WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 10, Issue 9, 1404-1417 Review Article ISSN 2278 – 4357

A REVIEW ON MEDICINES EVALUATION BOARD IN NETHERLANDS

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Article Received on
05 July 2021,

Revised on 26 July 2021,
Accepted on 16 August 2021,

DOI: 10.20959/wjpps20219-19893

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ABSTRACT

The Medicines Evaluation Board (MEB) is an independent authority that regulates the quality, efficacy and safety of medicines, and encourages better use of medicines for the right patient. This includes everything from pain relievers available from drugstores, to treatments prescribed by medical specialists. From medicines that have been in use for decades, to completely new medicines. From medicines in the Netherlands, to medicines across Europe - in co-operation with European colleagues. This review gives information about Medicines Evaluation Board members and marketing authorization medicines for human use.

KEYWORDS: Medicines Evaluation Board members, Marketing authorization medicines for human use.

1. INTRODUCTION

Medicines Evaluation Board, Netherlands

The MEB is aware of the fact that medicinal products are not always marketed immediately after authorisation. Following the European decentralised or mutual recognition procedures (DCP/MRP), it is possible that medicinal products are authorised but subsequently not released on the Dutch market. There are various reasons for this, such as copy procedures with NL as RMS or a delayed market introduction due to patents. In addition, as a result of Review 2001, starting in 2013 it should be taken into consideration that medicinal products submitted and authorised 8 years after the innovator will only be marketed after 10 years.

Taking these abovementioned facts into consideration, the MEB has decided to allow the following exceptions: 1) The option of awarding a marketing authorisation in the Netherlands for a product accepted via an MRP or DCP without having to submit Dutch translations of the product information and mock-ups. The MEB will register medicinal products from the MRP/DCP procedure that will not be released on the Dutch market with only the European (English) confirmed product information. 2) The option of submitting a request for a marketing authorisation with further conditions for medicinal products with Dutch product information that have already been registered, but have not been introduced on the market yet. 3) The option of awarding a marketing authorisation in the Netherlands for a product accepted via an MRP or DCP with a Dutch translation of the product information or accepted via a national recognition procedure without submitting mock-ups. The obligation to keep the Dutch product information up-to-date remains for medicinal products for which the Dutch product information has already been approved and that have already been introduced on the market.

The responsibility for assessing, authorizing and for monitoring the safety of human medicinal products lies with a Board consisting of doctors, pharmacists and scientists. The Medicines Evaluation Board consists of a chairperson and at least 9 and at most 17 other members (doctors, pharmacists and scientists). Chairman and members are appointed by the Minister of VWS. The term of office of the chairman and members is 4 years and can be extended twice by 4 years by reappointment. The method and responsibilities of the Board are laid down in the Medicines Act.

2. Marketing authorisation medicines for human use

MEB Application compass

The MEB Application compass facilitates your application.

1 Prior to marketing authorization application

Scientific and/or regulatory advice

During the development of a medicinal product or an extension of a therapeutic indication, a company may request scientific and/or regulatory advice.

Animal testing

The MEB strives for the development of medicinal products without animal testing and is critical of the added value of animal testing.

Reporting adverse events during clinical trials

Marketing authorization holders have a statutory obligation to report adverse events to the authorization agencies. Sponsors of clinical studies of medicines and bodies carrying out the trials are also required to follow specific instructions for the submission of reports.

Pre-submission meeting

During a European application procedure (centralized procedure, mutual recognition or decentralized procedure) with the Netherlands acting as Rapporteur or as Reference Member State (RMS), the company may request a pre-submission meeting with the MEB prior to initiating the application procedure. The purpose of this meeting is to discuss details regarding the procedure with the Rapporteur or RMS. As these meetings do not qualify as scientific advice, no application form is required and you may contact the head of the Pharmacotherapeutic (PT) group in question directly.

Compassionate use programme

Medicinal products that have not been given a marketing authorization may be prescribed in some cases through a compassionate use programme. This concerns a specific situation in which the MEB considers the availability of new medicinal products for multiple patients (cohort) to be essential prior to the granting of the definitive marketing authorization.

Site clearance

When considering a marketing authorization application, the MEB assesses whether each of the proposed manufacturers has the required permit and comply with the requirements for Good Manufacturing Practice (GMP). If the assessment outcome is positive, the manufacturer will be accepted for the marketing authorization application. This process is known as site clearance.

Pediatric use

The MEB attaches great importance to obtaining appropriate data on medicinal products for children. The development of new knowledge, as well as additional information about the use of medicinal products in children, will contribute to improved treatment.

TSE requirements

When producing medicinal products, specific measures should be in force to minimize the transmission of animal spongiform encephalopathy's (TSE).

3. MARKETING AUTHORIZATION PROCEDURES

Decentralized procedure

The decentralized procedure (DCP) should be used to obtain a marketing authorization in several Member States when the applicant does not yet have a marketing authorization in any country. To request a time slot for a DCP application with the Netherlands as Reference Member State (RMS), you can use our Planning tool to support application for time slots for DCP (NL=RMS). The planning tool shows how many time slots are available per month and for which Pharmacotherapeutical Group.

Mutual recognition procedure

In the case of the mutual recognition procedure (MRP), the RMS has already issued a marketing authorization. The RMS's assessment report forms the basis for requesting the other Member States' mutual recognition of the marketing authorization (including the product information), unless they have objections on the grounds of a potentially serious risk to public health.

Centralized procedure

Pharmaceutical companies that wish to follow the centralized procedure submit a dossier to the European Medicines Agency (EMA). The main advantage of this procedure is that new, innovative medicinal products can be made available to all European residents at the same time once marketing authorization has been granted. The dossier is assessed by the Committee for Medicinal Products for Human Use (CHMP), the EMA's medicines assessment committee.

National procedure

Applicants following the national procedure will be granted a marketing authorization that is valid only in the Netherlands. It is granted by the MEB. The medicinal product to which the dossier relates can only be placed on the market in the Netherlands.

Renewal

A marketing authorization has a limited period of validity when first granted. After 5 years, the MEB must decide based on a benefit-risk assessment if this authorization can be renewed and, if so, whether the renewal can be granted with unlimited validity or, as a result of aspects related to pharmacovigilance, with one additional 5-year period. Once a year, the MEB will make a decision with respect to renewal of the marketing authorization, for each product that

has been authorized via the national procedure for which the marketing authorization expires in that year.

Variation

A variation is a change in the dossier of an authorized product. There are four different types of variations: Type IA, Type IB, Type II and Line extension.

Line extension

A line extension is a marketing authorization the same marketing authorization holder, where for instance the pharmaceutical form and/or strength differs from one or more other pharmaceutical products for which the applicant already holds a marketing authorization.

Legal status of supply and OTC medicinal products

The availability of medicinal products is divided into two main groups: medicines available Only on Prescription from doctor or specialist (PO) and medicines available without prescription (OTC, over-the-counter).

Clarification meeting

In addition to routine contact between the MEB and the company during the course of an application procedure for marketing authorization or subsequent amendment, a company can request further clarification of the questions asked by the MEB.

Hearing

A hearing can be organized in the case that an intention of refusal of the application has been issued, or for MEB decisions the addressee is expected to object to. In a European application procedure this is also called a ‘break-out session’ or ‘oral explanation’.

Withdrawal request

As a marketing authorization holder, you may decide to have your marketing authorization withdrawn for various reasons. To do so, you must submit a request via a withdrawal form together with the requested annexes.

Product types and fees

The list of product types indicates the various product types handled by the MEB. The choice of product type determines the work flow in which the application will be processed. You

will receive a confirmation of receipt, informing you which product type your application will be processed under.

4. TYPES OF MARKETING AUTHORIZATION

New active substance

A new active substance is one which has not already been used in another medicinal product that has been granted marketing authorization in the EU/EEA. Dossiers for medicinal products with a new active substance must contain the test results of pharmaceutical, preclinical and clinical trials.

Well-established use

If the applicant can show that the active substance in the medicinal product has already been in medical use in the EU/EEA for at least ten years (in the form of medicinal products without marketing authorization), and that its efficacy is recognized and its level of safety is acceptable, the requirement to submit results of preclinical or clinical studies may be waived under certain conditions. In this case, studies will be replaced by the appropriate scientific literature.

Generic medicinal product

Generally, a complete dossier must be submitted with a marketing authorization application. A generic medicinal product is a medicinal product that is authorized via an abridged procedure, in order to prevent unnecessary repetition of pharmacological, toxicological, and clinical human and animal trials. The applicant may refer to the complete dossier belonging to another product, the reference medicinal product, as long as the requirements for the accelerated procedure are met.

Informed consent

If you wish to apply for a marketing authorization for a medicinal product that is identical to another product that is already on the market, can do so using the national informed consent marketing authorization application.

Bio-similar medicinal product

As with all other medicinal products, marketing authorization must be obtained for a bio-similar medicinal product before it can be marketed. Marketing authorization is granted once

the European Assessment Committee CHMP, in which the MEB is represented, has scientifically assessed the efficacy, safety and quality of the medicinal product.

Parallel import

When a medicinal product is imported from another European country, this is referred to as parallel import. With parallel import, the medicinal product is marketed in the Netherlands by an importer who has not been designated by the original authorization holder.

Duplex marketing authorization

A duplex marketing authorization is a marketing authorization for a product of which the dossier is identical to that of a product which is already authorized. In a duplex marketing authorization procedure, the MEB can waive a full evaluation, and the marketing authorization can be quickly granted. As from 1 September 2015, a duplex marketing authorization is only permitted under specific conditions.

Replica marketing authorization

A replica marketing authorization concerns a medicinal product which is exactly similar to the reference product, with the exception of the following information: the product name, the name and address of the marketing authorization holder, and the RVG registration number. The replica marketing authorization has no SmPC itself.

Traditional herbal medicinal product

Herbal medicinal products, also referred to as phytotherapeutic products, are medicinal products whose active ingredients contain exclusively plants, parts of plants or plant materials or combinations thereof, in crude or processed form. Just like all other medicinal products, herbals require authorization. This means that they may only be traded after authorization by the MEB.

Homeopathic medicinal product

A homeopathic medicinal product is prepared according to a homeopathic manufacturing procedure described in the European Pharmacopoeia or in one of the official homeopathic pharmacopoeias of the Member States. For this group of medicinal products there are specific quality and safety requirements. The Botanicals and Novel Foods Unit of the MEB decides, on assessing the marketing authorization application prepared by the applicant, whether a

homeopathic product is safe and complies with current quality standards for the manufacture of a medicinal product.

Medicinal gas

Any medicinal gas with a pharmacological effect, as stated in Article 1 of the Medicines Act, and classified as a medicinal product in accordance with Article 1 of Directive 2001/83 (65/65) EC must be authorized before it is allowed on the market.

Medical device

A medical device may contain a substance that is an integral part of the medical device but that is a medicinal product when used separately. When assessing medical devices of this kind, Notified Bodies need to seek advice from a competent authority with regard to the substance, via the consultation procedure).

Novel foods

An application for market authorization of a novel food in the European Union must be submitted electronically to the European Commission. There are 2 different application procedures for this.

5. SUBMITTING A DOSSIER

Dossier modules

A company has to submit a dossier for the assessment of a medicinal product. This dossier, which has to meet current European requirements concerning content and layout, consists of 5 modules.

Submission via CESP

In the Netherlands, the dossier of an application for marketing authorization for medicinal products for human use must be submitted electronically. This electronic submission should preferably be done via the Common European Submission Platform (CESP).

Technical validation

The dossier as part of an application for marketing authorization of a medicinal product must be submitted electronically to the MEB. The MEB carries out the technical validation of your electronic submission. If the dossier you have submitted is not technically valid, or does not comply with the prescribed format, it will not be processed. The MEB carries out the technical validation in accordance with European harmonized standards.

Correspondence during procedure

In the Netherlands it is mandatory to also submit responses to questions via electronic submission. The responses to questions should thus be included in the electronic dossier and should not be submitted in separate documents. Not all correspondence with the MEB is related to the contents of the dossier - e.g. the correspondence about payment of invoices or an application for postponement of the period for responding to questions.

MEB Portal

The MEB Portal offers applicants for a marketing authorization and marketing authorization holders online access to information about the status of procedures.

6. PRODUCT INFORMATION REQUIREMENTS

QRD template

The product information of medicinal products is based on a specific template, the QRD template. There is a distinction between the template for the centralised procedure and the template for the decentralized procedure, the mutual recognition procedure and referrals.

Summary of Product Characteristics (SmPC)

The Guideline on Summary of Product Characteristics contains general guidelines for the way in which information needs to be stated in the Summary of Product Characteristics (SmPC). The MEB has drafted a commentary on this Guideline. It states per SmPC category if there are specific MEB requirements or preferences.

Package leaflet

The package leaflet is derived from the Summary of Product Characteristics (SmPC). This package leaflet is intended for the patient or the consumer, so medical terms are translated in a patient-friendly manner in this document. The package leaflet is assessed and approved by the MEB.

Labelling

The MEB assesses the labelling text submitted by the company. There are fixed items that have to be printed on the label, such as the name of the medicinal product, the active ingredient, including its strength, and the expiry date.

Nomenclature, excipients, abbreviated indications

There are several requirements for the nomenclature of pharmaceutical products, stating the excipients on the packaging and package leaflet, and stating abbreviated indication on OTC medicinal products.

QR code

If a QR code is printed on the packaging and/or in the package leaflet, the conditions listed in Medicines Act and the MEB policy documents on the labelling of pharmaceutical products and the package leaflet must be met. Among other things, this entails that the QR code, and thus the underlying information, may not contradict with the approved summary of product characteristics, must be useful for the patient and may not promote the medicinal product.

Marketing authorization without Dutch translation of the product information and/or mock-up

Following the European decentralized or mutual recognition procedures (DCP/MRP), it is possible that medicinal products are authorized but subsequently not released on the Dutch market. There are several exceptions to the obligation to submit the product information and/or mock-ups in the Dutch language.

Falsified Medicines Directive

As a marketing authorization holder you must implement 2 safety features on the packaging of prescription-only medicinal products for human use. This is stated in the implementation measures derived from Directive 2011/62/EU for the prevention of the entry of falsified medicinal products for human use in the legal supply chain. From 9 February 2019, these safety characteristics must be present on the packaging of medicinal products.

Implementation of agreed wording

The MEB strives to harmonize product information across all medicinal products with the same active substance. As a marketing authorization holder, you are responsible for keeping the product information updated. The implementation of these European agreements for harmonization of product information occurs via variation procedures that must be submitted by the marketing authorization holder.

Patented indication

To conform with patent law, the marketing authorization holder can remove the patented indication from the printed SmPC and package leaflet as present in the packaging of a medicinal product. The marketing authorization holder must notify the MEB about this. The MEB Medicines Information Bank does mention all indications, including patented indications. Patented indications are clearly marked as such.

7. Availability and shortages

Marketing discontinuation, suspension and shortage

As a marketing authorization holder, you are legally obliged to maintain a stock, so that the demand can be met quickly. If a company is (temporarily) unable to supply a medicinal product, they can notify the Medicine shortages and defects notification centre.

GMP and quality defects

Good Manufacturing Practice (GMP) is a quality assurance system for the pharmaceutical industry. The quality of a medicinal product can only be assured by a carefully defined and controlled production process. A marketing authorization holder must always report a quality defect to the MEB.

Marketing authorization for reasons of public health

In case of a shortage of a medicinal product, the MEB may issue a marketing authorization for reasons of public health. This is a marketing authorization without an application. In such cases, at the request of the MEB a company acts as the marketing authorization holder and places a medicinal product that is authorized in another EU Member State on the Dutch market.

Proposed withdrawals

Sometimes the withdrawal of the marketing authorization may pose problems to patients. In those cases, the MEB explores which other possibilities there are to retain the product for the Dutch market. The MEB will usually do this in consultation with the marketing authorization holder. The MEB publishes the proposed withdrawal in an overview. This withdrawal becomes final 6 months after publication in the overview. The MEB announces this in advance to offer other companies the opportunity to take over the marketing authorization. Once a marketing authorization has been withdrawn, it is no longer possible to transfer the withdrawn marketing authorization to another company.

8. Pharmacovigilance

Responsibilities following marketing authorization

As marketing authorization holder, you are responsible for the product's quality, efficacy and safety. You are also obliged to have in place the proper pharmacovigilance and risk management systems.

National contact person

As a marketing authorization holder you are required to appoint an EU Qualified Person responsible for Pharmacovigilance (QPPV). Additionally, if the QPPV is resident outside the Netherlands or does not speak and write Dutch, you are required to appoint a national contact person.

Periodic safety update report

A Periodic Safety Update Report (PSUR) is a pharmacovigilance document intended to provide an update of the worldwide safety experience of a medicinal product to regulatory authorities at defined time points post-authorization.

Reporting adverse events

As a marketing authorization holder, you are legally obliged to submit reports of adverse events to the medicines authorities. There are detailed instructions on what to submit and how this should be done.

Risk management plan

A risk management plan (RMP) provides information on a medicine's safety profile, describes the activities of the marketing authorization holder to further characterise the safety profile during post-marketing (pharmacovigilance activities), and explains the measures that are taken in order to prevent or minimize the medicine’s risks in patients (risk minimization measures).

Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is a single, additional risk minimization measure used to directly inform healthcare professionals about new, important information about a medicinal product. DHPCs are sent by the marketing authorization holder of the product, to healthcare providers. The MEB publishes the DHPCs on its website, together with a news message containing advice for healthcare professionals and patients.

Decision-making process at the European level

The EMA has a coordinating role in the decision-making process at the European level. Several committees have been appointed within the EMA to perform scientific evaluations and to provide advice about the safety of medicinal products.

9. MEB POLICY

Policy documents

Overview of MEB policy documents

Public consultation

Through public consultations, the MEB publishes proposals for new policy documents or major revisions of policy documents. A policy document with small revisions will not necessarily be published for public consultation. A public consultation is generally published for a period of 6 weeks. In case of a holiday period, a longer period applies. With each public consultation, input can be given on the published proposal via an electronic form.

Authorization Contact Committee (CCR)

The Authorization Contact Committee (CCR) is a consultation between the Medicines Evaluation Board and umbrella organizations for the pharmaceutical industry. During the meetings, topics of mutual interest are discussed and where possible agreements are made in order to solve common problems.

10. CONCLUSION

MEDICINES EVALUATION BOARD (MED) is one of the Drug regulatory agency world wide situated in Netherlands associated with Chairman and members are appointed by the Minister of VWS. This review gives an idea about marketing authorization of medicines for human use.

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