Compassionate Use and Early Access to the Market in the USA and EU (1)

Elisabeth Bourg and *Françoise de Crémiers* review the current situation in the USA for compassionate use and early access to the market for medicinal products intended to treat life-threatening diseases

Compassionate use of medicinal products

New medicines must authorised before marketing

Any new medicinal product must be approved by the regulatory authorities before it can be marketed. This approval is mainly based on the results of clinical trials. Many months or even years of clinical trials and analyses of the results in terms of safety and efficacy may be required before approval can be granted. Such a lengthy period is necessary in order to learn about the safety and the efficacy of the medicinal product; however, the efficacy of medicines has little meaning to people who cannot have access to them. This is especially true when people cannot take any of the approved medicinal products, and particularly when patients do not have access to medicines already approved in another region (e.g. the USA).

Access to new medicines is often faster in the USA

Consequently, the question could be asked: why do patients in the USA often have faster access to promising medicinal products than in the EU? Several issues need to be taken into consideration, such as the differences in timelines in terms of review processes between the EU and the USA, mainly due to medical practices as well as insurance coverage systems.

Compassionate use and accelerated development and approval programmes are intended to expedite the availability of new medicines

Nevertheless, procedures to expedite/accelerate the availability of such medicines exist in both regions. Firstly, the compassionate use programmes are intended to allow patients limited access to promising experimental treatments before they have been given full approval by the regulatory authorities. Secondly, accelerated development and approval programmes are designed to facilitate the development and expedite the review of selected medicinal products intended to treat life-threatening diseases. These procedures are developed jointly by the regulatory authorities and the pharmaceutical company and have been implemented in the EU and USA.

Current US situation

Since 1987, the US FDA has put in place regulatory procedures designed to speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and efficacy. These procedures are intended to facilitate the development, evaluation and marketing of such products, especially where no satisfactory alternative therapies exist.

These procedures recognise that physicians and patients are generally willing to accept greater risks or ADRs from products that treat life-threatening illnesses. In addition, they reflect the fact that the benefits of the medicinal product need to be evaluated taking into account the severity of the disease being treated.

US regulations

Treatment IND regulations form part of expanded access programmes...

Expediting the availability of promising new therapies has been a major priority of the FDA for some time. In the *Federal Register* of 22 May 1987, the FDA issued new regulations designed to increase the availability to desperately ill patients of promising INDs and biological products before general marketing begins. The treatment IND regulations became effective on 22 June 1987 and are part of the expanded access programmes[1, 2]. Building on these achievements, the FDA was requested to develop procedures for expediting the development, evaluation and marketing of new therapies.

In 1992, the FDA created a mechanism for accelerating the regulatory approval of drugs for the treatment of certain serious or life-threatening illnesses. The regulation was adopted as a final rule on 11 December 1992[3, 4]. This regulation was an innovative response to the increasing need for regulatory procedures that could facilitate efforts to develop and assess new treatments for serious or life-threatening diseases. Importantly, the accelerated approval regulation was introduced and implemented entirely within the context of the existing law.

In 1998, the FDA issued a guidance document describing procedures for the 'Fast Track Drug Development Programmes Designation, Development and Application Review'. This document

Elisabeth Bourg Pharm D, ML is Assistant to the Director Regulatory Advice Europe, Wyeth Ayerst Clinical Research and Development, France. **Françoise de Crémiers** PharmD, MSc, ML is Director Regulatory Advice Europe, Wyeth-Ayerst Clinical Research and Development, Worldwide Regulatory Affairs, Paris, France. The second part of this feature, covering the compassionate use of medicinal products in the EU will be published in a future issue of *The Regulatory Affairs Journal*.

was designed to facilitate the development and expedite the review of new drugs for the treatment of serious or life-threatening conditions. It provided guidance to industry on FDA's fast track programmes[5–8].

Drug submissions are now classified into one of two categories...

In order to prioritise the review of applications for promising new therapies, the FDA has classified drug submissions into two categories (Priority and Standard) for the purposes of review:

- P – Priority review: the drug product if approved would be a significant improvement over to marketed products in the treatment, diagnosis or prevention of a disease;
- S – Standard review: all non-priority applications are considered standard applications.

Expanded access programmes

These programmes are part of the FDA's comprehensive efforts to facilitate the development and availability of significant new therapies[1,2]. The US regulations address three expanded access programmes with respect to:

US legislation covers...

- emergency use;
- individual patient access; *and*
- treatment IND.

Emergency use

...use of an IND on a human subject...

Emergency use is defined as the use of an IND on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is insufficient time to obtain Institutional Review Board (IRB) approval for such use. In such a case, the FDA may authorise shipment of the drug in advance of the IND submission. Request for such authorisation may be made by rapid communication means. The emergency use must be reported to the IRB within five working days of its occurrence.

Individual patient access or compassionate IND

...use of an IND for a single patient...

This IND is requested by a practitioner for a single patient. The drug is provided on a case-by-case basis. Generally, there is little evidence that the proposed therapy is useful but it may be plausible on theoretical grounds or based on anecdotes of success. In these cases, the FDA permits the proposed use under a commercial sponsor's IND or under a new IND filed by the patient's physician for an identified patient. The sponsor, or clinical investigator, of the investigational drug submits to the IRB a clinical protocol describing the use of the investigational drug in a single patient. The FDA expects full reporting on outcome.

Treatment IND

...and a new treatment protocol for an existing IND application

Drug manufacturers may apply to the FDA to obtain a Treatment IND. Usually, this applies to drugs in Phase III clinical studies. A treatment protocol may begin 30 days after the FDA receives the protocol or earlier by notification from the FDA that the treatment use described in the protocol may begin. Thus, a treatment protocol is adding to an existing IND application. It allows use of promising new agents directed primarily at patient care by physicians who agree to follow the protocol. This protocol covers an unspecified number of patients. Although the primary purpose is to allow treatment, this mechanism also is intended to obtain additional data on the drug's safety and efficacy under certain criteria. Therefore all the information obtained by the treatment IND is collected and included into the NDA dossier for FDA review.

Criteria for qualification as a fast-track drug development programme

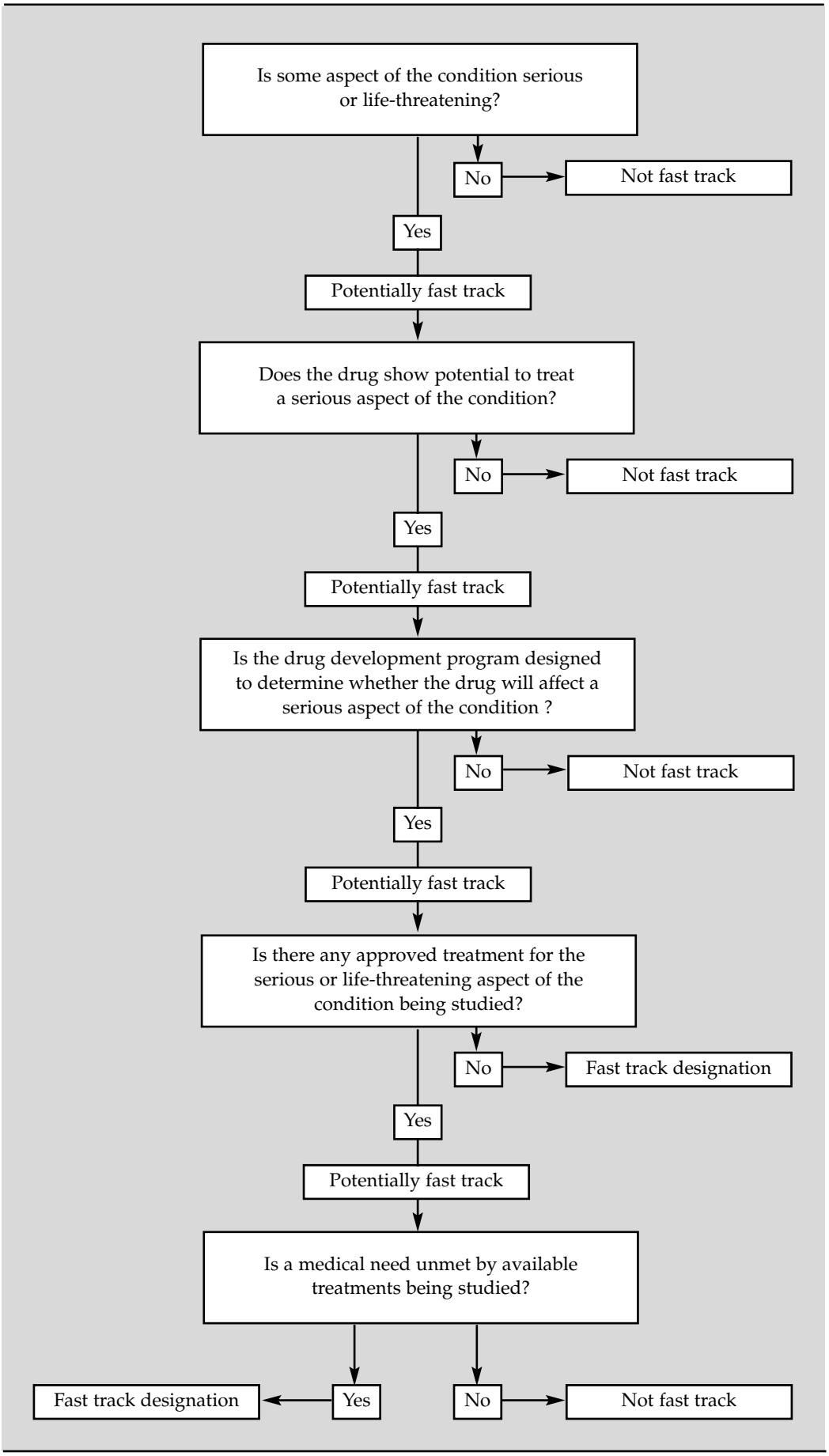
A drug designated as a fast-track product is intended for the treatment of a serious or life-threatening condition, which demonstrates the potential to address unmet needs for the condition. Some examples of drugs that can use this regulatory mechanism are treatments for HIV infection, cancer, advanced multiple sclerosis, advanced Parkinson's disease and cystic fibrosis[5].

Process for the designation as a product in a fast-track drug development programme

Requests for fast-tracking may be made at any time up to approval of the BLA or NDA

A sponsor may submit a request for fast track designation at the time of the original submission of its IND, or at any time prior to receiving marketing approval of its Biologics Licence Application (BLA) or NDA. The procedure to be followed for determining if a drug could have the fast track designation is summarised in Figure 1. The FDA will respond to a request for fast track designation within 60 calendar days of receipt of the request[5].

Figure 1. Procedure to be followed to determine whether a drug is eligible for fast track designation in the USA



Fast track products must treat a serious or life-threatening condition...

...for which there are no approved alternative treatments or for which there is an unmet medical need

Requirements for a drug to achieve accelerated approval

In order to pursue accelerated approval of a new drug treatment, the drug product must have an effect either:

Criteria for accelerated approval is given...

- on a surrogate endpoint that is reasonably likely, based on epidemiological, therapeutic, pathologic or other evidence to predict clinical benefit; *or*
- on a clinical endpoint other than survival or irreversible morbidity.

When such an endpoint exists, the sponsor must meet certain requirements in order to pursue accelerated approval of an NDA:

Sponsor must meet certain requirements...

- the effect of the drug on the surrogate endpoint must be studied in adequate and well-controlled clinical trials;
- the magnitude of this effect must be indicative of a meaningful therapeutic benefit to patients compared with existing treatments; *and*
- the sponsor must demonstrate diligence in conducting further studies to verify and describe the clinical benefit of the drug.

Accelerated approval can also be granted for drugs whose safe use required restricted distribution or use. Finally, the FDA may withdraw the accelerated approval for a drug if the post-marketing clinical study fails to verify the clinical benefit of the drug.

Conclusion

Without compromising the approval requirement for safety and efficacy of new drugs and biologics, the amount of time gained through accelerated approval is of interest to health regulatory authorities, pharmaceutical companies and patients. In the USA, patients with HIV infection and patients with various types of cancer have been the major beneficiaries of drugs emerging from the accelerated approval process.

Accelerated approval regulations have provided patients with earlier access to promising treatment

Since 1992, the drugs approved with the accelerated approval regulations have become commercially available considerably earlier than would have been possible through traditional approval alone. The accelerated approval mechanism has enabled each drug to reach patients at least one to two years earlier than would have been otherwise possible. Therefore, the mechanism has been successful in speeding access to these medically important therapies and in giving patients all the medical help possible.

References

1. 'Expanded Access to Investigational Therapies and Diagnostics', *Food and Drug Administration Modernization Act of 1997*; Section 1, Title IV, page 70.
2. Investigational New Drug Application (IND), 21 CFR Part 312, Chapter I, Subpart B, page 76 1 April 1998.
3. New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, Final Rule, *Federal Register*, 1992, **57**(239), 58942, 11 December 1992.
4. 'Expediting Study and Approval of Fast Track Drugs', *Food and Drug Administration Modernization Act of 1997*; Section 1, Title I, Subtitle B, page 14.
5. 'Guidance for Industry – Fast Track Drug Development, Programmes Designation, Development, and Application Review', September 1998, Procedural 9, 22 pages, FDA, CDER, CBER, US Department of Health and Human Services.
6. Accelerated Approval of New Drugs for Serious or Life-threatening Illnesses, 21 CFR Part 31, Subpart H, Chapter I, page 177.
7. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations ; Procedures for drugs intended to treat life-threatening and severely debilitating illnesses, interim rule, Opportunity for Public Comment, *Federal Register*, 1988, **53**(204), 41516.
8. Coccheto D and Jones D, 'Faster Access to Drugs for Serious or Life-threatening Illnesses Through Use of the Accelerated Approval Regulation in the United States, *Drug Information Journal*, 1998, **32**, 27.

■

The second part of this publication will address the current situation in Europe in terms of compassionate use and early access for new drugs intended to treat serious or life-threatening diseases.