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**Medicines: policy, authorisation and monitoring**

PHARM 794

**PHARMACEUTICAL COMMITTEE**  
**12 March 2020**

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**Subject: Market launch of Centrally Authorised Products <sup>1</sup>**

**Agenda item 6**

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<sup>1</sup> This document has not been adopted by the European Commission and, therefore, it does not reflect an official position of the European Commission. It is only meant to be a tool for discussion and the views expressed therein do not necessarily reflect those of the Commission and its services.

# PHARMACEUTICAL COMMITTEE

## Ad-hoc working group on ‘market launch of centrally authorised products’

### Problem analysis and proposed way forward

#### 1. Context and objectives

The market launch of centrally authorised products (CAPs) and the issue of unequal availability of medicines across the European Union (EU) is of recurrent debate.

During the Austrian Presidency (2nd half 2018) the Health Council and Pharma Directors met in Vienna (September 2018) and spoke about the fact that some Member States (MS) see a lot of CAPs in their market, while others face long delays or no access at all. Reasons include staggered roll-out of those products by companies and decisions to market those products in a selected number of countries only. Those decisions are often driven by commercial strategies or pricing and reimbursement considerations.

The lack of availability of medicinal products (MPs) in many Member States is a concern in general, but is a particular challenge to the underlying principle of the centralised authorisation procedure which allows marketing authorisation holders (MAH) to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation.

In an effort to increase availability of centrally authorised medicinal products (CAPs), the Pharmaceutical Committee members have welcomed the intention to consider actions within the current legal framework, which could provide more transparency on the actual marketing situation and help improve company engagement for a wider roll out of CAPs.

At the Pharmaceutical Committee meeting of April 1 2019, a group of 10 MS<sup>2</sup> and the EMA volunteered to participate in an ad-hoc working group (the ‘group’) chaired by the Commission to follow up the discussion and consider additional actions to increase market launch for CAPs.

The group examined three issues:

- Legal interpretation of the sunset clause;
- Improve knowledge on the planned marketing of CAPs in the pre-authorisation phase;
- Increase transparency on the actual marketing of CAPs in the post-authorisation phase.

The Pharmaceutical Committee has been consulted and kept informed on the subgroup proposals throughout this process.

The present document constitutes the consolidated reflection of the group and proposes next steps. This document will be submitted to the Pharmaceutical Committee for formal endorsement, ahead of preparing for implementation of the 2 main actions proposed by the group (see point 3 and 4 below).

#### 2. Legal interpretation of the sunset clause

The rules on marketing authorisation (MA) laid down in Regulation (EC) No 726/2004 (‘the Regulation’) foresee a 5-years validity of a MA, which may be renewed for an unlimited period (unless reasons relating to pharmacovigilance justify another 5-years renewal).

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<sup>2</sup> Austria, Cyprus, Estonia, Finland, Hungary, Ireland, Latvia, Malta, Netherlands, Spain.

The validity period is conditional to a ‘sunset clause.’ I.e., authorisation must be followed by an actual placing of the medicinal product on the Union market within 3 years (after authorisation). If, following authorisation, the medicinal product is not actually placed on the market the MA ceases to be valid.

Part of the function of the sunset clause aims to enhance transparency of the MA system. This is observed in the obligation to inform the EMA of the actual marketing of a MP (Art 13(4) and 14b(1) of the Regulation). For the purposes of the application of the ‘sunset clause’ (Art 14(4, 5 and 6 of the Regulation), the EMA has put in place a system to monitor the marketing status of CAPs. When a three consecutive year period without marketing has elapsed, EMA notifies the Commission accordingly.

A detailed description of the legal interpretation of the ‘sunset clause’ and of the modalities of its application can be found in Annex I.

The history of the provision and the modalities of application point towards a flexible approach towards marketing authorisation holders, who are in principle allowed to launch and cease marketing in line with the parameters set by the law. The group has also reflected on the possible unintended consequences of a stricter application of the ‘sunset clause.’

The availability of a CAP in a limited number of national markets may indirectly contribute to shortages if demand is seen from the perspective of the entire EU market. A shortage of a medicinal product occurs when supply does not meet demand from healthcare professionals or patients in response to clinical needs.<sup>3</sup> The obligation for continuous supply as defined in Article 81 of Directive 2001/83/EC (the Directive) relates to medicinal products already placed on the market of a specific MS and not to the Union as a whole. It follows from the above that there is a gap between how the applicable legislation regulates availability and how availability is actually defined and perceived.

The Pharmaceutical Committee concluded that the application of this provision to increase availability is limited and therefore agreed to prioritise the remaining two work strands.

### **3. Improve knowledge on the roll out marketing intention of CAPs in the pre-authorisation phase**

Notwithstanding the vast majority of innovative medicines being centrally authorised, there are still important differences in the timing of availability of new medicines among EU Member States and inequalities in access to (innovative) medicines.

Currently, applicants are not required in the pre-authorisation phase to provide information on their marketing plans after obtaining a MA. In order to overcome this lack of information, and as it would be useful to be aware of the applicant’s launch plans, the group is exploring the possibility to increase transparency regarding marketing intentions.

The aim is to request applicants to provide information regarding their launch strategy in the various MSs. This information request would consist of a voluntary submission of marketing intentions.

The group proposes to explore the applicants’ willingness to provide this information and to gather evidence on the usefulness of receiving this information during the pre-marketing stage, through a pilot project, and to check if this could also potentially have a positive impact on the actual marketing of CAPs.

In the pilot, the request to provide launch intention information would be applied to new marketing authorisation applications, submitted under Art 8(3) of Directive 2001/83/EC, for orphan and oncology medicinal products only. This links the pilot to the claimed benefit of meeting an unmet medical need (availability of orphan medicines) as well as to the Commission initiative ‘Europe’s Beating Cancer

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<sup>3</sup> Definition agreed by the European Medicines Agency and the Heads of Medicines Agencies Network

Plan' (availability of cancer medicines). After assessing the results of the pilot, the group will consider expanding it to also other products.

Though voluntary, this information request used in conjunction with the actual marketing status (see point 4. below) would also allow regulatory authorities to monitor how intended marketing is followed-up or not by actual CAP marketing in the MS concerned, and would allow obtaining a better understanding of the reasons why certain CAPs are in the end not launched in a MS despite the initial intention of the company concerned..

#### **4. Increase transparency on the actual marketing of CAPs in the post-authorisation phase**

MAHs of centrally approved medicinal products are obliged by Article 13(4) of Regulation (EC) No 726/2004 to inform the Agency of the dates of actual marketing<sup>4</sup> of centrally authorised medicinal products for human use in the MS, taking into account the various presentations authorised. MAHs are also obliged by Article 14b of Regulation (EC) No 726/2004 to notify the Agency if their product ceases to be placed on the market of a Member State, either temporarily or permanently<sup>5</sup>. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

The publication of information on the marketing status of CAPs is not mandated in the legislation except for what is included in Article 123(4) of Directive 2001/83/EC. According to this article, the Agency is required to annually make public a list<sup>6</sup> of human medicinal products which have been withdrawn from the EU market.

Possible **advantages** of making marketing status data available:

- Awareness on availability of medicines – MS would benefit from a greater evidence base to answer queries on availability of medicines from healthcare professionals (HCPs) and patients. If marketing status data would eventually be published online, HCPs and patients across the EU could directly check if a medicinal product is commercialised in their country, hence reducing requests to regulators.
- Public health monitoring - In case of urgent need for non-marketed products, MS would know what is available in other countries and take contingency measures, e.g. supply from other MS, look at therapeutic alternatives marketed in their own territory, etc.
- Pricing and reimbursement policies - MS could compare what is marketed in neighbouring countries.

Possible **disadvantages** of making marketing status data available:

- Duplication of information - Some Member States already have in place transparency measures, which include publishing online information regarding market launches. MS which already have their own system for collecting marketing status information may see a duplication of information for CAPs, and discrepancies might arise. This drawback could be partially mitigated by making it possible for the NCAs to extract and download the relevant data for their territory from an EMA system and then import it within their national reporting systems/databases.

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<sup>4</sup> For the definition of 'placing on the market' reference should be made to the Chapter 1 of volume 2A of the Notice to Applicants, see also Annex I and relevant EMA Q&A - <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/notifying-change-marketing-status>

<sup>5</sup> The "cessation of placing on the market" is defined by analogy to the placing on the market, as the "cessation of release into the distribution chain" with the consequence that the concerned product may no longer be available for the supply to the patients. It means that the date of cessation shall be the date of the last release into the distribution chain.

<sup>6</sup> <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/notifying-change-marketing-status#withdrawn-product-notification-section>

- Possible unintended effects on P&R process

Currently, the European Medicines Agency receives marketing status information at MS level in an unstructured format and is not able to place it in a central repository. A dedicated IT tool is being set-up to allow a faster and structured data collection and dissemination to Member States.

When the standardisation process of the article 57 database (SPOR) is completed (planned in 2022), the new Product Management Service (PMS) database will contain, inter alia, structured fields for marketing status by Member State for both CAPs and NAPs. The PMS database will be the repository of information on which products are marketed in which Member States of the EU and the EEA.

Under this work strand in the group, the EMA is exploring the possibility to set up an interim IT tool capable to track marketing status information for CAPs until the PMS database becomes available.

Under the envisioned interim solution, marketing information submitted by MAHs to EMA as per Art 13(4) of the Regulation, would be captured by a IT tool regarding all authorised CAPs and would provide data for each Member State in terms of date of first marketing, date of cessation, estimated/actual/re-introduction date, and reasons for marketing cessation. The form currently used by MAHs to notify marketing information to EMA will be adapted to capture the relevant information (using structured drop-down lists where feasible).

Through a dashboard created by EMA, MS would be able to track at given time points information of marketing of CAPs in their territory and in other EU MS (both ‘view’ and ‘download’ functionalities will be available via the dashboard). Information on marketing status could be made available only to EC/NCAs or to both NCAs and the public (e.g. via periodic reports published on the EMA website). The group decided that, as a first step, information will be made available only to EC/NCAs. Sharing marketing information with the general public will be considered as a second step.

It is important to highlight that, with both the IT tool described in this section and with the future PMS, the EMA has no technical and legal tools to verify the marketing status information received from MAHs, as well as to enforce MAH compliance with the reporting requirements. A note will be included in the dashboard to indicate that the data is provided by MAHs, who have an obligation to provide accurate information to the EMA, but that this is not systematically validated by EMA or MS. Ultimately, only MS, by involving all relevant NCAs and stakeholder groups (e.g. pharmacists) in their territory, will be able to verify that the marketing status information provided to EMA by MAHs corresponds to the reality in their country. Audits of the MAH reporting could be performed by NCAs in cooperation with the EMA on random samples of products.

In summary, the group agreed with the following approach for the increased transparency in marketing of CAPs:

1. To first make information collected by the EMA available to Commission and NCAs only. Providing access to the public will be considered in a second stage.
2. To have reporting obligations for all CAPs, including those already authorised.
3. To validate the information reported by MAHs through the audit of a random selection of products, by NCAs in cooperation with the European Medicines Agency.

## **5. Next steps**

The ad-hoc Working Group seeks the Pharmaceutical Committee’s endorsement of the following two proposed steps:

- Launch of a **pilot project** aiming to increase transparency regarding marketing intentions in the pre-authorisation phase as described in section 3. Before implementation, interested stakeholders will be invited to provide feedback on the proposed pilot during a 4-week online consultation period.
  
- To implement the recommendations of the group for increasing transparency on the actual marketing of CAPs in the post-authorisation phase, EMA will work on:
  - The creation of an **interim IT tool capable to track marketing status information for CAPs** until the PMS becomes available.
  - As a first step, information will be made available only to EC/NCAs.
  - Sharing marketing information with the general public will be considered as a second step.

## Annex

### Non-paper

#### Points to consider for the application of Article 14, paragraphs 4, 5 and 6 of Regulation (EC) No 726/2004 – the "Sunset clause"

**Note to the reader:** The below considerations have been prepared to support and guide the work of the adhoc working group. They neither change nor replace any legal guidance document, such as the Notice to Applicants. The considerations are published for transparency reasons only.

### 1. Introduction

The rules on marketing authorisation (MA) laid down in Regulation (EC) No 726/2004 (the Regulation)<sup>7</sup> foresee that the validity of a MA shall be 5 years and may then be renewed for an unlimited period<sup>8</sup>.

The validity period mentioned above is conditional to a "sunset clause". Authorization must be followed by an **actual placing** of the MP on the Union market within 3 years after authorization. If, following authorisation, the MP is not *actually* placed on the market the MA ceases to be valid<sup>9</sup>. The same applies when an authorised MP is no longer **actually present** on the market for **3 consecutive years**. The provision foresees an exemption to this rule for exceptional circumstances and public health grounds. Such exemptions are to be provided after due justification.

It is worth noting that Directive 2001/83/EC contains the same provision in an almost identical way. This new provision applies to all centrally authorised medicinal products from the date of application of Article 14 of the Regulation, i.e. 20 November 2005.<sup>10</sup>

### 2. Legal context

The relevant section in Article 14 of the Regulation reads as follows:

*'(4) Any authorization which is not followed by the actual placing of the medicinal product for human use on the Union market within three years after authorisation shall cease to be valid.*

*'(5) When an authorised medicinal product previously placed on the market is no longer actually present on the market for three consecutive years, the authorisation shall cease to be valid.*

*'(6) In exceptional circumstances and on public health grounds the Commission may grant exemptions from paragraphs 4 and 5. Such exemptions must be duly justified.'*

The corresponding provision for nationally authorised products in Article 24 of Directive 2001/83/EC reads as follows:

*'(4) Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.'*

### 3. The logic behind the provision

The "sunset clause" has been part of the Regulation since 2004. It was included in the first proposal made by the EC, where a period of 2 years was initially set in order to primarily avoid the administrative

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<sup>7</sup> Any citation to legislation made without mentioning the act refers to this Regulation.

<sup>8</sup> Unless reasons relating to pharmacovigilance justify another 5-year renewal

<sup>9</sup> Cessation of validity is automatic, no particular decision or administrative action is required for the validity to cease.

<sup>10</sup> <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/notifying-change-marketing-status#sunset-clause-monitoring-section>

burden of maintaining MAs for MPs which are not actually marketed.<sup>11</sup> It was hence, primarily introduced as a counterbalancing element to the fact that within the same amendment, marketing authorisations became in principle valid for an unlimited period after an initial period of validity of five years. Prior to that amendment, marketing authorisations were renewed every 5 years.

During the co-legislative procedure, this principle was maintained by the European Parliament (EP) and the Council and eventually made its way to the final text. Recital nr. 35 of the Regulation provides a justification for the provision which was introduced to "*avoid the administrative burden of maintaining such authorisations*".

*(35) [...] Furthermore, any authorisation not used for three consecutive years, that is to say, one which has not led to the placing on the market of a medicinal product in the Community during that period, should be considered invalid, in order, in particular, to avoid the administrative burden of maintaining such authorisations. However, this rule should be subject to exemptions when these are justified on public health grounds.<sup>12</sup>*

The reference to administrative burden in the recital highlights the link between the unlimited validity of a marketing authorisation and the sunset clause. While this may be considered as the main reason (see the use of the term "in particular" in the recital), there might also be additional reasons, such as to encourage companies to place a product on the market in a timely manner after the authorisation or to avoid long interruptions of supply.

The **EP** in its first reading expanded the 2-year period initially proposed by the EC to 3 years explaining that a two-year period is not sufficient to allow for the various factors which may cause actual placing on the market to be deferred.<sup>13</sup> It also amended the EC proposed text to allow for the exemptions on the basis of public health grounds. The changes proposed by the EP in first reading provided a flexibility to the MAH both in terms of time allowed as well as exceptions to the application of the sunset clause. This position was also mirrored by the **Council** in its adopted position in first reading which added the exceptional circumstances exception.

The EC accepted these changes in its amended proposal<sup>14</sup> and reiterated the four basic objectives of the Regulation:

- (1) to assure a high level of public health protection, notably by making safe, innovative products available to patients as quickly as possible, and by an increased supervision of the market through the strengthening of inspection procedures and of pharmacovigilance;*
- (2) to complete the single market for pharmaceutical products (...);*
- (3) to respond to the challenges of the future enlargement of the EU;*
- (4) to rationalise and simplify the system as well as to improve its overall coherence and visibility and the transparency of its procedures.*

Part of the function of the sunset clause aims to enhance transparency of the MA system. This is prevalent in the obligation to inform the EMA of the actual marketing of a MP (Art 13(4) and 14b(1)). For the purposes of the application of the so-called "sunset clause" (Art 14(4, 5 and 6), the European Medicines Agency has put in place a system to monitor the marketing status of centrally authorised

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<sup>11</sup> [https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52001PC0404\(01\)&qid=1560170934011&from=EN](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52001PC0404(01)&qid=1560170934011&from=EN)

<sup>12</sup> A similar recital appears in Directive 2004/27/EC (rec. 17) which amends the text of Directive 2001/83/EC.

<sup>13</sup> For example, a product intended to treat a sporadic disease will not be sold until that disease breaks out. Furthermore, small and medium-sized businesses may need to find a partner for the purpose of marketing a new product.

<sup>14</sup> [COM/2002/735/FINAL](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:COM2002735FINAL)



medicinal products. When a three consecutive year period without marketing has elapsed, EMA notifies the Commission accordingly.

#### 4. Modalities of application

The "sunset clause" has so far not been subject to an authoritative interpretation by the EU Courts, but many of the terms used in the wording of the provision, have been subject to Court rulings and Court interpretation, this includes notions such as "placing on the market" and " Union market", which are key to understand the scope of the provision.

Moreover, the Commission together with Member States provided some guidance regarding the modalities of the application in the 'Notice to Applicants'<sup>15</sup>.

**Placing on the market** means the date of release into the distribution chain (i.e. the date when the MP comes out of the control of the MAH). According to Decision No 768/2008/EC placing on the market has been defined as the "first making available on the market" (by the manufacturer or the importer). Similarly, Regulation (EC) No 764/2008<sup>16</sup>, which defines the rights and obligations for public authorities and enterprises that wish to market their products in another EU country, adopts the same interpretation of the 'union market.'

**Making available on the market** is defined in the same decision<sup>17</sup> as "any supply of a product for distribution, consumption, or use on the [...] market in the course of a commercial activity, whether in return for payment or free of charge". A good is "placed on the market" only once, but may be "made available" several times throughout the supply chain (first wholesaler, second wholesaler, retailer, etc.) before it reaches the final user (consumer or professional user) or is further processed into another product. The concept of placing on the market refers to each individual good, not to a type of good, and whether it was manufactured as an individual unit or in series. The making available of the product supposes an agreement for the transfer of ownership or possession concerning the product after the stage of manufacture. The transfer does not necessarily require the physical handover of the product.

For centrally authorised products, the product has to be placed on the **Union market**. According to the interpretation provided in the Notice to Applicants this means that the product is at least marketed in one Member State. This interpretation is in line with the concept behind the 'Union market' (or internal market or single market), which encompasses all Member States in the EU. According to Article 26(2) of the Treaty on the Functioning of the European Union, the internal market shall comprise an area without internal frontiers in which the free movement of goods [...] is ensured in accordance with the provisions of the Treaties. It follows that from a legal perspective the Union market is served as soon as and as long as the product is placed on the market somewhere in the EU. The concept cannot be linked to a specific or minimum number of Member State's markets, as the Union market does not include borders.

In this regard, it is also useful to point to the differences in wording between the sunset clause in Regulation 726/2004 for centrally authorised products and the sunset clause for nationally authorised products in Directive 2001/83/EC. Only the latter refers to markets that are related to the territory of an individual Member State.

The term "no longer actually present on the market" should be understood in the same way as "ceases to be placed on the market". Therefore, the sunset clause period in case of a complete marketing

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<sup>15</sup> [Chapter 1](#) (section 2.4.2), The rules governing medicinal products in the European Union, Notice to Applicants, Volume 2A.

<sup>16</sup> Regulation (EC) No 764/2008 lays down procedures relating to the application of certain national technical rules to products lawfully marketed in another Member State.

<sup>17</sup> Article R1(1) of Annex I to [Decision No 768/2008/EC](#) of the European Parliament and of the Council.

cessation of the product shall start from the last date of release into the distribution chain of the medicinal product.<sup>18</sup>

**The start of the 3-year period** should be the date when the medicinal product can be marketed by the MAH. For new products this is the date from which the marketing authorisation takes effect (i.e. as of the date when the MAH is notified of the Commission decision) for products authorised under abridged procedures, market protection rules need to be taken into account.

According to the Notice to Applicants the MA remains valid if **at least 1 presentation of the medicinal product is placed on the market** and if at least one pack-size of the existing pack-sizes for that presentation is marketed (i.e. is made available on the Union market). This interpretation corresponds to the established practice. A stricter interpretation however in regards pack-sizes and presentations would do little to increase accessibility to the medicine. The reason being that the core problem relates to the non-availability of the medicine *per-se* in each Member State and not to the number of its presentations.

In case a medicinal product is **withdrawn and placed back on the market** before the 3 consecutive years pass, the clock restarts. This process can be repeated. From a practical point of view however such practices are rarely encountered, if ever, as companies do not have the commercial interest to market a medicinal product in the first instance.

The marketing authorisation holder has an **obligation to inform the EMA** of the date of actual marketing of the medicinal product in each Member State and the date of cessation of placing on the market (permanent or temporary). The MAH must mention the reasons of such actions.<sup>19</sup>

## 5. Conclusions

The "sunset clause" included in Art. 14 of the Regulation was primarily introduced to reduce administrative burden of maintaining marketing authorisations that were not used but also to increase transparency including encouraging companies to place a product on the market in a timely manner after the authorisation or to avoid long interruptions of supply.

The history of the provision and the modalities of application point towards a flexible approach towards marketing authorisation holders, who are in principle allowed to launch and cease marketing as they see fit as long as they respect the parameters set by the law.

The flexibility provided should be read in the light of the general objectives of the Regulation and cannot lead to situations which go against those objectives. In this case assuring a high level of health protection (which includes availability) and the transparency of the Regulation's procedures.

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<sup>18</sup> Cf. footnote nr. 3

<sup>19</sup> Art. 13(4) and 14b of the Regulation.