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EU FINANCIAL PENALTIES FOR CENTRALLY APPROVED MEDICINAL PRODUCTS IN EUROPE - HOW TO PREPARE?

Commission Regulation No. 658/2007[1] (the "Penalties Regulation"), as recently amended by Commission Regulation No. 488/2012,[2] empowers the European Commission to impose financial penalties in relation to medicinal products approved through the centralised procedure. No financial penalties have yet been imposed, but the situation may change following the recent amendments, which added safety and paediatric obligations to the list of obligations that may be enforced by financial penalties.

This note briefly examines the Penalties Regulation and provides recommendations for preparing for investigations and avoiding financial penalties. A copy of the currently applicable version of the Regulation can be found here. The penalties regime applies to medicines for human use as well as veterinary medicines but this note primarily focuses on the former.

1. LEGAL BACKGROUND

Medicinal products approved through the centralised procedure are subject to many regulatory obligations, most of which are contained in Regulation (EC) No. 726/2004.[3] The Penalties Regulation empowers the Commission to impose financial penalties against marketing authorisation holders (MAHs) who infringe certain of those obligations. Fines are decided by the Commission after an infringement procedure which is initiated by the European Medicines Agency (EMA).

The EU enforcement system applies in parallel to national enforcement systems. Article 2 of the Penalties Regulation aims at preventing double penalties but does not guarantee that this will not happen.

a) Infringements Concerned

Article 1 of the Penalties Regulation lists 23 obligations contained in Regulation (EC) 726/2004 (briefly summarised in Table 1) and 8 obligations under the Paediatric Regulation (EC) No. 1901/2006[4] (summarised in Table 2) the infringement of which may trigger financial penalties (the "Enforced Obligations"). A broad set of obligations is covered, ranging from the need to

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[1] Commission Regulation (EC) No. 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No. 726/2004 of the Parliament and the Council. This regulation implements Article 84(3) of Regulation (EC) No. 726/2004.

[2] Commission Regulation (EU) No. 488/2012 of 8 June 2012 amending Regulation (EC) No. 658/2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No. 726/2004 of the Parliament and the Council.

3 Regulation (EC) No. 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

4 Regulation (EC) No. 1901/2006 of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

update the MA dossier to pharmacovigilance requirements and the obligation to complete deferred paediatric studies.

The penalties regime only applies to MAHs of centrally approved products and not as such to affiliates that participate in the development, production and marketing of the products or to independent distributors and other partners (except for lack of collaboration in investigation procedures). The regime also does not apply to MAHs of products approved under the DCP or MRP or that are merely nationally approved.[5]

Infringement of an Enforced Obligation is not sufficient for the EU authorities to get involved. The infringement must also have significant public health implications in the Union, take place or have effects in more than one Member State, or involve the Union's interests.

Table 1

Key Obligations for all MAHs Enforced by Financial Penalties

Obligation:

- to submit complete and accurate documentation in an application for an MA or in response to obligations laid down in Regulation 726/2004;
- to comply with conditions or restrictions included in the MA and concerning the supply or use of the medicinal product;
- to introduce any necessary variation to the terms of the MA to take account of technical and scientific progress and enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods;
- to keep the product information up to date; to provide any new information that may entail variations or that is relevant for the evaluation of risks and benefits of the product; and to notify any prohibition or restriction imposed by the NCA of any country in which the medicinal product is marketed;
- to provide, upon request, any data demonstrating that the risk-benefit balance of the product remains favourable;
- to place the medicinal product on the market in accordance with the content of the summary of the product characteristics and the labelling and package leaflet as contained in the MA;
- to observe or introduce the specific procedures subject to which the MA is being granted, including the conditions of a conditional MA;
- to notify the EMA of the dates of actual marketing and the date when the product ceases to be on the market, including data on the volume of sales and prescriptions;
- to operate a comprehensive pharmacovigilance system, to have a qualified person at disposal, and to observe the applicable recording, reporting and data assessment obligations in connection with that system;
- to operate a risk management system and to record and report suspected adverse reactions and to submit periodic safety update reports;
- to conduct post-marketing studies, including post-authorisation safety studies and post-authorisation efficacy studies, and to submit them for review; and
- to detect residues in the case of veterinary medicinal products

[5] Enforcement of obligations linked to national MAs remains subject to national rules.

Table 2

Obligations Under the Paediatric Regulation

MAHs of centrally approved medicinal products should also observe the following obligations that are set out in the Paediatric Regulation:

- to submit complete and accurate documentation in response to the obligations laid down in the Paediatric Regulation;
- to operate a risk management system;
- to conduct post-marketing studies and submit them for review;
- to comply with the time limits for initiating or completing measures specified in the EMA decision on deferral following the initial MA;
- the obligation to place the medicinal product on the market within two years of the date on which the paediatric indication is authorised, as provided for in Article 33 of Regulation 1901/2006;
- the obligation to transfer the marketing authorisation or to allow a third party to use documentation contained in the marketing authorisation dossier, as provided for in the first subparagraph of Article 35 of Regulation 1901/2006;
- to submit paediatric studies in accordance with Articles 41, 45 and 46; and
- to submit an annual report on the deferred measures to the EMA, and to inform the EMA in case the MAH intends to discontinue the placing on the market of the product.

b) Scope of the Enforced Obligations

The list of Enforced Penalties obviously provides limitative grounds for penalties, but several of the obligations are intrinsically vague and an infringement finding will imply a judgment call based on all relevant facts. This is, for instance, the case for the obligation to supply any new information that may entail a variation to the terms of the MA. Other obligations will require legal interpretation, such as the obligation to place a product with a paediatric indication on the market under Article 33 of Regulation 1901/2006. Finally, some Enforced Obligations are not directly based on Regulations 726/2004 or 1901/2006 but on a rewording in the Penalties Regulation. A striking example is the obligation to market the medicine in accordance with the content of the approved SmPC, labelling and package leaflet. An initial draft for the Penalties Regulation included compliance with advertising rules as an Enforced Obligation. This was not maintained in the final text because the EU advertising rules are laid down in Directive 2001/83[6] and a Directive cannot create direct legal obligations for companies. The final wording in the Penalties Regulation may be an indirect attempt to try to still cover advertising aspects and can be challenged in that respect, especially as the Enforced Obligations should in principle be interpreted restrictively.

c) Infringement Procedure

The infringement procedure comprises an investigation phase led by the EMA and a decision-making phase led by the Commission.

Preparatory Phase. -- Before starting an investigation, the EMA may request information from the MAH. The request must indicate that it is made in the context of the Penalties Regulation.

6 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Investigation Phase. -- This phase is initiated by the EMA, either at its own initiative or following a request from the Commission or a Member State. When opening an inquiry, the EMA sends a notification to the MAH (and to the Commission and Member States), which sets out the allegations, the alleged infringement(s), and the underlying evidence. The EMA then has a number of inquiry measures at its disposal to investigate and gather evidence of the suspected or alleged infringement. It works in close cooperation with the national authorities and can ask them to conduct investigative measures. It can also request the MAH or third parties to provide explanations and documents, and a lack of cooperation from the MAH may also lead to separate financial penalties. The EMA must conclude the inquiry within 18 months. Its final report may include a request to the Commission to apply financial penalties.

Decision-Making Phase. -- Where the Commission receives an EMA report requesting the application of penalties, the Commission has an additional period of 18 months to send the MAH either a Statement of Objections, which is a prerequisite for any decision imposing financial penalties, or an Explanatory Statement, which should close the procedure. The Statement of Objections sets out the Commission's allegations and the allegedly infringed provisions. In preparing its decision, the Commission may request more information from the MAH, the national authorities, the EMA or any third party; it may also hold an oral hearing. If having considered the EMA report and all relevant elements the Commission concludes to an infringement, it can order the company to cease the infringement and impose financial penalties.

Naming and Shaming. -- The Commission's decision will be published, including the names of MAHs involved as well as the amounts of and reasons for the financial penalties. Confidential information will be deleted.

Procedural Rights. -- The MAH benefits from a number of procedural safeguards. Most importantly, the Commission has the burden of proving the infringement, and the MAH is not required to provide incriminating information. Both the EMA report and the Commission decision may only be based on grounds on which the MAH has been able to comment, and the MAH has a right to access the evidence collected by the EMA and the Commission. The Commission decision can be appealed to the European Courts. On the other hand, the Penalties Regulation does not contain rules on legal privilege and the limited general EU legal privilege principles will apply. The Regulation also poorly secures the MAH's confidential information.

d) Financial Penalties

The Commission can impose financial penalties for two types of infringements.

The *first category of infringements* concerns the Enforced Obligations. The infringement may have been committed intentionally or negligently. The Commission will take the individual circumstances into account when deciding on the imposition of a penalty and on the actual penalty amount, including, *e.g.*, the turnover generated by the medicinal product concerned, the seriousness and effects of the infringement on the population or environment, the MAH's good faith, its cooperation in the procedure, or prior national sanctions. The Penalties Regulation does not encourage whistleblowing or self-reporting by removing or reducing the fines. The financial penalties may be up to 5% of the MAH's EU turnover in the preceding business year.

If the MAH did not yet cease the infringement when the Commission decides on it, the Commission may also impose a daily financial penalty of maximum 2.5% of the MAH's average daily EU turnover for the preceding business year.

The *second category of infringements* concerns the MAH's cooperation during the enforcement procedure. The MAH also faces significant financial penalties[7] if it does not comply with measures of inquiry or information requests, or if it provides inaccurate or incomplete information.

Although the Penalties Regulation expressly refers to the MAH's turnover, the Commission may try relying on the group's turnover as it does in the competition area.

2. RECOMMENDATIONS FOR MAHS

MA holders should organise and maintain a strong compliance system in general and, in light of the financial penalties regime, with regard to the Enforced Obligations in particular. Special attention should be given to the pharmacovigilance obligations because of their direct link with public health. The following measures are recommended to strengthen the internal systems, to react promptly and efficiently to initial requests for information, notifications of investigation or formal investigation measures, and to support a finding of good faith in case infringements have occurred:

Mapping of Products and Functions

- Every company should keep at a central location up to date records of all centrally approved products, with details on at least the following:
    - Complete list of what product presentations are marketed in which Member States.
    - Overview of regulatory submissions and decisions, and of major interactions with regulators.
    - Details on how the key regulatory functions are performed (regulatory, pharmacovigilance, quality, control of advertising and information,...).
    - Details on how each of the Enforced Obligations is complied with.
    - Details on the contractual arrangements with affiliates and independent entities (such as distributors) for compliance with the regulatory obligations.
    - Location of relevant documentation.
- The records should also contain historical data so that important changes over time can be reconstructed.
- The records should be accessible to key regulatory, compliance and legal staff.

Organisation and Maintenance of a Strong Compliance System

- *List of Tasks and Responsible Employees and Training* -- The MAH should ensure that all employees (or functions) who are responsible for complying with Enforced Obligations are fully familiar with the precise contents of the obligations and are in a position to comply with them. Where needed, additional training should be provided. The information should be regularly updated.
- *Compliance Programs and Audits* -- Special attention should be given to the Enforced Obligations in the company compliance and audit procedures and activities.
- *Confidential Documents* -- Documents that are confidential or contain confidential information should be clearly labelled as such. A redacted version of each confidential document should be prepared and stored together with the document.

[7] Up to 0,5% of the MAH's turnover in the preceding business year. In case the MAH's non-cooperation continues, a daily financial penalty of maximum 0.5% of the MAH's average daily turnover for the preceding business year may also be imposed.

- *Legal Privilege* – Documents that are covered by legal privilege should be identified and stored separately from any other documents. It is important to remember that, as a general rule, under EU principles in-house lawyers are not subject to legal privilege and therefore neither are the documents or emails exchanged with them.
- *Monitoring of Compliance and Audits* – The compliance and audit procedures in place should also specifically cover the Enforced Obligations.
- *Procedures in case of Infringement* – Appropriate procedures should be put in place to deal with internal findings of infringements. They should focus on corrective measures for the specific case of non-compliance, improving procedures for future compliance and protecting the company's rights through legal privilege.

Contracts with Independent Distributors and Other External Partners

- Outsourcing the performance of regulatory tasks is *de facto* unavoidable but does not diminish the MAH's legal responsibility. The MAH should, especially with regard to independent contractual partners, ensure that the agreements provide for the relevant information and notification provisions and appropriate supervision and control mechanisms. Awareness building, training and audits are often required. These steps will support better compliance, can help supporting good faith in case of infringement, and also strengthen rights of recourse against the contract partner.

During an Enforcement Procedure

- *Cooperation during Investigations* – The MA holder should ensure internally that it provides accurate and complete information upon request of the authorities. A pro-active approach can generally be recommended, which reduces the risk of misunderstandings on the authorities' side. Where information requests are unclear, the MA holder should request clarification. Cooperation in detecting an infringement must be taken into account by the Commission when deciding on the level of a penalty; and lack of cooperation can on its own also result in specific fines.
- *Centralisation of the Communications with the Authorities* – The MA holder should centralise the communication with the EMA and the Commission to one employee or small team, e.g., preferably the company's legal department.
- *Interviews of Employees* – The MA holder should organise a briefing of employees who may be interviewed by the authorities and give them instructions on the more appropriate way to answer questions. The MAH should refrain from imposing specific answers or advising not to disclose certain information except for the information which is confidential or covered by legal privilege.
- *National Investigations* – In case of a national investigation conducted at the request of the EMA or the Commission, reference can be made to the manuals and instructions used for dawn raids and similar procedures. Full records of all steps of the investigation should be provided to the central coordination point.
- *Legal privilege and Procedural Rights* – The company must claim the legal privilege it considers it is entitled to and must promptly react when procedural rights are not sufficiently respected.
- *Legal Counsel* – Legal counsel should immediately be involved.

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