Overhauling oversight—European drug legislation

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At the end of next month, the European Medicines Agency (EMEA) will implement a new legislative framework and several provisions that seek to provide incentives and streamline regulatory oversight of certain monoclonal antibodies and other biologic products.

Starting in November, several major pieces of legislation affecting the legal framework for medicinal products in the EU will come into effect. The most significant of these for developers of monoclonal antibody (mAb) and other biologic products is Directive 2004/27/EC (amending the Code for Medicines for Human Use set out in Directive 2001/83/EC)[1] and a new Regulation 726/2004 replacing the existing Regulation 2309/93 governing the EMEA Centralised Procedure[2]. Although the revision of legislation encompasses as many as 200 changes to the existing rules, I focus below on those provisions that have a significant impact on requirements for the application for marketing authorization, the approval process and the post-marketing of mAb products.

Consultation and registration

In 1987, European pharmaceutical legislation first defined (under Directive 87/22/EEC)[3] a new category of medicinal products manufactured by a biotechnological process, including hybridoma and recombinant technology. The first mAb medicinal product approved under this procedure was Raritan, New Jersey-based Ortho Biotech's Orthoclone (muromonab, OKT3), a murine anti-CD3 mAb for prevention of allograft transplant rejection. Like other biotech products, mAbs are now absorbed under the definition of 'biological medicinal product' created under Directive 2003/63/EC[4].

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A biological medicinal product is defined as a product that contains a biological substance that is produced by, or extracted from, a biological source and that requires a combination of physicochemical and biological testing, together with process control, to define its quality and characteristics. A biotech-derived product is therefore considered a subset of the broader definition of a biological medicinal product. All biotech-derived medicinal products are currently regulated under the so-called Centralised Procedure, which is administratively managed by the European Medicines Agency (EMEA). Approval granted by the EMEA is valid throughout all EU Member States under Regulation 2309/93; it is this law that will now be replaced in November by the new Regulation 726/2004 (ref. 2).

Under the new legislation, centralised assessment will be obligatory for products indicated for use in the treatment of AIDS, cancer, neurodegenerative disorders and diabetes, irrespective of whether they are biotech-derived, small molecules or natural products. From May 20, 2008, this will be extended to two additional therapy areas (autoimmune diseases (and other immune dysfunctions) and viral diseases). As a consequence, many more new products will be assessed by the Centralised Procedure.

One of the first significant changes in practice under the new rules will be made to the fee structure for companies submitting products for marketing authorization under the Centralised Procedure. Until the law change, every company had paid the same fee to submit a new application for marketing authorization at the EMEA. Because of the high cost of the process (over a quarter of a million dollars for a typical application and extra fees for each new

Canary Wharf, the location of the EMEA's headquarters in London.

presentation and medicine strength), most small biotech firms have partnered with larger companies with the financial resources and expertise to negotiate the process. Under the new Regulation 726/2004, however, a fee structure is being introduced that will offer small-medium enterprises (SMEs) fee reductions compared with larger corporations (**Box 1**).

According to some sources[5], the cost of accessing scientific advice at EMEA may be reduced to as little as €8,000 ($9,850). And for those SME

companies that do seek scientific advice at the agency, the €232,000 ($285,327) fee required for marketing authorization will be payable only once the drug is approved. The European Commission (EC) has published a consultation paper in which it set out provisions for fee structure for applications submitted by SME companies. It has proposed a 90% fee reduction for new applications that, if implemented, may represent a significant cost saving[6].

Many companies developing mAbs target orphan indications—diseases affecting less than 5 in 10,000 people in the EU. Orphan designation is granted based on two alternative criteria: rarity of the disease on the basis of prevalence, and financial considerations. Both criteria must meet the test that there is no satisfactory method of diagnosis, prevention or treatment of the condition or, if a satisfactory method exists, the product will be of significant benefit to those affected by that condition. The designation provides a drug with 10 years of EU market exclusivity (more generous than that provided by the US Orphan Drugs Act) in a particular indication against drugs with the same principal molecular structural features and that act via the same mechanism (Article 3(2.1) of Regulation 847/2000/EC states that mAbs that bind to the same target epitope would normally be considered similar). Currently, there are 18 mAb products (out of over 300 products) approved for orphan status and 20 mAbs currently given orphan status under EMEA review. Orphan designation does not automatically translate into product approval under the European pharmaceutical legislation. Approval of a given product, irrespective of whether it is orphan or not, requires demonstration of meeting the criteria of safety, quality and efficacy. A period of market exclusivity for orphan medicinal product is only crystallised when a favourable assessment has been conducted against these criteria. It is therefore noteworthy that the agency offers fee reductions for the registration and authorization of orphan products. Initial applications for marketing authorizations and post-authorization applications/annual fees are discounted by 50% and fees for EMEA assistance (e.g., during protocol development) is completely waived or deferred. Indeed, in a recently published EMEA public statement[7], the agency has set aside over €3.5 ($4.3) million as funds for fee reduction in 2005.

Help is also on the way to allay the administrative costs associated with producing the paperwork submitted, edited, exchanged, finalized and approved by EMEA during the review process for a product. For complex products such as mAbs, in some cases more than 800 separate documents, needing translation into 21 national languages, have been required in the past[8]. The EMEA plans to implement a translation service for SMEs to ease this administrative burden.

Box 1 What is a SME?

Commission Recommendation 2003/361 of 6 May 2003 defines the category of micro, small and medium sized enterprises (SMEs) as enterprises which employ fewer than 250 persons and which have an annual turnover not exceeding € 50 ($61) million and/or an annual balance sheet total not exceeding € 43 ($52.5) million. Within this broad category, a small enterprise is defined as an enterprise, which employs less than 50 persons with annual turnover and/or annual balance sheet total not exceeding € 10 ($12.2) million. A microenterprise is defined as an enterprise, which employs fewer than 10 persons and whose annual turnover and/or annual balance sheet total does not exceed € 2 ($2.4) million.

Marketing authorization

The revisions to EU pharmaceutical law do not change the standards for approval; this will continue to be based upon an assessment of risk/benefit balance. Indeed, the European Court of Justice consistently declares in various decisions that the granting or refusal of an authorization must depend on whether the product meets the objective criteria of safety, quality and efficacy that underpin assessment of risk/benefit.

Although the new rules make clear that pharmacoeconomic and other considerations are not relevant to grant of an approval, European regulators are, however, increasingly demanding evidence of comparative efficacy for a given product. Indeed, in 2003 the EC, in amending Directive 2001/83/EC, emphasized that ordinarily a three-arm controlled clinical trial design using a placebo and a product of

Box 2 Accelerated assessment and exceptional approvals

Accelerated assessment is permitted under the Centralised Procedure if a product is likely to be of major interest in relation to public health or therapeutic innovation. Operationally, implementation is overseen by the CHMP/EMEA Implementation Task Force. The accelerated process was first developed by the EMEA in its policy of 2001 to expedite evaluation of products indicated for serious diseases (that is, those considered to be life-threatening or heavily disabling diseases)[10]. According to this policy, the Committee for Proprietary Medicinal Products (the predecessor of the CHMP) could give the first opinion that forms the basis of marketing authorization within a shorter period (120 instead of 210 days). Usually a product that is considered under the 'accelerated evaluation' meets the following conditions: it treats a serious disease; it stands alone as the only therapeutic approach; and it is anticipated to have an exceptionally high therapeutic benefit. Post-approval conditions are usually attached to the authorization to fully elucidate the risk/benefit balance.

If an applicant cannot provide the type of comprehensive data on safety and efficacy of a product under normal conditions of use that is usually required by the EMEA, it is also possible under existing EU legislation to obtain an approval under exceptional circumstances. This is available to products for indications that are so rare that the applicant cannot reasonably be expected to provide comprehensive evidence (e.g., certain orphan diseases); where in the present state of scientific knowledge, comprehensive information cannot be provided (e.g., the study is not sufficiently powered to establish clinical efficacy due to a small sample size or a lack of clear clinical endpoint(s) for demonstrating clinical benefits) or where providing/collecting such information would be contrary to generally accepted principles of medical ethics. The applicant is obliged upon grant of such an approval to agree with the competent authority on an identified program for reassessment of risk/benefit balance. Moreover, the product approved must be supplied by medical prescription and, in certain cases, be administered only under strict medical supervision. The package leaflet and any medical information must draw physicians' attention of the to the fact that the particulars available concerning the product are, as yet, inadequate in certain specific respects. Products approved under exceptional circumstances are often indicated for treatment of orphan diseases.

'proven therapeutic value' would be expected to establish the efficacy of the new product. Any other trial design must therefore be justified. This demand for comparative efficacy data essentially requires applicants to demonstrate the therapeutic benefit or added value. It is said this regulatory requirement erects additional barriers to market entry, where the legal test for approval is based on an assessment of clinical safety and efficacy in relation to the product and not on relative efficacy against another established therapy. That said, demonstration of therapeutic position or benefit or relative efficacy against an established therapy (commonly known as "the fourth hurdle") is becoming necessary for the purposes of seeking approval for pricing and reimbursement.

One important new approval process under the Centralised Procedure is the so-called conditional marketing authorization. In this process, a product granted conditional approval under Regulation 726/2004 will be reviewed annually by the EMEA. Similar to the existing process for approval under exceptional circumstances (see Box 2), the types of product that qualify for conditional approval include orphan medicinal products and products to be used in emergency situations in response to public health threats (thus, this regulatory path may be relevant to certain mAb products being developed for biodefense or orphan indications). The EC has published a draft implementation regulation that sets out the detailed procedure for such an approval[9]. The request for consideration under conditional approval can be made either by the EMEA's Committee for Human Medicinal Products (CHMP) or by the applicant. However, it is for the applicant to demonstrate the notion of "presumed positive benefit/risk" balance of the drug. Although the process allows full clinical data to be provided post-approval, the applicant still must provide full preclinical (animal) data of the requisite quality and type. As opposed to standard authorizations, which are valid for 5 years subject to product renewal, conditional approvals are valid for only 1 year, subject to continuing risk/benefit monitoring by the CHMP.

Another positive development is that the deadlines for EMEA's administrative decision-making procedure may in some cases be significantly shortened. Under the Centralised Procedure, expedited scientific review by the CHMP is possible for products that provide a major therapeutic innovation or are, in another way, of major public health interest (see Box 2). Under the current CHMP/EMEA policy, accelerated review may be shortened from 210 to 120 days (although actual scientific review can extend beyond 210 days). The deadlines for sending the CHMP's definitive report and the Commision's draft decision are to be reduced from 30 to 15 days and the deadline for the presentation of observation on the part of the European member states, reduced from 28 to 21 days.

Post-marketing

Perhaps the most wide-ranging impact of the changes on the EU drug legislation will be in the areas of pharmacovigilance and post-market surveillance. The EC Directive 2003/63/EC[4] imposes an obligation on any marketing authorization holder to monitor the risk/benefit balance of its product on an ongoing basis, taking account of all post-approval safety information. The revised legislation now places even greater emphasis on post-approval market surveillance. This reflects the heightened concern over post-approval drug safety following a number of high-profile product withdrawals, including Biogen-Idec/Elan's voluntary withdrawal of Tysabri (natalizumab) anti-$\alpha_4\beta_1$ integrin mAb for the treatment of multiple sclerosis[11].

In the new legislation, Chapter 3 of Regulation 726/2004 includes substantial changes to the procedures for pharmacovigilance of products authorized under the Centralised Procedure. More than before, the EMEA now has a central role in coordinating drug safety. Member states and the marketing authorization holders are required to report all relevant information relating to suspected adverse reactions to the EMEA. The marketing authorization holder must have 'permanently and continuously at his disposal' an appropriately qualified person responsible for conduct of pharmacovigilance. The law also imposes certain legal obligations (and thus potential personal legal liability) upon this qualified person, who is responsible for managing the pharmacovigilance system, preparing reports to the competent authorities and responding to the authorities on matters relating to assessment of risks and benefits of a medicinal product.

Compulsory submission of periodic safety update reports (PSURs) will also follow a tightened time line. In the new regime, the marketing authorization holder will be required to submit such reports every 6 months after approval until the product is physically placed on the market. In the first 2 years after the product's entry onto the EU market, PSURs must be submitted every 6 months. PSURs must then be submitted once a year for another 2 years; thereafter, they must be submitted at 3-yearly intervals. Moreover, the competent authorities, at their discretion, may request a PSUR at any time.

Regulators also must be made aware of any new toxicity data surfacing about a product. Thus, under the new rules, marketing authorization holders are not permitted to communicate pharmacovigilance information to the general public without first notifying the competent authorities in the member states (for nationally authorized products) and the EMEA (for all centrally assessed products). The information contained in all communications to the public must be presented objectively and not be misleading.

Information pertaining to emerging drug safety issues for centrally authorized products will be coordinated through the EMEA. For example, in the past, EMEA safety reviews of three mAbs—Centocor's Remicade (infliximab; Horsham, PA, USA), Genentech's Herceptin (trastuzumab; S. San Francisco, CA, USA) and Amgen/Wyeth Europa's Enbrel (etanercept; Thousand Oaks, CA, USA and Madison, NJ, USA)—resulted in EMEA public statements for the healthcare professionals and patients with respect to their conditions of use. These three reviews precipitated changes to the Summary of Product Characteristics (SmPC). The SmPC sets out the agreed upon position of the medicinal product as distilled from the assessment process and forms the basis of information on how to use the medicinal product safely and effectively. Indeed, the new law governing variations to marketing authorizations issued in 2003 provides under the head of 'urgent safety restrictions' that in the event of serious risk to public health, the marketing authorization holder must notify the competent authorities (in the case of mAbs approved centrally, EMEA) when taking an urgent safety restriction (e.g., restricting the conditions of use) with respect to an authorized product. If the competent authorities do not raise any objections within 24 hours following receipt of the information, the request is considered to be acceptable.

The EC, the EMEA, the CHMP and its expert advisory group the Pharmacovigilance Working Party have developed a number of policy statements and guidance. The recently revised Volume 9 of the European Rules Governing Medicinal Products in the European Union (which relates to pharmacovigilance) and other regulatory guidance provide greater emphasis on the risk management plan, which necessitates risk assessment, transparency in regulatory action and risk communication. On August 12, the EMEA also published a draft guidance on pharmacovigilance for medicines used in children, over 50% of which are prescribed for off-label use. This is in anticipation of the final adoption of the rules concerning approval of pediatric medicines. Moreover, EU regulators are increasingly applying the general principle of 'precautionary measure' as the basis of initiating regulatory action in

matters where the science is uncertain. The European courts have considered such action to be permissible provided that the test for proportionality is met, that is, that the means used are no more than is necessary to achieve the objective of public health protection.

It has been announced that closer cooperation among the EU member states and other non-EU authorities is contemplated to strengthen drug safety monitoring covering the entire life-cycle of a medicinal product. The confidentiality arrangements concluded on September 12, 2003 between the EU and the US Food and Drug Administration is one such initiative to facilitate an exchange of information, including information relating to pharmacovigilance, between the two agencies.

The opinions of the CHMP on matters relating to pharmacovigilance, product defects and serious adverse reactions will be available to the public. Indeed, patients are encouraged to communicate adverse reactions to healthcare professionals, an initiative that has been used extensively in various jurisdictions. Clearly, of particular interest to industry is an appreciation of the relationship between publication of information relating to drug safety and potential product liability exposure as such information may potentially be used as evidence to support the notion of 'defective product' under the strict liability law. Given that the EMEA has adopted a policy of greater transparency in its regulatory decision-making, there is also reduced flexibility in withdrawing applications from the Centralised Procedure in that such withdrawals are published, particularly in the event that a 'premature' application is submitted.

With the EMEA's enhanced role in coordinating the verification of pharmacovigilance compliance, an increase in inspections can be expected. In addition, the legislative changes have given the European regulatory agency more teeth. From November, EU member states must report to the EC immediately any litigation instituted because of infringement of the regulation governing the Centralised Procedure. Moreover, at the request of the EMEA, the EC may impose financial penalties. In its recent proposal to implement the regulation, the EC considers two types of financial penalties: one relates to fines (lump sums) for the infringement of obligations in connection with the marketing authorization; the other relates to periodic penalties for the enforcement of measures of inquiry (which relate to requests for an explanation or a document to assist an investigation of a potential infringement of the regulatory rules) and of decisions finding the existence of an infringement. For lump sum fines, it is proposed that marketing authorization holders can be fined to levels not exceeding 10% of the total turnover in the preceding year to that in which the infringement was committed. The periodic penalty payments currently being proposed are set at a level not exceeding 1% of the average daily turnover in the preceding business year per day. These proposals are currently subject to public consultation and are likely to attract extensive feedback.

Conclusions

By emphasizing the pivotal role of the EMEA in drug regulatory oversight, the changes to European regulations offer companies a simplified process (e.g., allowing a single brand name to be used across Europe, parallel centralised approvals for the same product) and potentially a quicker approval process, with potential benefits for business.

Closer co-operation between the EU and US has paved the way for the introduction of a pilot program to allow companies to seek parallel scientific advice. The goal of this is to provide a platform for the EMEA and FDA officials and companies to exchange their views on scientific issues regarding early phase development of new products. The pilot program is currently limited to products that are deemed innovative or used for orphan indications or for use in pediatric populations where there are no existing guidelines or if such guidelines exist, the regional guidelines differ significantly.

Regulation 726/2004 also lays out provisions to reduce the cost of the Centralised Procedure for biotech companies via fee reduction and deferment mechanisms, assistance in translating paperwork and other administrative assistance. This indicates a willingness of the EC to recognize the specific needs of biotech companies compared with their larger pharmaceutical brethren. On the other hand, the new rules give the European regulators greater punitive powers: for the first time, the EC itself, rather than European member states, may impose financial penalties for regulatory infringements. And it remains to be seen whether increased regulatory scrutiny and public pressure on drug safety in the light of recent high-profile product withdrawals will raise the bar for approvals.

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