Raft of Regulations

Recent legislation may have potentially significant implications for pharmaceutical companies. Law firm Hogan and Hartson summarises the regulatory changes and the newly published medicinal products legislation

The beginning of May brought important changes in the European Union (EU) – not only the accession of 10 new Member States, but also to the export controls applied by the US FDA as well as regulation of pharmaceuticals and clinical trials in the expanded EU.

By 1 May, 2004, Member States were required to have in effect their legislation implementing the EU Clinical Trials Directive (2001/20/EC) for pharmaceuticals, which aims to make the regulation of clinical trials uniform across the EU while protecting patient safety.

With few exceptions, Member States have been late publishing the necessary legislation and explanatory guidance. The delays are understandable, due to the complexity of the changes, but are creating confusion as manufacturers and other clinical trial sponsors attempt to comply with the new requirements.

Generally speaking, ongoing clinical trials do not need to be resubmitted to Ethics Committees and Member State drug regulatory agencies. However, because all clinical trials require authorisations now — including Phase I studies in the UK that in the past needed only a clinical trial exemption (CTX) — the UK is deeming existing CTX studies as possessing Clinical Trial Applications (CTAs) on an interim basis. Effectively, the CTX procedure is a thing of the past.

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ethics committee

New EU-level requirements for Ethics Committees are imposed, many of them mirroring the International Conference on Harmonization Good Clinical Practices (ICH GCP). One challenging feature is the requirement for a single key Ethics Committee opinion per member state, even for clinical trials with multiple sites in a country.

Ethics Committee review and regulatory agency review can run concurrently, although a change in the protocol by one could necessitate resubmission to the other. Time limits are placed on both Ethics Committee and agency reviews to reduce delays in launch of clinical trials. Variations of the protocol must be notified in some cases and logged in others.

Every clinical trial sponsor must either be established in the EU or European Economic Area (EEA) or have a legal representative there. Sponsors must enter information about their clinical trials into the EUDRACT database. Also, Member States must apply both GMPs and the Qualified Person release requirements to investigational products as well as for marketed products.

Furthermore, Member States must set up inspection systems for both GMPs for investigational medicines and Good Clinical Practices (GCPs). Sponsors and Member States face stepped up requirements on safety monitoring; pharmacovigilance; insurance for subjects; and compliance with labelling standards for investigational medicinal products.

‘Non-interventional’ studies are exempt from the Directive but may be subject to other EU or Member State requirements.

Because this legislation is a Directive, Member States have some latitude in issuing their own implementing regulations. Those in the pharmaceutical and biotech industry must monitor and comply with all the Member State clinical trial regulations implementing the Directive, wherever in the EU or the EEA they are conducting clinical trials.

US export control

Accession of the 10 new Member States will simplify industry compliance with FDA drug export requirements to those countries, as they automatically become ‘listed countries’ under FDA export law. A new drug, biological product, or medical device that does not have FDA approval may be exported to any country in the world if it possesses a valid marketing authorisation by the appropriate authority in the EU (21 USC § 382 (b)(1)(A)).

Also, for companies wishing to conduct clinical trials in any of the 10 new Member States it will no longer be necessary to request FDA’s permission under the agency’s 312 Export Program to export unapproved drugs, biologicals, and devices. The Congressional intent underlying this provision is that ‘listed countries are advanced countries capable of imposing effective controls on product investigations without the need for FDA protection under the 312 Export Program. The 10 new Member States effectively graduated to listed country status, and sponsors of clinical trials need to worry less about FDA export controls and more about the entry into force of the new EU Clinical Trials Directive.

new EU pharma rules

New EU rules on pharmaceuticals were published on 30 April, 2004. The legislation covers the authorisation and regulation of human and veterinary medicines, provides for an increased role for the

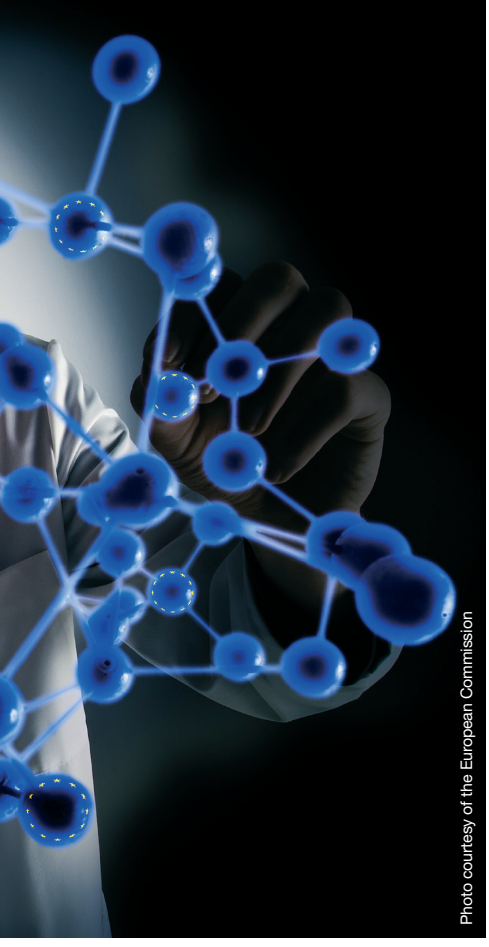
Photo courtesy of the European Commission

renamed European Medicines Agency (EMA), and aims to speed up product approvals. The new rules also simplify authorisation procedures and improve transparency without changing the existing system's basic principles of in which a centralised authorisation procedure exists alongside a decentralised procedure based on mutual recognition.

The package consists of the following:

- Regulation on authorisation and supervision of medicinal products for human and veterinary use and on the EMA (replacing Regulation 2309/93 which set up EMEA)[1]
- Directive on the Community code relating to medicinal products for human use (amending Directive 2001/83/EC)[2]
- Directive on the Community code relating to medicinal products for veterinary use (amending Directive 2001/82/EC)[3]
- Directive on traditional herbal medicinal products (amending the Community code Directive 2001/83/EC)[4]

The latter three directives entered into force on 30 April, but Member States have until 30 October, 2005 to implement the measures in national law.

The regulation on authorisation and supervision of medicinal products is directly effective in the national law of the Member States without the need for additional implementing legislation at Member State level. The regulation entered into force on the 20 May, 2004 (the 20th day following its official publication), although most of its provisions do not apply until 20 November, 2005.

Under the new regulation, assessment of new medicines by the EMA will be faster. The authorisation procedure will be changed so that more categories of medicine will be obliged to use the centralised procedure instead of seeking authorisation in first a 'reference Member State' then in other Member States through the decentralised mutual recognition system.

Currently, the centralised procedure must be used for authorisation of biotech products. Under the new rules, the centralised procedure becomes mandatory for medicines to treat AIDS, cancer, diabetes, neurodegenerative disorders and orphan diseases; after four years it will be extended to cover medicines for autoimmune and viral diseases. A general review clause will enable further extension of the EMA exclusive jurisdiction to medicines for other diseases.

A fast-track registration procedure for products of significant therapeutic interest has been introduced, allowing them to be assessed and authorised expeditiously. The possibility of a conditional marketing authorisation has also been introduced. It allows the granting of a one-year authorisation, provided there is an important expected health benefit for the patients concerned and that the company agrees to carry out additional monitoring and clinical studies, which will be reviewed at the end of this period.

Finally, subject to further additional provisions, a Europe-wide system to make medicinal products available in advance of authorisation for a 'compassionate use' will also be possible. This will enable patients to be allowed access to products still undergoing investigation even if there are no clinical trials performed of the product in that country.

promoting innovation

The revised legislation provides for an overall increase in transparency and improves access to more information on the results of the pharmaceutical decision-making process, including assessment reports and the summaries of product characteristics.

One of the biggest changes is in regulatory data exclusivity, which will now be harmonised across the EU25 in a compromise policy called '8+2+1'. Data submitted by companies for the approval of medicines will be protected for 10 years across the EU from the time of first authorisation, and it will not be possible to market generics until 10 years have elapsed. This can be extended by a year if a further innovative indication for the drug is authorised.

It is, however, possible for a generic company to submit an abridged application, seeking to rely upon the innovator's data, eight years after the date of the marketing authorisation of the innovative product. This improves the current situation in many countries in the EU25 that currently offer only six (and in some cases three) years' protection. The 8+2+1 formula applies only to medicines approved after the legislation's effective date.

Regarding the generic sector, the new 'Bolar' rule introduces the possibility for companies to start development work while the innovator's product is still under patent protection.

clarifying generics

'Generic medicinal product' is defined as 'a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies'.[5] This should provide greater legal certainty and better application of the regulatory procedures for generic medicines.

For biological medicinal products that are similar to a reference biological product but do not meet the definition of a generic, the results of 'appropriate' pre-clinical tests or clinical trials must be provided, the type and quantity of supplementary data must comply with the 'relevant criteria' for full application, and 'the results of other tests and trials from the reference medicinal product's dossier shall not be provided'.[6]

The new directives clarify key definitions and the scope of directives 2001/83/EC and 2001/82/EC. The definition of 'medicinal product'[7] now clearly includes new therapies and the growing number of so-called 'borderline' products between the medicinal product sector and other sectors. It specifies the type of action that the medicinal product may exert on physiological functions. It covers medicinal products such as gene therapy, radiopharmaceutical products as well as certain medicinal products for topical use.

The new directive on traditional herbal medicinal products provides for a simplified registration procedure for products requiring fulfilment of European standards of quality, safety and efficacy.

The new legislation includes important changes in the EU legislative framework for regulation of product quality, safety and efficacy and also for innovator and generic rights, and has significant implications for pharma companies selling their products in the EU, particularly those exporting products from the US to the EU. ■

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3. OJ L 136, 30.04.2004, p58.
4. OJ L 136, 30.04.2004, p85.
5. Article 1(8), OJ L 136, 30.04.2004, p39; new Article 10.2(b) of the Community code directive.
6. Article 1(8), OJ L 136, 30.04.2004, p39; new Article 10.4 of the Community code directive.
7. Article 1, OJ L 136, 30.04.2004, at p36; revised Article 1.2 of the Community code directive.