United States

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REGULATORY OVERVIEW

1. Please give a broad 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 will pay 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.

2. Please briefly describe the regulatory environment for medicinal products/pharmaceutical products/drugs, by whatever name known (referred to below as medicinal products).

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 6*) 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 Centre 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/#other*.

MANUFACTURE AND CLINICAL TRIALS

3. Is authorisation required to manufacture medicinal products? If so, please give an overview of the authorisation process, in particular:

- **To whom should the application be made?**
- **What criteria need to be satisfied to obtain authorisation?**
- **Are there any specific restrictions on foreign applicants?**
- **What are the key stages and timing of the process?**
- **What fee is payable?**
- **Is authorisation given for a fixed period? If so, for how long 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 of the FDCA* (*21 USC § 360*)).
- **Criteria**. 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*.
- **Restrictions on foreign ownership.** 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*.

- **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. A global manufacturing supplement, which applies to multiple products and requires only one review, can also be filed.

4. What powers does the regulator have to monitor compliance with manufacturing authorisations? Does it exercise those powers?

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 pertinent 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/iomtc.html)* and also the FDA Enforcement Manual.

5. In the event of a breach of the terms of a manufacturing authorisation, what are the regulator's powers of enforcement?

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.

6. Are clinical trials regulated? If so, please give an overview of the necessary consents, authorisations and procedural 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*).

- 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 a completed, signed statement of investigation (FDA Form 1572) (*21 CFR § 312.53(c)*). The investigator must agree to conduct the study in accordance with 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*).

PRICING AND STATE FUNDING

7. 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.

8. In what circumstances will the cost of a medicinal product be funded or reimbursed by the state? How is pricing determined in these circumstances?

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 7*).

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. The Medicare prescription drug plans replace the Medicare-approved drug discount cards, which were phased out by May 2006. Like other insurance, Medicare prescription drug plans require payment of a monthly premium, yearly deductible and part of the prescription cost. Assistance with payments associated with the Medicare prescription drug plans is available for individuals with limited resources.

MARKETING

9. Is authorisation required to market prescription-only medicinal products? If so, please give an overview of the authorisation process, in particular:

- **To whom should the application be made?**
- **What conditions must be satisfied by the applicant?**
- **What are the key stages and timing of the process?**
- **Is there an abridged procedure?**
- **What fee is payable?**
- **Is authorisation given for a fixed period? If so, for how long 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 approval of an NDA is given, there are ongoing requirements for the reporting of post-marketing adverse drugs 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*.

- **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 a flowchart on the new drug development process, see *www.fda.gov/cder/handbook/nda.htm*). 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 6*) to the FDA (*21 CFR § 312.23*) (for a flowchart on IND Review Process, see *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.

- **Abridged procedure**. 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 6*).
  - **Fast track programmes (*21 CFR § 312.80, et seq.*).** The manufacturer interacts with the FDA to speed up the FDA review process for drugs designed to treat serious or life threatening conditions and which demonstrate the potential to address unmet medical needs. The benefits include meetings with the FDA for its input into development plans, the option of submitting an NDA in sections rather than all components simultaneously, and requesting an evaluation of studies using surrogate endpoints for Accelerated Approval (*see below, Accelerated Approval (Subpart H)*). The 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 assesses each application as either Standard or Priority. Priority drugs are those that appear to have significant improvement compared to products already on the market in the treatment, diagnosis, or prevention of a disease. Standard drugs are those that appear to have therapeutic qualities similar to those of one or more already marketed drugs. The FDA seeks to perform an accelerated, six-month review on Priority drugs. 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 Priority review. All non-priority drugs are considered Standard applications.
  - **Accelerated Approval (Subpart H).** This is intended to make promising products for life threatening diseases available on the market on the basis of preliminary evidence before formal demonstration of patient benefit. The studies of products are made to measure and the FDA evaluation is performed on the basis of a surrogate endpoint (a substitute measurement for the clinical measurement of interest, usually prolongation of survival) that is considered likely to predict patient benefit. Approval is provisional and a written commitment to complete clinical studies that will formally demonstrate patient benefit is required.
  - **Parallel track approval.** Under this FDA policy, AIDS patients whose condition prevents them from participating in clinical trials can receive investigational drugs that have been shown to be potentially useful.
  - **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. These supplements can be reviewed on a priority basis of 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.
- **Fee**. Fees are set by the FDA Prescription Drug User Fee Act. For fee information, see *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.

10. Are the marketing authorisation requirements for over-the-counter (OTC) medicinal products the same as those outlined above? If not, please briefly outline how the requirements differ.

The FDA regulates most OTC drugs by a monograph system (*21 CFR § 330.1, et seq.*). This is designed to establish which active ingredients can be marketed in OTC drugs without additional product approval and for what recommended uses. The system covers acceptable ingredients, doses, formulations and labelling for each class of OTC drugs.

OTC products that conform to the monograph can be marketed without further review by the FDA. Products that do not conform to the monograph, or contain an ingredient that would be OTC for the first time, must go through the NDA process. Typically, these products are approved as prescription drugs and later switched to OTC status.

11. What powers does the regulator have to monitor compliance with marketing authorisations? Does it exercise those powers?

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.

12. In the event of a breach of the terms of a marketing authorisation, what are the regulator's powers of enforcement?

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.

13. Is there a procedure for mutual recognition of foreign marketing authorisations? If so, please briefly outline the procedure.

There is no procedure for mutual recognition of foreign marketing authorisations.

14. Are there any 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 in exchange for prescribing products or a promise to continue prescribing products. Gifts should be primarily for the benefit of patients and of minor value (that is, less than US$100 (about EUR78)). Gifts of a minimal value that are to be used in the physician's practice (for example, pens and notepads) are also allowed. Items intended for the personal benefit of the physician, including cash or cash equivalents, are considered inappropriate (except as compensation for bona fide services). Therefore, gift certificates, tickets to a sporting event, artwork, music and floral arrangements are prohibited.

Representatives of drug manufacturers can supply healthcare providers with various promotional materials. Certain educational and practice-related items can also be offered to medical professionals under limited circumstances.

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 17*).

In addition to the above, the following guidelines exist:

- The American Medical Association (AMA) Guidelines on Gifts to Physicians from Industry.
- Pharmaceutical Research and Manufacturers of America Code on Interactions with Healthcare Professionals.

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*).

15. How are parallel imports regulated?

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

The Medicare Prescription Drug Improvement and Modernization Act 2003 (MMA) gives the Secretary of Health and Human Services the authority to implement a system for the importation of Canadian prescription drugs (*Pub. L. 108-173, 8 December 2003, 117 Stat. 2066*). However, the Secretary can implement this system only if he is first able to certify to the Congress that it will be safe and cost effective (*§ 1121, MMA*).

16. Is it possible to market medicinal products online, by e-mail and/or mail order?

Pharmaceutical products can be 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.

ADVERTISING

17. Are there any restrictions on advertising medicinal products (both prescription-only and OTC)? If so, please briefly outline what these are.

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(n)*). Generally, prescription drug advertisements do not need prior approval by the FDA (*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 advertisements 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

18. Please give a broad overview of the regulatory framework governing the packaging and labelling of medicinal products.

General labelling provisions

These 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*).

The label must contain information on the following in the order shown:

- Description.
- Clinical pharmacology.
- Indications and usage.
- Contraindications.
- Warnings.
- Precautions.
- Adverse reactions.
- Drug abuse and dependence.
- Overdosage.
- Dosage and administration.
- How supplied.

The following categories can also be used if appropriate:

- Animal pharmacology and/or animal toxicology.
- Clinical studies.
- References.

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

For some prescription medicines, the FDA approves special patient materials to instruct patients about the safe use of the product. These patient package inserts 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 (FDA-approved patient information) 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, dose 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 §§ 201.300-320*).

TRADITIONAL HERBAL MEDICINES

19. Is the manufacture and marketing of traditional herbal medicinal products regulated in your jurisdiction? If so, please give an overview of the regime.

Homeopathic drugs must meet the standards for strength, quality and purity established in 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 (those used for minor health problems, such as colds or headaches, can be sold without a prescription). In April 2004, the FDA used its regulatory authority in this area by prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra). In April 2005, a district court judge overturned the FDA's ban on sales of ephedra. The judge concluded that the FDA's use of a risk-benefit analysis was improper, and the FDA failed to meet its burden of proof that a ten milligrammes or less dosage of ephedra presented an unreasonable risk of illness or injury (*Nutraceutical Corp., et al. v Crawford, 364 F.Supp.2d 1310 (D. Utah 13 April, 2005)*). Specifically, the judge prohibited the FDA from banning sales of supplements containing ten milligrammes or less of ephedra. While some ephedra manufacturers interpret the *Nutraceutical* ruling to have completely overturned the ban on ephedra, the FDA interprets the ruling as banning all products containing more than ten milligrammes of ephedra. The FDA continues to assert this position and has seized shipments of supplements containing more than ten milligrammes of ephedra. The FDA has appealed the April 2005 *Nutraceutical* ruling.

INTELLECTUAL PROPERTY

20. What are the criteria for patentability?

To obtain patent protection, a pharmaceutical product must be both:

- New.
- Non-obvious in light of existing art.

21. What is the procedure for obtaining patent protection, in particular:

- **To whom should the application be made?**
- **What are the key stages of the process and timing?**
- **What fee is payable?**
- **For how long is protection given?**
- **What is the renewal process?**
- **In what circumstances can a patent be revoked?**
- **Is your jurisdiction a party to any international conventions on patent protection?**

- **Application.** Applications should be made to the Commissioner for patents at the US Patent and Trademark Office (USPTO).

  Contact details. PO Box 1450
  Alexandria, Virginia 22313-1450
  T For information on filing a patent application electronically, contact the Electronic Business Center at +1 866 217 9197. All other questions can be directed to the USPTO Contact Center at +1 800 786 9199.
  F Patent applications cannot be faxed into the USPTO.
  E Patent applications can be filed electronically through the Electronic Filing System (EFS) at *www.uspto.gov/ebc/efs/index.html*. Questions regarding patents can be emailed to *usptoinfo@uspto.gov*.
  W *www.uspto.gov*

- **Process and timing.** The timetable for the issue of a patent ranges between 18 and 30 months from application to issue. 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 of the US Patent Office (for further details of the application process, see *35 USC §§ 111 and 112*).

- **Fee.** For a complete fee schedule, see *www.uspto.gov/web/offices/ac/qs/ope/fee2006may15.htm*
- **Duration of protection.** A patent 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.
- **Renewal process.** An extension of the patent term for up to 14 years from the time of product approval is available for pharmaceuticals. This offsets FDA regulatory delay preventing commercialisation during the regular patent term (*35 USC § 156*).
- **Revocation.** A patent can be revoked if it is shown that the idea was not unique when the patent was issued or that the patent was procured by fraud.
- **International conventions.** The US is a party to international conventions on patent protection, including the:
  - WIPO Paris Convention for the Protection of Industrial Property 1883; and
  - Patent Cooperation Treaty 1970.

22. When is a patent infringed? What is the process for enforcing patent infringement and what remedies are available?

Patent infringement consists of the unauthorised making, using, 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 the appropriate federal court for relief. The patent holder can ask the court for an injunction to prevent the continuation of the infringement and can also seek damages.

If a drug patent is infringed, the enforcement process is generally the same as when any other patent is infringed (for the patent infringement and remedy process, *see 35 USC §§ 271-297*).

23. Can product brands be protected by registration as a trade mark? If so, what is the test for obtaining trade mark protection?

A trade mark must be capable of distinguishing goods or services from those of another and it must be in use.

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. What is the procedure for obtaining registration of a trade mark, in particular:

- **To whom should the application be made?**
- **What are the key stages of the process and timing?**
- **What fee is payable?**
- **For how long is protection given?**
- **What is the renewal process?**
- **In what circumstances can a trade mark be revoked?**
- **Is your jurisdiction a party to any international conventions on trade mark protection?**

- **Application.** The preferred method of filing a trade mark application is directly over the internet using the Trademark Electronic Application System (TEAS), available at *www.uspto.gov/teas/index.html*.

  Paper applications are also possible and forms can be obtained by calling the USPTO's automated telephone line (+ 1 800 786 9199).

  Contact details. By mail: Commissioner of Trademarks
  P.O. Box 1451
  Alexandria, Virginia 22313-1451
  By hand or courier: Trademark Assistance Center
  James Madison Building
  East Wing, Concourse Level
  600 Dulany Street
  Alexandria, Virginia 22314
  T +1 800 786 9199 (Trademark Assistance Center)
  F Trade mark applications cannot be faxed into the USPTO. Facsimile details for the Trademark Office can be found at *www.uspto.gov/teas/contactUs.htm*.
  E *TrademarkAssistanceCenter@uspto.gov* (for general trade mark information) and *TEAS@uspto.gov* (for technical questions).
  W *www.uspto.gov*

- **Process and timing.** The applicant should receive an initial response from the Office within six to seven months from filing the application. However, the total time for an application to be processed can vary from roughly a year to several years, depending 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/. The Trademark Assistance Center also provides general information about the trade mark registration process and responds to enquiries about the status of specific trade mark applications and registrations.

- **Fee.** For a complete fee schedule, *see www.uspto.gov/web/offices/ac/qs/ope/fee2006may15.htm*
- **Duration of protection**. The duration of a trade mark registration is ten years. A trade mark can last indefinitely provided the owner continues to use the trade mark to identify the goods, renews its registration and pays the applicable fees (*15 USC §§ 1058-59*).
- **Renewal process**. With the approval of the Director of the Trademark Office, a trade mark can be renewed after each ten-year registration period by filing a written application and paying the appropriate fee. This application can be made either one year before the end of the ten-year registration period or during a six-month grace period after the end of the ten-year registration period (*15 USC §§ 1058-59*).
- **Revocation.** 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.

  If the trade mark's registration is revoked, the aggrieved party can either appeal to the US Court of Appeals for the federal circuit or file a civil action within 60 days of the decision (*15 USC § 1071*).
- **International conventions.** The US is party to international conventions on trade mark protection, including:
  - the WIPO Paris Convention for the Protection of Industrial Property 1883; and
  - the WIPO Protocol Relating to the Madrid Agreement Concerning the International Registration of Marks 1989.

25. When is a registered trade mark infringed? What is the process for enforcing brand or trade mark infringement 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.

PRODUCT LIABILITY

26. Please give an overview of product liability law, in particular:

- **Under what laws can liability arise (for example, contract, tort or statute)?**
- **Who is potentially liable for a defective product?**
- **What is the substantive test for liability?**
- **What is/are the limitation period(s) for product liability claims?**
- **What defences are available?**
- **What remedies are available to the claimant?**

- **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 warranties claims (quasi-contractual in nature). Criminal liability can arise.
- **Who is liable?** 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. This includes all parties along the chain of manufacture and distribution (for example, the component manufacturer, assembling manufacturer, wholesaler and retailer). The claimant can also sue its physician for malpractice within the same lawsuit.
- **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 many jurisdictions (*see www.ali.org*). This sets separate tests for manufacturing

defects, design defects and defects in warnings. Strict no-fault liability applies only to manufacturing defects. Design defects claims require risk-utility balancing and proof of a reasonable alternative design, the lack of which renders the product not reasonably safe.

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 49 of the 50 states. The UCC recognises three different types of warranties:

- express;
- the implied warranty of merchantability;
- the implied warranty of fitness for a particular purpose.

- **Limitation period.** 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.

- **Defences**. 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 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.

  - **Pre-emption.** 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 pre-emptive effect of a statute or regulation can be expressly stated or implied from the comprehensive nature of the enactment.

  In January 2006, the FDA issued a rule and commentary amending prescription drug labelling regulations (*see Food and Drug Administration Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 15, 3922 (24 January, 2006)*). The preamble and commentary to the rule included discussion regarding the FDA's views on the pre-emptive effect of its labelling decisions in the context of state product liability tort law. Specifically, the FDA reaffirmed its position that its approval of labelling under the FDCA pre-empts conflicting or contrary state law. This commentary by the FDA provides further support for asserting federal pre-emption as a defence in certain types of pharmaceutical product liability actions.

- **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.

THE REGULATORY AUTHORITIES

United States Food and Drug Administration (FDA)

Contact details. 5600 Fischers Lane
Rockville, Maryland 20857
T +1 888 463 6332
E Contact through the FDA website at *www.fda.gov/comments.htm*.
W *www.fda.gov*

Main areas of responsibility. 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)

Contact details. CDER, Division of Drug Information
5600 Fishers Lane, HFD-240
Rockville, Maryland 20857
T +1 301 827 4573 or +1 888 463 6332
E Questions and comments for the CDER can be sent via the internet at *www.fda.gov/CDER/comment.htm.* Emails for the Division of Drug Information can be sent to *druginfo@fda.hhs.gov.*
W *www.fda.gov/cder*

Main areas of responsibility. The CDER has regulatory responsibility for all drugs for human use except biological products.

Center for Biologics Evaluation and Research (CBER)

Contact details. 1401 Rockville Pike
Rockville, Maryland 20852-1448
T +1 301 827 1800 or +1 800 835 4709
E Consumer questions: *octma@cber.fda.gov*
Manufacturers assistance questions: *matt@cber.fda.gov*
W *www.fda.gov/cber*

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

Federal Trade Commission (FTC)

Contact details. 600 Pennsylvania Ave, NW
Washington, DC 20580
T +1 202 326 2222
E Consumer complaints forms available at *https://rn.ftc.gov/pls/dod/wsolcq$.startup?Z_ORG_CODE=PU01*
W *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)*).

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

27. Are class actions permitted for product liability claims? If so, how common are they?

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.

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 forth 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. And 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. For example, in May 2005, a judge refused to certify a proposed class of women seeking medical monitoring in a pharmaceutical product liability case due to their lack of commonality and failure to meet the state's requirements for medical monitoring (*Albertson, et al. v Wyeth, et al., 2005 WL 3782970 (Pa. Com. Pl. May 3, 2005)*).

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 EUR3.9million).

- 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.

This provision of the CAFA eliminates the complete diversity rule for class actions, and circumvents the fraudulent joinder of non-diverse defendants by claimants to defeat diversity and prevent removal.

The second component of CAFA protects consumers in federal court class actions from abusive class action "coupon" settlements. In particular, the CAFA provides that any contingency fees in coupon settlements must be based on the amount of coupons redeemed.

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*).

FUTURE DEVELOPMENTS

28. Please summarise any impending developments in the regulation of medicinal products, patent and trade mark law, and product liability.

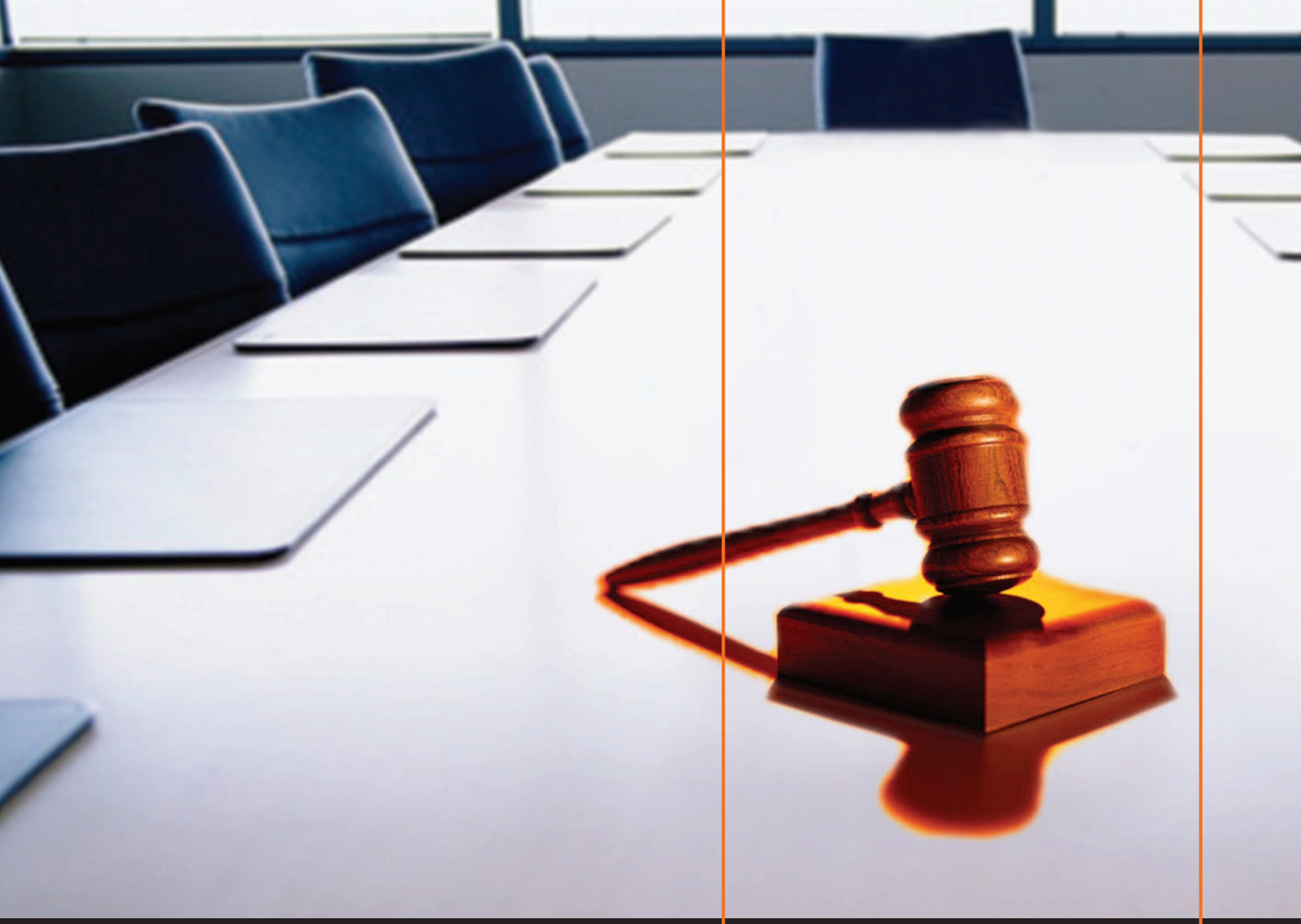
Product liability litigation continues to be a threat to life sciences companies doing business in the US. In 2004, tort costs in the US were over $260 billion (about EUR203 billion) and they continue to rise annually. It is projected that in 2007, the tort costs in the US will exceed $314 billion (about EUR245 billion). However, tort reform is being enacted throughout the country and continues to gain support. Since 1986, all but two states have enacted some measure of tort reform. However, much of this reform is not complete and significant reforms are required in many states and at the federal level.

One area of important reform involves appeal bonds. In many states, defendants are required to post an appeal bond of up to 150% before they can appeal an adverse verdict. As billion-dollar verdicts are becoming more common, the appeal bond requirement can force a company or industry into bankruptcy. Therefore, 34 states have adopted some form of reform to limit the size of appeal bonds in certain circumstances.

In February 2005, The Help Efficient, Accessible, Low-cost, Timely Healthcare (HEALTH) Act of 2005 was reintroduced. This Act would impose changes on the product liability system, including the following:

- Non-economic damages would be capped at US$250,000 (about EUR195,000).
- Personal injury claims would have a three-year statute of limitations.
- There would be no joint and several liability.
- The standards for imposing punitive damages would be stricter.
- Apart from a few exceptions, pharmaceutical manufacturers could not be liable for punitive damages if they complied with FDA standards.
- A physician who prescribed an FDA approved medication could not be named a defendant in a product liability suit against the pharmaceutical manufacturer.

The House of Representatives passed the HEALTH Act in July 2005, and it is currently before the Senate. The HEALTH Act's reintroduction into Congress, along with the enactment of the CAFA (*see Question 27*), demonstrate continued progress in the area of tort reform.



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