

EU pharmaceutical legislation: an overview of the main changes

Peter Bogaert, Covington & Burling

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A MAJOR OVERHAUL

On 30 April 2004, the day before the accession of ten new member states to the EU, four important new pieces of legislation affecting the legal framework for medicinal products in Europe were published in the *Official Journal* (often referred to as the Future Medicines Legislation or FML project). They include:

- A new Regulation 726/2004 replacing the existing Regulation 2309/93 governing the centralised procedure.
- Directive 2004/27 amending the Code for Medicines for Human Use, set out in Directive 2001/83.
- An additional amendment to Directive 2001/83 providing a new regime for traditional herbal medicinal products.
- A directive amending the existing Code for Medicines for Veterinary Use (*Directive 2001/82*) in parallel to Directive 2004/27.

The revision of the EU pharmaceutical legislation is substantial. There are up to 200 changes to the existing rules, ranging from clarifications of definitions and administrative and procedural provisions, to crucial changes in the approval process for generics and in the regulatory powers of the competent authorities, and a widening of the mandatory scope of the centralised procedure (*see also box, General trends*).

Most provisions take effect at the end of 2005 (30 October 2005 for Directive 2004/27 and 20 November 2005 for Regulation 726/2004) but some take effect now and the new harmonised data exclusivity rules will only take practical effect in 2014.

This chapter focuses on the first two changes listed in the bullet points above. It discusses specific elements of them and covers:

- New rules for the approval of generic products.
- Specific rules for follow-on biologicals (biosimilars).
- Scope of the centralised procedure.
- Legal standards for marketing authorisations.
- Information to patients.
- Business flexibility issues.
- Quicker approval process.

- Stricter pharmacovigilance.
- Increased transparency.
- Validity of marketing authorisations.
- Compassionate use.
- Supply obligations.
- Marketing authorisations granted at the initiative of a member state.
- Support of small and medium-sized entities (SMEs).

NEW RULES FOR THE APPROVAL OF GENERIC PRODUCTS

One of the major revisions is a harmonised data exclusivity period for all innovative products, irrespective of whether they are approved under the centralised or the mutual recognition procedure. This will replace the current protection periods of ten years, six years or zero years beyond patent life.

"Eight plus two years of data exclusivity"

Under the new rules, abridged applications for generics can be filed after eight years following the approval of the reference product in the EU, but the generic product can only be marketed after ten years. An extra year of data exclusivity (extending the two-year period) is obtained in the case of approval during the first eight years of a new therapeutic indication that is of significant clinical benefit compared to existing therapies. This extra protection cannot be renewed.

The new data exclusivity periods will apply to innovative products for which a marketing authorisation application is submitted under the revised legislation and will therefore probably only affect abridged applications from 2014 at the earliest. Some new member states are seeking further extensions for their territory.

Definition of a generic product

For the first time, the legislation formally defines a generic medicinal product. This definition replaces the existing concept of "essential similarity" but builds on the existing explanation of that concept in the Notice to Applicants and in the European Court of Justice (ECJ) decision in *Generics (Case C-368/96)* (now updated in *Novartis (Case C-106/01)*). The key elements of the definition are:

GENERAL TRENDS

The revision of the EU pharmaceutical legislation contains a multitude of changes, some of which are fundamental while others are more technical or cosmetic. However, a couple of general trends emerge:

- The revised rules envisage more active and centralised supervision of the market and industry practices. This will, among other things, apply to compliance with pharmacovigilance obligations and is also likely to result in more centralised decision making for older products. In addition, the European Commission can, for the first time, impose financial penalties for regulatory infringements.
- Regulators will benefit from wider discretion due to more flexible standards for suspension, revocation or variation of approvals.
- The revised rules call for much more transparency towards the public, including conditions attached to product approvals, pharmacovigilance information and the reasons for revocation of approvals.

The new rules also show an underlying trend in the regulatory system of considering marketing authorisations more as a tool of public health, to be managed by the regulators for the common good, than as an asset of the pharmaceutical company.

- **Same qualitative and quantitative composition in active substances.** Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives are considered to be the same active substances provided they do not differ significantly with regard to safety and/or efficacy (the generic applicant will have to demonstrate this). It is understood that this only applies when these different substances contain the same active moiety.
- **Same pharmaceutical form.** Various immediate-release oral forms are considered to be in the same form. In addition, in *Novartis* the ECJ recently held that a macroemulsion, a microemulsion and a nanodispersion (after mixing of the liquid product in a drink) can be treated as the same pharmaceutical form if the differences are not significant from a scientific point of view.
- **Bioequivalence** has to be demonstrated by bioavailability studies, unless the product meets criteria set out in detailed bioequivalence guidelines.

Line extensions

There was a debate under current legislation as to under what circumstances line extensions can attract new data exclusivity and the ECJ decided in *Novartis* against extra exclusivity for line extensions that involve a new:

- Indication;

- Route of administration; or
- Strength (or possibly another change implying absence of bioequivalence).

The new legislation provides that approvals of new strengths, pharmaceutical forms, routes of administration and presentation (as well as other variations or extensions) must "be considered as belonging to the same global marketing authorisation" for purposes of the abridged application rules. This is apparently intended to exclude additional data exclusivity for line extensions, but this is not explicitly stated.

Broader flexibility to allow "hybrid" applications

The new rules continue to allow authorities to accept applications that refer to a reference product but contain data that bridge differences between the reference product and the new product. The provision which allows authorities to accept such applications is sometimes described as the "proviso" and its scope is now widened. It can apply if there are different indications, strengths, pharmaceutical forms or routes of administration or when bioequivalence is not demonstrated, but also where there is a change in the active substance or other instances where the product does not meet the definition of a generic product. The provision should not, however, be applied too widely since it remains tied to the general rules on approving generic copies. When it is used, appropriate pre-clinical and/or clinical data must be submitted.

Generic copies of centrally approved products

The new legislation allows for generic copies of centrally approved products to be approved under the mutual recognition procedure, subject to certain conditions. The European Commission (Commission) has confirmed that this does not apply to biotechnology products, which are also subject to the specific rules on biosimilar products (*see below, Specific rules for follow-on biologicals (biosimilars)*).

Generic approval in a member state without a reference product

The new rules contain a mechanism that allows the approval (under the national or mutual recognition procedure) of a generic in a country where the reference product is or was not authorised. This mechanism is sometimes described as the "Eurogenerics" clause.

New indication for a well established product

A new indication for a well established substance (normally a substance approved for at least ten years) triggers a one-year data exclusivity period if significant pre-clinical or clinical studies were conducted. The exclusivity is likely to relate only to the therapeutic indication, but this is not clear from the text.

Bolar amendment and exclusivity for switch data

In connection with these new rules, EU legislation now also contains a so-called Bolar amendment. The revised Directive 2001/83 provides that tests conducted in preparation of abridged applications and other "consequential practical require-

ments" do not constitute a patent infringement. Based on the wording of the article, the exemption only applies to the preparation of abridged applications (and possibly applications for similar biologicals) and does not extend to activities in preparation of bibliographical applications or applications for new combinations (see chapter, *The Bolar clause in the new European pharmaceutical regulatory package in this Handbook*).

Proposals to extend this provision to manufacturing for export to a third country where there is no patent or where a compulsory licence was granted (in implementation of the Doha declaration) were not accepted. It was considered that rules specifically governing exports could not be part of a directive dealing with the placing of medicines on the Community market. The Commission has undertaken to address the implementation of the Doha declaration in the EU as a matter of the highest priority in early 2004.

Finally, the new rules also provide for additional exclusivity for switch data. The revised Directive 2001/83 provides that where a change in classification of a medicinal product has been authorised on the basis of significant pre-clinical and clinical tests, the competent authority must not refer to the results of those tests or trials when examining an application by another applicant for a change of classification of the same substance for a year after the initial change was authorised.

SPECIFIC RULES FOR FOLLOW-ON BIOLOGICALS (BIOSIMILARS)

There is explicit acknowledgement that biological medicinal products similar to a reference medicinal product do not usually meet all conditions necessary to be considered a generic (in particular because of differences related to raw materials or in manufacturing processes). Where this is the case, the results of appropriate tests must be provided covering safety and/or efficacy, in accordance with the relevant criteria in Annex I to Directive 2001/83 and related guidelines. This new provision strengthens the existing rules on biosimilar products that were adopted in June 2003 as part of the revised Annex I to Directive 2001/83, and which came into effect in November 2003.

SCOPE OF THE CENTRALISED PROCEDURE

The centralised procedure is currently mandatory for biotechnology medicines, which cover products developed by biotechnological processes involving recombinant DNA technology, hybridoma and monoclonal antibody methods, and gene therapy. The procedure is optional for new chemical entities (NCEs) and for other products that are sufficiently innovative in the eyes of the European Medicines Agency (EMA) (see box, *New names*).

The Commission's original proposal for a new regulation required all NCEs to be authorised under the centralised procedure, but the pharmaceutical industry raised concerns about the lack of choice and flexibility and ultimately the proposal was narrowed down considerably. Under the new rules, the centralised procedure will be compulsory for:

- All biotechnology products.

NEW NAMES

The EMA's full name has been changed to the European Medicines Agency, but for practical reasons the Agency decided to keep using the existing acronym EMA. The old CPMP is now the Committee for Medicinal Products for Human Use (CHMP). The CHMP should not be confused with the newly established Committee for Herbal Medicinal Products, established by Directive 2004/24 on traditional herbal medicines, and which will be described as HMPC.

An officially created Co-ordination Group will co-ordinate the mutual recognition procedure.

- Products containing NCEs for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes.
- Orphan medicinal products.
- From 20 May 2008, products containing a new active substance for the treatment of auto-immune diseases, other immune dysfunctions and viral diseases.

This will only apply from 20 November 2005 (and 20 May 2008 where relevant) but will probably be applied earlier in practice. Later on, other product categories may be added to this list through a simplified procedure involving only the Commission and the Council and it is expected that this will gradually be done to make the centralised procedure more pivotal.

Companies retain the choice between following the centralised procedure or the mutual recognition procedure, for:

- All other NCEs.
- Products that constitute a significant therapeutic, scientific or technical innovation.
- Products for which centralised approval is in the interests of patients' health at Community level.

NCEs are defined in Regulation 726/2004 as new active substances that were not authorised in the Community as at 20 May 2004.

LEGAL STANDARDS FOR MARKETING AUTHORISATIONS

The revised rules confirm the general principle (also reflected in the *Pierrel (Case C-83/92)* decision) that marketing authorisations can only be granted or refused for reasons related to quality, safety and efficacy. However, there is a new definition of risk and risk/benefit ration. There are also some additional provisions relating to the assessment of environmental risks, but environmental considerations do not legally form part of the approval criteria.

"Added therapeutic value" is not required to obtain a marketing authorisation, but it is expected that the EMA will collect information on the methods used by member states to assess added therapeutic value. This may be a preparatory stage for the Commission and the EMA to become more involved in pricing

and reimbursement decisions (especially given the expertise the Commission can gain from the ongoing study on price-setting mechanisms for orphan medicines and a recently announced study on pricing of non-reimbursed medicines). However, Article 1 of Regulation 726/2004 reconfirms that its provisions do not affect national pricing and reimbursement powers.

The standards for refusing, suspending, revoking or varying marketing authorisations have been amended to grant more discretion to the authorities. They now refer to situations where the risk-benefit balance "is not considered favourable" or where "the view is taken" that the product is harmful.

INFORMATION TO PATIENTS

The Commission had proposed a pilot project to disseminate information, in which the pharmaceutical industry would be involved, to the general public on treatments for AIDS, asthma, chronic bronchopulmonary disorders and diabetes. This drew a lot of political attention, especially during the first reading in the European Parliament. However, the provision was dropped. Instead, the revised Directive 2001/83 requires the Commission to present a report to the European Parliament and the Council within three years of the entry into force of the revised Directive on current information provision practices, particularly on the internet, discussing the risks and benefits for patients. Following analysis of the report, the Commission can put forward information strategy proposals to ensure good quality, objective and reliable and non-promotional information on medicinal products and other treatments. The Commission is also invited to review the question of the provider of information's liability.

BUSINESS FLEXIBILITY ISSUES

Business flexibility is reduced by the broader mandatory scope of the centralised procedure and by the policy (not clearly reflected in the new legislation) that withdrawals of applications in specific member states to avoid arbitration will no longer be possible under the mutual recognition procedure.

In other respects, the rules provide business flexibility:

- The new Regulation 726/2004 codifies the single trade name policy for centrally approved medicines (only one brand name for the entire Community for the same centrally approved product) but specifically allows for exceptions related to trade mark law.
- The use of two or more commercial designs for a centrally approved product is permitted.
- Co-promotion is permissible. This will overturn existing restrictions in Italy and Greece.
- Parallel centralised approvals are allowed for the same product for co-marketing reasons (or when there are public health reasons). However, such parallel approvals will have to be used within three years as any marketing authorisation lapses if the product is not placed on the market within three years or ceases to be marketed for that period.

QUICKER APPROVAL PROCESS

The deadlines for the administrative decision making procedure are substantially shortened. This applies to centralised marketing authorisations and to Community referrals under the Directive (arbitration under the mutual recognition procedure, and Article 30, 31 and 36 referrals).

Under the centralised procedure, expedited scientific review by the Committee for Medicinal Products for Human Use (150 days instead of 210 days) is possible for products that provide a major therapeutic innovation or are, in another way, of major public health interest. However, the standard time allowed for scientific review can be extended beyond 210 days.

STRICTER PHARMACOVIGILANCE

The revised legislation imposes much more extensive and stricter post-market surveillance. It also imposes sanctions for non-compliance with regulatory requirements. The EMEA is in charge of co-ordinating the verification of pharmacovigilance compliance and an increase in inspections can be expected. All this is, in part, intended to meet the concerns raised by the indefinite validity of marketing authorisations after their first renewal.

Marketing authorisation holders will be prohibited from communicating information relating to pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the EMEA (under the centralised procedure) or competent authority (under the national and mutual recognition procedure). The information must be presented objectively and must not be misleading. Member states are to take the necessary measures to ensure that companies that fail to comply with these obligations are subject to effective, proportionate and dissuasive penalties. For centrally approved products the Commission will also be able to impose financial penalties. In addition, marketing authorisation holders will be required to provide the EMEA or competent authority, as appropriate, with all data relating to the volume of sales and prescriptions, when requested.

The opinions of the CHMP on pharmacovigilance matters, alerts regarding manufacturing defects, serious adverse reactions and other pharmacovigilance information will be made available to the public. Patients are also encouraged to communicate adverse reactions to healthcare professionals.

The deadlines for compulsory submission of periodic safety update reports (PSURs) have also been shortened. Marketing authorisation holders were previously required to submit PSURs:

- Every six months during the first two years following authorisation;
- Once a year for the following three years; and
- At five yearly intervals after that.

The requirement is now for PSURs to be submitted:

- Every six months after authorisation until they are placed on the market;

- Every six months during the first two years following the initial placing on the Community market;
- Once a year for the following two years; then
- At three yearly intervals.

In addition, PSURs can be requested at any time.

INCREASED TRANSPARENCY

The new legislation provides for additional transparency. This will, among other things, apply to:

- Reasons for withdrawals of marketing authorisation applications under the centralised procedure.
- Refusals to grant marketing authorisations.
- A general pharmacovigilance database.
- National public assessment reports.

The need to protect confidential information is reflected in several but not all transparency provisions and substantial work will be required to adopt balanced practical procedures implementing the new rules.

VALIDITY OF MARKETING AUTHORISATIONS

Marketing authorisations will continue to be valid for an initial five-year period but, on renewal, they will in principle be valid for an unlimited time. Under the centralised procedure a conditional authorisation will also be possible. They will be valid on a renewable basis for periods of one year at a time.

Marketing authorisation holders will be required to inform the EMEA (in the centralised procedure) or the competent authority of the authorising member state (in the national or mutual recognition procedures) of the dates of actual marketing. Notification will be required if a product ceases to be placed on the market. The legislation also contains "sunset provisions" under which marketing authorisations that are not used for three consecutive years will cease to be valid, subject to exemptions on public health grounds.

COMPASSIONATE USE

For the first time the legislation contains provisions on compassionate use. These apply to products:

- That must or can be approved under the centralised procedure (although the application of the rules to the latter category of products is not always clear);
- That are used for serious diseases for which there is no therapeutic alternative; and
- That are in clinical trials or for which a marketing authorisation application is pending.

Responsibility to allow compassionate use rests with the member states but an advisory opinion of the CHMP can be obtained. The

company organising the compassionate use must also ensure supply to participating patients between the grant of the marketing authorisation and the actual placing on the market. Named-patient sales rules remain unaffected.

SUPPLY OBLIGATIONS

The revised Directive 2001/83 requires marketing authorisation holders and distributors to ensure appropriate and continued supplies of a medicinal product to pharmacies and other persons authorised to supply medicinal products, to meet the needs of patients in the member state concerned. However, this only applies when the product in question is actually placed on the market in the member state in question. A proposal to require marketing authorisation holders in general to provide an uninterrupted supply of medicinal products to wholesale distributors was not accepted, contrary to the ambitions of the parallel import industry. Wholesalers importing medicines in a member state must also inform the marketing authorisation holder.

MARKETING AUTHORISATION GRANTED AT INITIATIVE OF A MEMBER STATE

Member states will be able to authorise the placing on the market of a medicinal product for public health reasons when the company in question has not applied for approval. The practical implementation of this provision remains unclear.

SUPPORT FOR SMEs

Under the new Regulation 726/2004, provisions are to be adopted to reduce the cost of marketing centralised procedure products for SMEs by:

- Fee reduction or deferment.
- A translation service
- Other administrative assistance.

THE FUTURE

The revision of the EU pharmaceutical legislation will have a major impact on the regulatory framework for medicines in Europe. It is a major project that went through the lengthy and, at times, difficult co-decision procedure and as can be expected reflects divergent interests and incorporates several compromises. It will make the regulatory controls more intense and will also lead to more harmonised rules and practices for approving generic products. It will probably also lead to a further shift towards more centralised regulatory decision making.

The package also clarifies several aspects of the rules, but it also raises numerous legal and practical questions. These questions will eventually have to be addressed by administrative guidance, such as a revision to the Notice to Applicants (*available on the website of the Pharmaceutical Unit at <http://pharmacos.eudra.org/F2/eudralex/vol-2/home>*) and some will almost certainly be submitted to the EU courts.