http://www.ftccomplaintassistant.gov/).  
 Contact [antitrust@ftc.gov](mailto:antitrust@ftc.gov) for the FTC's Bureau of Competition.  
**W** [www.ftc.gov](http://www.ftc.gov)

**Areas of responsibility.** The FTC is responsible for regulating the marketing and advertising of over-the-counter (OTC) drugs (*Updated FTC-FDA Liaison Agreement Advertising of Over-the-Counter Drugs*, 4 Trade Reg. Rep. (CCH) 9,851 (1971)).

### 33. Are class actions allowed for product liability claims? If so, are they common?

Class actions are permitted for product liability claims in both state and federal courts. They are commonly filed in the product liability context because of the ease with which each individual can assert a claim for personal injury and the potential that exists for large damage awards. In addition, there is a growing trend for claimants in pharmaceutical product liability cases to file class actions seeking damages for medical monitoring, as well as class actions seeking drug refunds or disgorgement of profits, alleging deceptive trade practices for drugs withdrawn from the market. That being said, no federal appellate court or federal district court has ever certified a multi-state class alleging personal injury claims related to a prescription drug (see *In re Prempro*, 230 FRD 555, 571 (WD Ark 2005) and *In re Fosamax Products Liability Litigation*, 248 FRD 389, 396 (SDNY 2008)).

There are prerequisites to a class action in federal courts (see *Rule 23, Federal Rules of Civil Procedure*). Under Rule 23(a), the prerequisites for a class action are:

- The class is so numerous that joinder of all members is impracticable.
- There are questions of law or fact common to the class.
- The claims or defences of the representative parties are typical of the claims or defences of the class.
- The representative parties fairly and adequately protect the interests of the class.

Once these prerequisites are established, a class action is maintained as long as it meets one of the requirements set out in Rule 23(b).

While state court rules can differ, the class action requirements in many states parallel those set out in the Federal Rules. While class actions are commonly used in product liability cases, courts still refuse to certify classes that do not meet the requirements for a class action (see for example, *Blain, et al v Smithkline Beecham Corp*, 240 FRD 179 (ED Pa 2007)).

In February 2005, the Class Action Fairness Act (CAFA) was enacted. The CAFA contains two primary components, both of which are intended to reform class action practice as it currently stands. The first component expands federal jurisdiction over interstate class actions, allowing claimants to file certain class actions in federal court and defendants to remove certain class actions to federal court. The CAFA expands federal jurisdiction over any class action in which:

- There are at least 100 class members.
- The aggregate amount in controversy exceeds US\$5 million (about EUR3.5 million).
- Any member of a claimant class is one of the following:
  - a citizen of a state different from any defendant;
  - a foreign state, or a citizen or subject of a foreign state, and any defendant is a citizen of a state;

- a citizen of a state and any defendant is a foreign state or a citizen of a foreign state.

In addition to class actions, Multidistrict Litigation (MDL) provides a method for consolidating multiple product liability claims filed in different federal court jurisdictions by allowing litigation pending in multiple federal districts to be transferred to one district court for consolidated pre-trial proceedings (28 USC § 1407).

## REFORM

### 34. Please summarise any proposals for reform and state whether they are likely to come into force and, if so, when.

The US Supreme Court recently decided two cases which address the issue of federal preemption, and is expected to decide a third preemption case next term. These rulings will hopefully provide clarity as to the US Supreme Court's position on the issue of federal preemption.

On 20 February 2008, the US Supreme Court, in an eight to one decision in *Riegel v Medtronic, Inc*, held that state law claims against medical devices requiring FDA pre-market approval are preempted (128 S Ct 999 (2008)). This decision hinted at the possibility that the Supreme Court might subsequently adopt federal preemption in a broader context.

Two weeks after the *Riegel* decision, the Supreme Court handed down a four to four split decision in *Warner-Lambert Co v Kent*. This decision upheld the Second Circuit ruling that allowed pharmaceutical cases to proceed under a Michigan statute requiring plaintiffs to prove the company misled the FDA (128 S Ct 1168 (2008)). Even though the split-decision has no precedential effect, it came as a surprise to some who thought that *Kent* would continue to broaden the scope of preemption.

Whether the Court will expand preemption may be answered in *Wyeth v Levine*. In *Levine v Wyeth* (944 A2d 179 (Vt 2006)), the Vermont Supreme Court held that there was no conflict between state failure-to-warn claims and federal labelling requirements. The US Supreme Court granted certiorari in *Levine* on 18 January 2008 and is expected to hear oral argument in October 2008. In *Wyeth v Levine*, the Court will address the question of whether the FDA's authority to regulate prescription drug labelling, including warnings and precautions, preempts state law claims. A ruling in favour of Wyeth will significantly impact plaintiffs' ability to bring failure to warn claims in prescription drug cases.

## CONTRIBUTOR DETAILS

Harvey L Kaplan and John C Vaglio  
Shook, Hardy & Bacon LLP

T +1 816 474 6550  
F +1 816 421 5547  
E hkaplan@shb.com  
jvaglio@shb.com  
W www.shb.com

