Legal and regulatory update

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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought. Please contact:

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NOTES FROM THE EU

Greek Competition Commission rules in favour of GSK in parallel trade case

The Greek Competition Commission issued a decision on 5th September, 2006 which held that GlaxoSmithKline (GSK) had not abused its dominant position in restricting supplies to Greek wholesalers to prevent goods being parallel traded outside Greece. This is likely to encourage pharmaceutical companies who are considering taking measures to restrict the parallel trade of their products, especially in Greece.

GSK stopped supplying Greek pharmaceutical wholesalers with three of its products (Imigran for the treatment of migraines, the epilepsy drug Lamictal and the asthma drug Serevent) in 2000. GSK stated that it would supply hospitals and pharmacies directly. Previously GSK had met all the orders placed by the wholesalers, who had then exported a large proportion of these orders to other member states where prices for the drugs were higher. GSK subsequently resumed supply in 2001 on a restricted basis so that supply exceeded the consumption needs of the Greek market but did not meet the wholesalers' orders in full.

The wholesalers complained to the Greek Competition Commission, who referred the question of when a dominant pharmaceutical company can refuse to fully meet wholesalers' orders with the intention of restricting parallel trade to the European Court of Justice (ECJ). The ECJ held in 2005 that it could not rule on the issue due to lack of jurisdiction. Advocate General Jacobs had, however, previously issued an Opinion that in the circumstances of this particular case, it was not an abuse for GSK to refuse to supply the orders from the wholesalers in full to prevent parallel trade. In particular, the Advocate General recognised the current specific characteristics of the pharmaceutical sector.

The Greek Competition Commission ruled that GSK had abused its dominant position for a limited period from November 2000 to February 2001 but thereafter the supply restrictions had not infringed Greek competition law. The Greek Competition Commission also suspended its ruling on whether GSK's quota system of not meeting more than 125 per cent of demand infringed competition law. There is a pending European Commission decision on a similar case. Therefore, it seems likely that there will continue to be a degree of uncertainty for dominant companies implementing quotas for the supply of pharmaceutical products until there is a European Commission, Court of First Instance or ECJ decision on the matter.

European Commission required to reconsider GSK parallel imports decision

On 27th September, 2006, the European Court of First Instance (CFI) handed down its judgment on an appeal by a Spanish subsidiary of the British pharmaceutical company GSK against a 2001 Commission decision which found that a dual-pricing system for the sale of commonly used drugs infringed Article 81(1) European Commission (EC) Treaty (*GlaxoSmithKline Services Unlimited v Commission* (Case T-168/01)). The CFI has partially annulled this decision; and in doing so, it examined the need to give the 'legal and economic context' of the pharmaceuticals sector special consideration when assessing alleged infringements of EC competition law.

In 1998, GSK notified its new sales and distribution conditions (the 'Conditions') to the European Commission, as was then required under the EC competition law rules. The Conditions established a dual-pricing

system for a number of commonly used drugs to be sold to wholesalers in Spain: wholesalers wishing to engage in parallel trade to other member states, primarily the UK, would have to pay more for GSK's products than if they were to sell these products to hospitals and pharmacists in Spain.

The CFI held that agreements that aim to treat parallel trade unfavourably must in principle have as their object or effect the restriction of competition. The Commission was, however, not entitled to conclude that such terms were *de facto* contrary to Article 81(1); rather the Commission should have conducted a competitive analysis to determine whether the agreement had as its object/effect the restriction or distortion of competition, to the detriment of the final consumer. The Commission should have considered the 'specific and essential characteristics of the pharmaceutical sector'; in particular, the fact that the price of medicines reimbursed by national health insurance schemes are insulated from competitive forces due to the fact that they are fixed by an administrative process in most member states. In other words, it could not be presumed that parallel trade in pharmaceuticals had a detrimental impact on the prices paid by consumers; an economic analysis was required.

The Commission had established that dual-pricing had a deleterious effect on the welfare of consumers (both national health schemes and patients): the difference between the prices of medicines available in Spain and other member states had been reduced, affecting in the process the ability of the Spanish parallel traders to compete with parallel traders from other member states. Therefore, despite finding that the Commission had mistakenly assessed the anti-competitive object of the dual-pricing scheme, the CFI upheld the Commission's conclusion that the Conditions constituted an agreement that had the effect of restricting competition, contrary to Article 81(1).

While not reaching a conclusion on the matter, the CFI appears to imply that the unique characteristics of the pharmaceuticals sector may justify an exemption under Article 81(3) EC on the grounds of efficiency if parallel trade reduces the level of funds available to the pharmaceutical companies to invest in research and development of new medicines.

The partial annulment of the Commission's decision means that the Commission is now required to reconsider GSK's application for an exemption as originally submitted to the Commission.

While the decision is unlikely to impact their immediate activities, it provides further encouragement to pharmaceutical companies considering their strategies in relation to parallel imports following the favourable outcome for GSK's parallel trade case in Greece earlier in September.

Sweden: Producers of reference drugs are given the right to appeal the Authority's approval of generics

In order to market a generic drug in Sweden, the generic must be approved as such by the Swedish Medical Products Agency (SMPA). Until recently, the SMPA's decisions in these matters could only be appealed by the producer of the generic drug. Since the producer of the reference drug was not entitled to appeal SMPA's decision, an approval for the marketing of the generic version was final. According to Chapter 4 of Directive 2001/83/EC, every member state is obliged to comply the principle of mutual recognition of marketing authorisations, thereby giving an approval from the SMPA legal effect in the European Economic Area.

A dispute between Pfizer and SMPA arose when SMPA approved of a generic version of one of Pfizer's reference drugs. Pfizer claimed that the drug should not be approved as generic because of an alleged discrepancy in the quality and chemical composition between the reference and the generic version. In the judgment (case no 3778-3779-04) delivered on 7th March, 2006, the Swedish Supreme Administrative Court held that the producer of the reference drug, in this case Pfizer, was entitled to appeal against the SMPA's decision to approve the generic product.

Under the Swedish Administrative Act, a decision from an administrative authority, such

as the SMPA, can only be appealed by a party directly affected by the decision on the basis that the decision constitutes a disadvantage for the appealing party. The marketing of a generic version can, however, result in loss of income for the producer of the reference drug, and sometimes loss of goodwill as well. A generic product with reduced performance and quality, or even new side effects, will affect the sale of the reference drug as well and, most likely, the goodwill of the producer of that reference drug.

With this in mind, the Swedish Supreme Administrative Court came to the conclusion that Pfizer had a *de facto* interest in the quality of the generic drug and that the SMPA's approval of the generic version was a decision that affected the producer of a reference drug, thereby giving Pfizer the right to appeal.

The consequences of this case remain to be seen but the decision gives producers of reference drugs an important opportunity to play a more active role in the approval procedure for generic drugs.

UK: Interim report of the Expert Scientific Group on phase 1 clinical trials

The Expert Scientific Group (ESG) on Phase 1 Clinical Trials was set up after six healthy volunteers received the monoclonal antibody TGN1412 drug and experienced severe adverse reactions during the first-in-man trial of TGN1412. The volunteers started experiencing adverse symptoms within an hour of receiving the test drug and within 12–16 h all six participants were admitted to intensive care with a severe inflammatory reaction and multi-organ failure. Preclinical safety studies of TGN1412 in non-human primates had not demonstrated any adverse effects. The preclinical studies, however, had not predicted a safe starting dose for human trials. The initial investigation by the MRHA had found no errors in the manufacture or formulation, dilution or administration of the drug.

The Interim Report (http://www.dh.gov.uk/assetRoot/04/13/75/69/04137569.pdf) contained 22 recommendations for increasing the safety of first-in-man trials. These recommendations were particularly targeted at the transition from pre-clinical to Phase 1 studies of biological molecules with novel mechanisms of action, new agents with highly species-specific action and new drugs directed towards immune system targets. The ESG's recommendations focussed on the calculation and administration of first doses, sharing of information relevant to safety and regulatory access to external specialist opinion in the appraisal of trial applications for higher risk new medicines.

The ESG noted that some new medicines may be intrinsically more hazardous because of their nature and composition and the type of molecular target in the body at which they are aimed. Many of the ESG's recommendations were aimed at the increased sharing of information, knowledge and training between researchers, regulators, research ethics committees and pharmaceutical industry, particularly in respect to unsuccessful preclinical studies. They also recommended that the regulator should be given access to independent specialist advice by experts in the relevant field. The ESG recommended that much more attention be given to all factors including the degree of species-specificity of the agent when calculating dosage of the drug during the phase 1 trial. To this end, where preclinical information was likely to be a poor guide to an *in vivo* response in humans, researchers should consider using the Minimum Anticipated Biological Effect Level (MABEL) approach and err on the side of caution for calculating the starting dose. The ESG recommended that new agents should be administered sequentially to participants with an appropriate period of observation between dosing and careful monitoring for adverse reactions. All phase 1 clinical trials should be staffed by appropriately trained clinical staff and, in the event of an adverse reaction occurring, a prearranged contingency of ITU facilities.

Public consultation has now closed on the Interim Report of the ESG on Phase 1 Clinical Trials, which was published on 20th July, 2006. The ESG's final report is expected to be published at the end of November 2006.

UK: Update on the human tissue act

The Human Tissue Act came into force on 1st September, 2006. For the first time, postmortem services, anatomy schools and establishments storing human tissue, bodies and organs for research, transplantation, education and training and sites displaying human tissue, such as museums, must be licensed by the Human Tissue Authority (HTA). An HTA licence will ensure that these establishments meet the requirements and standards needed for the taking, storage and use of human tissue.

Consent is the cornerstone of the new legislation. The HTA has published its Code of Practice (see July 2006 Life Science Update) and will shortly publish model consent forms.

Living donor transplantation

From 1st September, 2006, the HTA will regulate across the UK, the donation of all solid organ transplants, allogenic bone marrow and peripheral blood stem cells for transplantation from living donors, whether or not the donor is related to the recipient. For the first time, the Act makes trafficking in human material for transplantation an offence punishable by a fine and/or imprisonment.

Deceased organ donation

The Act permits cold perfusion (techniques used to preserve organs following death) until the wishes of the deceased are discovered. Relatives no longer have the legal right to overrule a person's wish to donate organs or tissue. If no record of consent exists, consent to donate can be obtained from a person nominated by the deceased or their family.

DNA testing

A new offence of DNA 'theft' has come into force. This has implications for a number of areas including paternity testing. Any person carrying out paternity testing or requiring another person to do so should make sure that the correct consent has been given.

UK: Implementation of the good clinical practice directive

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928) (the '*Amendment Regulations*') came into force on 29th August, 2006. The Amendment Regulations principally implement the Good Clinical Practice (GCP) Directive 2005/28/EC (the '*GCP Directive*') by amending The Medicines for Human Use (Clinical Trials) Regulations 2004/1031 (*Clinical Trials Regulations*) which implement the Clinical Trials Directive 2001/20/EC.

The key features of the GCP Directive relate to: (i) sponsors' delegation of functions; (ii) new requirements on sponsors/investigator's brochure and trial documentation; (iii) changes to the obligations of ethics committees; (iv) sharing of information between ethics committees and the licensing authority; (v) qualifications and procedures for inspectors; (vi) retention of documents and archiving; (vii) scope of, and procedures for obtaining, manufacturing authorisations and the obligations on the holders of such authorisations; and (viii) revision of the conditions and principles of good clinical practice.

The Amendment Regulations also include additional changes to the Clinical Trials Regulations, which do not arise from the GCP Directive. These additional provisions relate to arrangements for payment of fees, the extension of the infringement notices (warning notices) regime and notification to the licensing authority of serious breaches of GCP or the trial protocol. The Amendment Regulations define a 'serious breach' as a breach likely to affect the safety, physical or mental integrity of trial subjects, or the scientific vale of the trial.

NOTES FROM THE USA

Patent office to re-examine Wisconsin stem cell patents

The United States Patent and Trademark Office (USPTO) is believed to have granted a request to re-evaluate the validity of three fundamental patents on human embryonic stem cells granted to a University of Wisconsin scientist, James A. Thompson (US patents 5,843,780, 6,200,806 and 7,029, 913). It is understood that the Wisconsin Alumni Research Foundation (WARF), a patent

licensing organisation that represents the interests of the University of Wisconsin, provides free licences to academic researchers and charges them $500 for access to stem cell lines, while companies are charged $75,000 to $400,000 depending on the size and the terms of the licence. Geron Corporation holds exclusive rights on the Wisconsin patents to heart, nerve and pancreatic cells derived from the embryonic stem cells.

The request for re-examination of Wisconsin patents was filed with the USPTO in July 2006 by a California consumer group (the Foundation for Taxpayer and Consumer Rights) and a New York organisation backing patent reform (the Public Patent Foundation). According to these two citizen groups, the Wisconsin patents are holding back research making it more difficult for academic laboratories and biotechnology companies to develop the potential of stem cells as well as driving research abroad since protection in other jurisdictions is not as broad as that in the US. It is argued that the patents are invalid for lack of novelty and obviousness as there is evidence of three scientific papers and one pattern pre-dating Dr Thompson's work and which describe how to derive embryonic stem cells in various animals. WARF intends to defend the re-examination and is reported to have refuting the allegations made by these organisations contending that the patents did not inhibit research as WARF has given free licenses to 324 academic research groups.

Two of the three recent challenges to the WARF stem cell patents are *ex parte* re-examination requests and one *inter partes* re-examination request. Under an *ex parte* re-examination request, challengers have no contribution beyond their initial request for a patent review, unless there is a direct response from the patent holder, which is rarely the case. Should the USPTO establish the re-examination challenge to be without merit, the patent stands. In situations where the USPTO establishes an *ex parte* challenge does have merit, the scope of the patent is subject to further discussion between the patentee and the USPTO, essentially reprocessing the patent application.

The comparatively new *inter partes* re-examination request allows greater participation by the challenging party. If the USPTO decide the *inter partes* challenge has merit, the challenger will be allowed to counter with its own papers each time the patent holder files a document at the USPTO. Once the USPTO's decision is made the patent holder can appeal it in court, which can be an expensive and time-consuming process.

Data published by the USPTO indicates that 400–500 requests for re-examination are filed each year and 90 per cent of them are granted. Also, among similar requests filed between 1981 and 2005, 29 per cent of the claims were upheld as granted, 12 per cent cancelled and in 59 per cent of cases more minor changes were made to the claims. It is not known when a decision on these cases is likely to be given by the USPTO.

Patent interpretation and the meaning of 'consisting of'

Although it concerned a non-biotechnological field of technology, the decision of the US Court of Appeals for the Federal Circuit in the case of *Conoco Inc v Energy & Environmental International LC*[1] is of general interest because of its construction of the term 'consisting of' in patent claims. The phrase is generally considered to be a term of art introducing a limitation on the scope of a claim by restricting it solely to those elements of which the invention is said to consist such that a product or process containing further elements would not fall within its scope. The *Conoco* case pointed out that this was not an invariable rule.

The patents in suit related to processes for making drag-reducing agents that are injected into oil and gas pipelines to reduce friction in pumping operations. The relevant claim of one of the patents referred to a process that 'consists of water or water/alcohol mixture in which the drag reducing agent is suspended'. The defendant argued that the use of the language 'consisting of' limited the scope of the claim to product performing the recited steps of the patent and nothing else. It was further argued that this excluded as a result a process where the suspension medium included a non-alcohol component called methyl isobutyl ketone (MIBK).

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Previous decisions of the Federal Circuit have made clear that 'consisting of' does not exclude additional components or steps that are unrelated to the invention. In *Conoco*, the Federal Circuit went further and stated that impurities that a person of ordinary skill in the relevant art would ordinarily associate with a component on the 'consisting of' list do no exclude the product or process in dispute from infringement. The intentional addition of a component does not change its status as an 'impurity ordinarily associated' with a listed element. In the present case, it was found that if the MIBK was added to adjust the stability of the suspension, it may have been more than merely an impurity and would therefore be unlikely to infringe. It was, however, ultimately decided that the presence of the substance was in the nature of an impurity associated with the claim elements recited and therefore did not take the disputed process outside the scope of the claim in spite of seemingly limiting words 'consisting of'.

Waxman introduces follow-on biologics bill

The Access to Life-Saving Medicine Act was introduced before the US Senate on 29th September, 2006 by Representative Henry Waxman, Senator Charles E. Schumer and Senator Hillary Rodham Clinton.[2] The Bill aims to establish a procedure enabling the Food and Drug Administration (FDA) to approve generic or follow-on biotech drugs comparable to that for small molecule-based therapeutics introduced in 1984 by the Drug Price Competition and Patent Term Restoration Act (the 'Hatch–Waxman Act').

The route established by the Hatch–Waxman Act is designed to allow generic version of small molecules to be approved without the need for full clinical testing to demonstrate safety and efficacy. Rather, the generic can be approved where it is demonstrated in small-scale studies that the generic is identical, or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. This is known as the abbreviated NDA route. But due to the much larger size and complexity of biological molecules and specific characteristics imparted by the particular manufacturing process used, the test of bioequivalence measured by reference to the comparative bioavailability of the two compounds is not suitable in the biologic context.

The only follow-on biologic approved by the FDA is Sandoz's Omnitrope human growth hormone, but only after the intervention of a court ordering the FDA to consider Sandoz's application. The FDA then pointed out that the approval of Omnitrope does not set up a pathway for approval of biotech products licensed under the Public Health Service Act, nor does it signify that more complex proteins approved as drugs under the Federal Food Drug and Cosmetic Act could be approved by the FDA as follow-on products.[3] In addition, Omnitrope is considered less complicated than most other biotech products. If the abbreviated NDA route is not generally suitable and the route followed by Sandoz (the bibliographic route or 'paper NDA') is not to be seen as setting a precedent for follow-on versions of innovative drugs approved under BLA, the only route left to the generic is to undertake full clinical testing.

Under the proposed Bill, applicants wishing to obtain the FDA's approval would have to demonstrate that: (a) there is no clinically meaningful difference between the new product and the product that has been previously approved (ie that the new product is 'comparable' to the 'reference' product); (b) the comparable product shares the 'principal molecular structural features' of the reference product; (c) the comparable product possess the same mechanism of action as the reference product (if this is known); (d) the comparable product label carries one or more of the approved indications for the reference product; and (e) the comparable product's route of administration, dosage, form, and strength of, are the same as the reference product.

The FDA must approve a comparable product application unless for example: (a) the reference product has been, or is being, withdrawn for safety or effectiveness reasons; or (b) the application contains an untrue

statement of fact. Also, the Secretary may approve an enhanced version of the reference product if the application contains sufficient information to establish safety and efficacy. But due to the high complexity of the biotech products, the FDA has discretion to consider each application individually and require a clinical study or studies necessary to establish comparability of the new product. The Bill requires the FDA to meet with the sponsors of comparable biotech products with the view to reaching written agreements on the design and size of studies to be carried out.

Applicants for comparable products may choose to establish that the new product is 'interchangeable', that is it is expected to produce the same clinical results as the reference product in any given patient. Applicants are not required to apply for 'interchangeability', but the Bill grants tax credits for the cost of studies necessary to establish that the new product is interchangeable as well as a period of exclusive marketing to the first applicant to get approval of interchangeability.

The FDA must approve or disapprove an application for a comparable biotech product eight months after submission, or 180 days after the application is accepted for filing, whichever the earlier. The final action date, however, may be extended by joint agreement of the applicant and the FDA.

Finally, an applicant for comparable product has an option to request a patent holder to disclose relevant patents and the patent holder has 60 days to satisfy the request, otherwise he will lose the right to enforce the patent against the applicant. In addition, if the patent holder fails to bring a patent infringement action within 45 days of the request, the remedies in any later action to enforce patent against the applicant are going to be limited to reasonable royalties.

It is not expected that this particular will be pass into law before the end of the current session of Congress; however, it sets the legislative agenda for establishing a pathway for the approval of follow-on biologics in the next session. It should be noted that a comparable pathway has existed in the EU since 2004 when Article 10 of European Parliament and Council Directive 2001/83 on the Community code relating to medicinal products for human use was amended.

FDA encourages use of technology to advise of product recalls

When a prescription product manufacturer is confronted with the need to initiate a Class I recall, time is of the essence. Recognising this, the United States Food and Drug Administration has announced that the use of e-mail may be a very effective means of conveying information to customers and governments about the need for a recall.[4]

Once the decision to undertake a recall is made either by a company or at the suggestion of FDA, the company must create a recall strategy. The strategy is a detailed course of action for the recall tailored to the unique characteristics and nature of the risk posed by the product. The plan addresses the depth of recall, the need for public warnings, and the type and extent of effectiveness checks to measure the success of the recall.[5]

21 CFR 7.42 provides that a recall strategy must include a plan that includes an evaluation of the depth of a recall, the scope of a public warning, a scheme for checking the effectiveness of the recall, and a schedule for updating FDA. The regulations and Guidance for Industry – Product Recalls, Including Removals and Corrections from ORA/Office of Enforcement, Division of Compliance Management and Operations[6] are explicit as to the content of the communications with those who are being asked to return the prescription product (again dependent upon the seriousness of the hazard involved). The purpose of the communication, as detailed by 21 CFR 7.43 whatever its form, should be:

- that the product … is subject to a recall;
- that further distribution or use of any remaining product should cease immediately;
- where appropriate, that the direct account should in turn notify its customers who received the product about the recall; and
- to provide instructions regarding what to do with the product.[7]

The regulations emphasise that the communication can be sent by telegram, mail or first class letter.[8] Yet with breadth of distribution of a prescription product throughout the world mail can serve at time to delay recalling the product. Furthermore, any type of delay can pose an even great risk for the prescription product manufacturer: a product liability claim for negligence in conducting the recall.

Generally, evidence of recalls is excluded from trial in claims for personal injury. One court has ruled, however, that if there is negligence in conducting the recall there may be a claim made against the manufacturer. *Figueroa v Boston Scientific Corp* (2003 WL 21488012 at *5 (SDNY, 2003)).

To treat female stress incontinence, Natalie Figueroa's physician implanted a ProteGen Sling in late 1997. Two years later, in January of 1999, the manufacturer initiated a voluntary recall of the device. The FDA agreed with this decision and classified it as a Class II recall.[9] The implanting physician learned about the recall in April 1999, four months after the recall began, when Ms Figueroa faxed him a copy of the notice. Months before this, Ms Figueroa had a variety of complications. The recall notice prompted the physician to diagnose Ms Figueroa with vaginal erosion caused by the device and then to surgically remove it. Ms Figueroa then sued the prescription product manufacturer alleging, in part, that the recall had been negligently conducted, causing a delay in the removal of the device. As the case approached trial the manufacturer filed a motion to exclude evidence about the recall. The court denied the motion and accepted the plaintiff's arguments and denied the defence motion, noting that a jury could find that the recall was defective because:

- it was limited only to unused devices and did not describe implanted devices;
- the recall was insufficient to ensure that physicians acted promptly to follow-up with patients; and
- if the recall had been undertaken promptly and effectively, Ms Figueroa's prescribing physician may have acted sooner and the injury might not have been as serious.

Time is of the essence. A manufacturer should take all steps reasonably available to ensure that the word of the recall reaches its customers.

In March 2006, FDA issued Guidance for Industry: Using Electronic Means to Distribute Certain Product Information.[10] The Guidance emphasises that 21 CFR 7.49, the regulation governing communications used during recalls, permits 'the use of e mail and other electronic communication methods, such as fax or text messaging, to accomplish any recall notification…' FDA recognises the benefits of using e-mail communications:

> Electronic communications … can significantly shorten the time between an event and the public's knowledge of the event. Rapid communication is especially important when the event involves product safety. E-mail and other electronic communications can be more efficient and more timely than regular or traditional mail. They involve considerably less cost to the sender than older, more traditional delivery services. Recipe or delivery can be automatically verified through various means such as a delivery or read receipt confirmation or other electronic receipt acknowledgement mechanisms. Any necessary follow-up (such as when receipt of e-mail is not acknowledged in some fashion) can also be accomplished electronically. If receipt of the electronic communication is not acknowledged appropriately by the recipient (as determined by the sender) or the electronic communication is undeliverable, the sender can resort to more traditional notification methods or other means to ensure the communication is received.

FDA is also clear as to the form and content of all communications about recalls. If printed notice is used, the written communication should be 'conspicuously marked, preferably in bold red type, on the letter and the envelope' that the matter involves a recall. 'The letter and the envelope should be also marked: urgent for class I and class II recalls and,

when appropriate, for class III recalls. Telephone calls or other personal contacts should ordinarily be confirmed by one of the above methods and/or documented in an appropriate manner.'

If e-mail or another form of electronic communication is used, the 2006 Guidance recommends:

- Follow all specifications for written communications that are feasible including marking the e-mail 'URGENT'.
- The electronic communication 'should be distinctive in appearance so that it will be promptly recognised and read'.
- Use the subject line to convey the importance of the message that includes the name of the product.
- The content of the e-mail should follow the same requirements as a written communication.
- The guidelines are that the communication is 'to convey that a particular product is subject to recall, that further distribution of the product should cease, and, if applicable, directly notify customers who received the product, and provide instruction for return.'

The regulations also provide what the contents of the communication, in whatever form, should include:

- be brief and to the point;
- identify clearly the product, size, lot number(s), code(s) or serial number(s) and any other pertinent descriptive information to enable accurate and immediate identification of the product;
- explain concisely the reason for the recall and the hazard involved, if any;
- provide specific instructions on what should be done with respect to the recalled products; and
- provide a ready means for the recipient of the communication to report to the recalling firm whether it has any of the product, for example by sending a postage-paid, self-addressed postcard or by allowing the recipient to place a collect call to the recalling firm.

Section 7.49 also details what should not be included in the communication: the recall communication should not contain irrelevant qualifications, promotional materials, or any other statement that may detract from the message.

In this global economy dependent on electronic communications, a prescription product manufacturer faced with an urgent need to advise its worldwide customers about a safety issue with its product should explore all means available to make sure that all receive timely and accurate information about the risk.

Notes and references

1. Case Nos. 05-1363 and 05-1461 (Fed. Cir., 17th August, 2006).
2. Available from http://www.house.gov/waxman/pdfs/bill_generic_biologics_9.29.06.pdf.
3. See Reed Smith (2006). US and EU legal and regulatory update. *J. Comm. Biotechnol.* **13**(1), 52–63.
4. See http://www.fda.gov/oc/guidance/electronic.html.
5. 21 CFR §7.3.
6. See http://www.fda.gov/ora/compliance_ref/recalls/ggp_recall.htm.
7. 21 CFR §7.49(a).
8. 21 CFR §7.49(b).
9. A Class II recall is defined 'as a situation which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious health consequences is remote'.
10. See http://www.fda.gov/oc/guidance/electronic.html.