REVIEW-THEMED ISSUE

Regulatory aspects of the development of drugs for metabolic bone diseases – FDA and EMA perspective

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Regulation of medicines involves complex scientific and public health policies which are reflected in the regulatory approaches used by the European Medicines Agency and the United States Food and Drug Administration for the approval of products developed for metabolic bone diseases. For osteoporosis therapies, utilized by many patients, the approaches and existing guidance for product development of both agencies are similar; confirmatory studies for the approval of osteoporosis products can rely on well-defined efficacy outcome parameters. Therapeutics for rare bone diseases, a rapidly expanding area, often require an individualized regulatory approach. This review outlines key aspects of these regulatory approaches applied by the two agencies for products for metabolic bone diseases.

Introduction

Similar regulatory pathways exist for the authorization of new medicinal products (as chemical or biological products) in the European Union (EU) via the European Medicines Agency (EMA) and the registration of new drug or biologic products in the US via the US Food and Drug Administration (FDA).¹ In the EU, marketing authorizations for new products for the treatment of metabolic bone diseases can be obtained via either the EMA's centralized procedure or applications in EU member states. The EMA procedure is mandatory for several product classes, such as monoclonal antibodies, and has been used for most of the recent applications for innovative products. This procedure is based on a single EU-wide scientific assessment of the application by the EMA's Committee

for Medicinal Products for Human Use (CHMP) [1]. The subsequent marketing authorization is then valid throughout all EU member states. In the US, all marketing applications for new drug or biologic products are reviewed at the federal level, using the central processes of the FDA.

Although most readers may focus on the clinical data showing the safety and efficacy of a given product, data from multiple disciplines are needed for product registration. Pharmaceutical quality data are required to ensure the manufacture and quality attributes of the drug substance and the drug product, including container and closure systems. Non-clinical pharmacology and toxicology data provide early evidence of safety and proof of concept for efficacy prior to the initiation of clinical trials in humans. Later in development, nonclinical carcinogenicity studies provide important safety information. Clinical pharmacology and biopharmaceutics data provide information on the pharmacokinetics, pharmacodynamics, exposure–response relationship and interactions with other drug products. For any new product, the data requirements for registration are large, and multiple

¹Equivalent terminology used in both jurisdictions is used interchangeably throughout the article – e.g. chemical or biologic medicinal products (in the EU) and drug or biological products (in the US) are both referred to as 'products' throughout the text.

guidance documents on general drug development [2] are available, including from both the EMA and FDA [3, 4], to assist with product development. For the development of drugs for metabolic bone diseases, some specific guidance has been published by the agencies (see below).

Osteoporosis therapies

Osteoporosis is the most common metabolic bone disease worldwide and remains a leading cause of fracture and subsequent disability in older individuals. The development of osteoporosis therapies follows the general regulatory pathway for product development. However, since the first osteoporosis therapy was approved more than 40 years ago, scientific knowledge has advanced and safety concerns have become apparent that mandate specific assessments for osteoporosis indications. Since the mid-1990s, bisphosphonates (BPs) have rapidly become the standard of care for the treatment of osteoporosis, and are currently the most widely used product class. Several BPs have been approved for this indication by the EMA and FDA. The first selective oestrogen receptor modulator for the treatment of osteoporosis, raloxifene, became available in 1997 in the US and in 1998 in the EU.

Since 2000, several innovative therapies have been developed. In 2003, teriparatide [5], a small peptide representing the amino-terminal portion of human parathyroid hormone (PTH) and acting as an agonist at the PTH-1 receptor, was approved in the EU and the US as a new osteoanabolic treatment option. More recently, in 2017, another osteoanabolic treatment, abaloparatide [6] was approved in the US. Newly discovered signalling pathways of bone metabolism led to the development of denosumab [7], approved in 2010 as the first monoclonal antibody for the treatment of osteoporosis. The discovery of another signalling pathway that is important in bone metabolism led to the development of a monoclonal antibody against sclerostin, romosozumab, which has been investigated in phase III studies [8] and submitted for approval to regulatory agencies. The further development of odanacatib, a cathepsin K inhibitor, was recently terminated at the stage of advanced confirmatory clinical trials [9].

General regulatory requirements for approval

For medicines intended for human use, drug development usually begins with studies in animals. These include required nonclinical pharmacology and toxicology studies. Studies that evaluate carcinogenic potential are also needed for all new chronically administered products. For medicines specifically targeting bone diseases, long-term nonclinical assessment of bone quality and biomechanical bone strength is needed. Additionally, because of findings of osteosarcomas in a specific rat strain after long-term exposure to PTH products, although absent in other species, the potential for carcinogenicity is an important issue for anabolic products. Unique carcinogenicity design features may be needed for products that stimulate osteoblastic bone formation [10]. These nonclinical data provide important information and inform the future clinical development of potential osteoporosis therapies.

From the clinical perspective, the intention of treating osteoporosis is to decrease the incidence of fractures. Products initially approved decades ago used whole-body calcium or bone mineral density (BMD) as outcomes to support registration. The case of sodium fluoride, where there were large increases in BMD but a lack of associated fracture efficacy, led to a re-evaluation of requirements for the demonstration of product efficacy. Since 1994, the FDA has required trials for the registration of new drug and biologic products for the treatment of osteoporosis to have fracture as the primary efficacy endpoint [11], and this is also required by the EMA [12]. Randomized controlled trials are needed and can either be placebo controlled or active comparator controlled. Although biomarkers can be very useful in dose finding and phase II studies, changes in BMD and bone biomarkers provide only supportive evidence of efficacy for the treatment of osteoporosis. Bone histomorphometry data demonstrating adequate bone mineralization and safety are also needed. The minimum duration of the trials should be 2 years. For the demonstration of a reduction in the incidence of new fractures for the approval of a product, the FDA requires only proof of an effect on morphometric vertebral fracture, as detected by standardized measurements of height reduction of vertebrae on radiograms; EMA guidance requests the estimation of benefit to be based on both vertebral (clinically detected or morphometric) and nonvertebral (hip or major nonvertebral) fractures [12].

Product approval in specific osteoporosis populations

Once a product has demonstrated fracture efficacy in one population, changes in BMD with that product are considered validated and, under certain conditions, BMD can be used as a primary endpoint for subsequent indications for that product in different populations or for different dosing regimens. Most commonly, applicants seek an approval for the population of postmenopausal women first. EMA guidance [12] suggests that, once an indication in postmenopausal women has been granted, a separate bridging study based on changes in BMD can be sufficient to grant an authorization also for men with osteoporosis. Requirements for such an extrapolation include the use of the same formulation, dose and route of administration; the inclusion of a male population with a fracture risk of a similar magnitude compared with that of the postmenopausal women studied; and demonstration of similar changes in BMD in a 1-year study. The FDA also allows the bridging concept to be used for new dose regimens, such as moving from daily to weekly or monthly administration, and new dose formulations, such as a move from an immediate-release formulation to a delayed-release formulation.

Based on a similar bridging study concept, several products have also been authorized for use in glucocorticoid-induced bone loss/osteoporosis, most recently for denosumab in 2018, both in the EU and the US.

Aspects of trial design

It is recognized that it is no longer ethical to enrol women at high risk of fracture into placebo-controlled trials, given the trial duration and the availability of approved therapies.

However, alternative trial designs to consider in that population are superiority trials against a comparator, or non-inferiority trials against established therapies. Nevertheless, from a regulatory perspective, the target population in the osteoporosis clinical fracture trials submitted to the agencies has evolved over time. Although the mean age of enrollees has remained relatively constant, at approximately 70 years old, the percentage of subjects with baseline fracture has markedly decreased. Seventy per cent to 100% of enrolled subjects had a fracture at baseline in fracture outcomes trials initiated prior to 2000. Since 2000, the percentage of subjects with a baseline prevalent vertebral fracture has decreased to 63% of enrolled subjects in a trial initiated in 2002 and 24% of enrolled subjects in a trial initiated in 2004 [13]. With a decreasing risk of fracture, larger numbers of patients are needed to power the fracture studies adequately.

Clinical fracture trials are usually multinational and frequently submitted to both the EMA and FDA for registration. Both agencies are also aware of the ongoing efforts to validate surrogate endpoints for use in osteoporosis registration trials, which may allow, once data are available for review, use of endpoints other than fracture in future trials.

For approved osteoporosis therapies, there are subtle differences in the wording of the indication between the EMA and FDA. For EMA-approved products, the generally granted indication is 'treatment of osteoporosis in postmenopausal women at increased risk of fracture', based on an appropriate 10-year probability of fractures as enrolment criteria for fracture trials [12]. For the FDA, the predominant indication is 'treatment of osteoporosis in postmenopausal women'. These two indication statements would largely target the same treatment population. The recommendations for which patients should receive pharmacological therapy for osteoporosis may vary and are generally based on the national guidelines of the respective countries. Generally, guidelines are based on BMD criteria, a history of a hip or vertebral fragility fracture, or use of a risk model algorithm such as FRAX [14]. A safety concern such as the nonclinical osteosarcoma findings in PTH-related products may prompt the FDA to use the narrower indication, 'treatment of osteoporosis in postmenopausal women at high risk of fracture', to target those patients who are most likely to derive benefit that outweighs the risks of the product. In this scenario, a high risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or failure of or intolerance to other available osteoporosis therapy.

Other metabolic bone diseases

Although osteoporosis receives the most attention and drug development focus, therapies are available for other metabolic bone diseases, such as Paget's disease of bone. For the development of new therapies for Paget's disease, osteogenesis imperfecta and other metabolic bone diseases, the general principles of product development apply. Discussion regarding the design and endpoints for phase II and III trials is important as the efficacy endpoints required may vary. Most applicants seek advice on their planned development via the EMA's Scientific Advice/Protocol Assistance procedure

and/or the mechanisms outlined in the FDA's guidance for formal meetings [15]. Although, for instance, BMD invariably increases with BP treatment in osteogenesis imperfecta, based on experience from past trials, this does not necessarily translate into fracture reduction. Therefore, relevant clinical endpoints beyond BMD are required as efficacy endpoints in clinical trials for this disease. In the EU, one development programme for osteogenesis imperfecta recently received Priority Medicines (PRIME) scheme designation [16], a scheme intended particularly to enhance support for the development of medicines that target an unmet medical need by offering early dialogue with developers and speed up evaluation.

Rare bone diseases

As scientific knowledge of the regulation of bone metabolism advances, interest in the development of therapies for rare bone diseases has increased. The development of such therapies presents unique challenges. Similarly to development programmes for common diseases, the approval of a therapy for a rare disease is based on substantial evidence of efficacy and safety, but the individualized advice of regulatory agencies is needed on the design of early-stage trials, as well as that of later-stage adequate and well-controlled clinical trials to support safety and effectiveness. A thorough understanding of the pathophysiology and natural history of a disease contributes substantially to the design of a development programme. It is always preferable for natural history data to be collected and available prior to designing and initiating the clinical trials supporting product registration, especially if novel biomarkers are used.

Development plans for rare bone diseases are evaluated on a case-by-case basis. In general, clinical outcomes data and/or biomarkers are needed to support product registration. One recent example of a flexible approach to rare bone diseases is burosumab for the treatment of X-linked hypophosphataemia (XLH). XLH is caused by inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome gene (*PHEX*), which leads to excess activity of fibroblast growth factor 23, resulting in chronic renal phosphate wasting, hypophosphataemia and reduced secretion of 1,25 dihydroxyvitamin D. XLH affects up to 1/20 000 live births, with an estimated prevalence of 3000 paediatric and 12 000 adult patients in the US and up to 2000 in the EU. Burosumab therefore received orphan designation both in the EU and US. Most patients with XLH are diagnosed in early childhood, with leg bowing after beginning to walk or because of a family history. The characteristic radiographic changes of rickets are readily identified. Burosumab is a human monoclonal antibody that inhibits the function of fibroblast growth factor 23.

As study data in adults were incomplete at the time of assessment of the initial marketing authorization application in the EU, the indication agreed by the CHMP was for the treatment of XLH with radiographic bone disease in children age ≥ 1 year and adolescents with growing skeletons. The CHMP issued a positive opinion in December 2017,

recommending the granting of a conditional marketing authorization for burosumab, which was issued subsequently. More information on the available studies and their assessment by the CHMP can be found in the European Public Assessment Report [17].

In the US, during the burosumab development programme, the product received Fast Track designation and then Breakthrough Therapy designation. The marketing application submitted to the FDA contained clinical data for both paediatric and adult patients with XLH [18]. The biologics licencing application was granted priority review. The paediatric trials were open label and uncontrolled because of the ethical concerns of using a placebo control in patients at a time when the negative impact to the skeleton is most pronounced. The primary endpoints were serum phosphorus level and radiographic rickets severity score. In children, serum phosphorus increased and radiographic evidence of rickets improved. Studies in the adult population provided placebo-controlled trial data. The primary endpoint was the proportion of subjects who achieved serum phosphorus above the lower level of the normal range at 2 weeks postdose. Normalization of phosphorus was demonstrated, as was improvement in radiographic evidence of osteomalacia in affected patients. In a separate uncontrolled bone biopsy study in adults, treatment with burosumab resulted in decreases in osteomalacia-related histomorphometry indices. This study did not have a control group but one would not expect the bone mineralization defects to resolve spontaneously in XLH patients. When the totality of the evidence was evaluated, the data supported the approval of burosumab for the treatment of XLH for patients greater than 1 year of age [18].

This example demonstrates the individualized approach of both the EMA and the FDA for the development programmes for rare bone diseases. It is important to recognize that each disease state and development programme must be considered separately. What is found acceptable for one disease state and development programme may not translate to another disease or product.

Postmarketing surveillance

Development programmes and the necessary clinical fracture trials currently required for osteoporosis therapies provide premarket safety evaluation on thousands of subjects with drug exposure for at least two years. Despite these very large safety databases, there are adverse events that occur and are not seen until after drug approval. After a product is approved for marketing, regulatory agencies remain involved in safety surveillance and pharmacovigilance activities. Since 2012, the EMA has had a committee dedicated to these activities, the Pharmacovigilance Risk Assessment Committee (PRAC). Patients and health care professionals can submit reports of adverse events associated with a product to the marketing company or directly to the regulatory agency. In the EU, all suspected adverse reactions that are reported by patients and healthcare professionals are entered into EudraVigilance, the EU web-based information system operated by the EMA, which collects, manages and analyses reports of suspected adverse reactions with medicines. The programme used by the FDA is MedWatch, for reporting

serious reactions, product quality problems, therapeutic inequivalence/failure and medication errors with human medical products. Reports can be made online, in written form or by calling MedWatch directly. The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports that have been submitted to the FDA. The FAERS database is available to the public via a web-based tool or raw data files. Examples of rare but serious adverse events for osteoporosis therapies detected in the postmarketing setting include hypersensitivity reactions and anaphylaxis, osteonecrosis of the jaw, and atypical femoral fractures. Once new postmarketing events are detected, product labelling can be updated to reflect the new safety information. In some cases, further safety communications and interventions, such as Risk Minimization Measures/Risk Evaluation and Mitigation Strategies (REMS),² in addition to product labelling, can be implemented.

Generic and biosimilar product development

Generic medicines are the most commonly prescribed medications. In the EU, a generic medicine contains the same qualitative and quantitative composition, in terms of the active substance(s); has the same pharmaceutical form and is bioequivalent to the reference medicine; and is used at the same dose(s) to treat the same disease(s). In the US, a generic medicine has the same active ingredient(s), dosage form, strength, route of administration and conditions of use as a listed drug. With the rapid rise in therapeutic biologic products, a biosimilar regulatory pathway has been developed in both the EU and US. In the EU, the term 'biologic product' refers to any biologic therapeutic product. In the US, a biological product is a protein with >40 amino acids, excluding chemically synthesized polypeptides of <100 amino acids. Peptide products with ≤40 amino acids and chemically synthesized polypeptide products with <100 amino acids continue to be regulated as drug, not biologic, products in the US [19]. A biosimilar product is compared to an already approved biologic reference product, and development must demonstrate that the biosimilar product is highly similar to the reference product and has no clinically meaningful differences in quality, safety or efficacy/safety, purity and potency.³ A biosimilar of teriparatide was the first biosimilar product for a metabolic bone disease to be authorized in the EU [20]. Development of and access to follow-on products are also affected by aspects of data protection and patents, which are beyond the scope of the present review.

Competing Interests

There are no competing interests to declare.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties or on behalf of or reflecting the position of the US Food and Drug Administration.

²EMA and FDA safety intervention terms, respectively

³EMA and FDA biosimilar definitions, respectively

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