

This is a translation of the Danish executive order no. 898 of 23 June 2016 on monitoring of adverse reactions from medicinal products (Danish title: Bekendtgørelse om bivirkningsovervågning af lægemidler). Only the Danish version has legal validity.

Executive order on monitoring of adverse reactions from medicinal products¹

The following is laid down pursuant to sections 53(4), 56(1) and (2) and 104(3) of the Danish Medicines Act, see the consolidation act no. 506 of 20 April 2013:

Scope, definitions etc.

1.-(1) This executive order covers medicinal products for human and veterinary use that have been granted a marketing authorisation by the Danish Medicines Agency, see section 7 of the Danish Medicines Act.

(2) The executive order does not cover medicinal products included in a clinical trial authorised by the Danish Medicines Agency under section 88(1) of the Danish Medicines Act.

(3) This executive order does not affect the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, title II, chapter 3, and title III, chapter 3 or Commission Regulation (EF) No 540/95.

2.-(1) Adverse reaction to a medicinal product for human use means a noxious and unintended response to a medicinal product.

(2) Adverse reaction to a medicinal product for veterinary use means a noxious and unintended response, resulting from doses normally used for animals to prevent, diagnose or treat a disease or modify, restore, correct or influence a physiological function.

(3) Exposure-related reaction means a noxious and unintended response, occurring in humans after contact with a veterinary medicinal product.

(4) Serious adverse reaction caused by a medicinal product for human use means a reaction which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

(5) Serious adverse reaction caused by a medicinal product for veterinary use means a reaction which results in death, is life-threatening or results in significant disability, reduction in production output or incapacity, or is a congenital anomaly or birth defect, or which results in persistent or long-term symptoms in the animal treated.

(6) Unexpected adverse reaction means a reaction caused by a medicinal product, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

(7) Post-authorisation safety study means any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product or measuring the effectiveness of risk management

¹ The executive order contains provisions implementing parts of 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, Official Journal of the European Communities 2001, no. L 311/67, as amended by e.g. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010, Official Journal of the European Union 2010, no. L 348/74, Directive 2012/26/EU of the European Parliament and of the Council of 27 October 2012, Official Journal of the European Union 2012, no. L 299/1, as well as parts of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, Official Journal of the European Communities 2001, no. L 311/1, as last amended by Regulation (EC) No 596/2009 of the European Parliament and of the Council of 18 June 2009, Official Journal of the European Union 2009, no. L 188/14.

measures.

(8) Pharmacovigilance system means a system used by the marketing authorisation holder to fulfil the tasks and responsibilities listed in the Danish Medicines Act, rules issued under the act and rules laid down by the European Commission and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

(9) Pharmacovigilance system master file means a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more medicinal products for human use.

(10) Risk management system means a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.

(11) Abuse of medicinal products means persistent or sporadic, intentional excessive use of medicinal products for human use which is accompanied by harmful physical or psychological effects.

(12) Non-prescribed use means use of a medicinal product for veterinary use, which is not in accordance with the summary of product characteristics, including misuse and serious abuse of the medicinal product.

3. The European Medicines Agency and the European Commission have prepared guidance on good pharmacovigilance practices for the competent authorities and marketing authorisation holders. The guidance on good pharmacovigilance practices for medicinal products for human use is published on the European Medicines Agency's website and the guidance on good pharmacovigilance practices for medicinal products for veterinary use is published in "The Rules Governing Medicinal Products for veterinary use in the European Union, Volume 9B".

Requirements for marketing authorisation holders

4.-(1) The marketing authorisation holder must have permanently at his disposal a qualified person responsible for pharmacovigilance.

(2) The qualified person, who must reside and operate in the Union, is responsible for:

- (i) The establishment and maintenance of a pharmacovigilance system ensuring that information about all suspected adverse reactions, which are reported to the company, is collected and collated in order to be accessible at least at one point within the Union.
- (ii) The use and update of a pharmacovigilance system master file and on request make a copy of the master file available to the Danish Medicines Agency, but see subsection (3).
- (iii) The preparation of the reports referred to in sections 5-9.
- (iv) Ensuring that any request from the Danish Medicines Agency, the competent authorities in other EU/EEA countries or the European Medicines Agency for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales.
- (v) The provision to the Danish Medicines Agency, the competent authorities in other EU/EEA countries or the European Medicines Agency of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation safety studies.
- (vi) The use and update of a risk management system for the relevant medicinal product as well as the monitoring of the outcome of risk minimisation measures, which are contained in the risk management system.

(3) Subsection (2)(ii) does not apply to authorised medicinal products for veterinary use.

(4) The Danish Medicines Agency may at any time ask the marketing authorisation holder of a medicinal product for human use to submit a copy of the pharmacovigilance system master file, see subsection 2(ii). The marketing authorisation holder must submit the copy of the master file at the latest 7 days after receipt of the request from the Danish Medicines Agency.

(5) The marketing authorisation holder must perform a regular audit of the pharmacovigilance system. The marketing authorisation holder of a medicinal product for human use must place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

(6) Marketing authorisation holders for parallel import of a medicinal product, see part 4 of the Danish executive order on marketing authorisation for medicinal products, etc., are not comprised by subsections 1-5, but they must be equipped to receive enquiries concerning suspected adverse reactions and exposure reactions from the use of the parallel imported medicinal product.

5. The marketing authorisation holder must maintain records of all suspected adverse reactions and all suspected exposure reactions, of which the holder can reasonably be expected to have knowledge, regardless of the country in which the relevant adverse reactions or exposure reactions occurred.

6.-(1) The marketing authorisation holder must report to the Danish Medicines Agency all suspected serious adverse reactions and all suspected exposure reactions seen in Denmark and which are reported to the holder by a healthcare professional, a patient, a relative or the animal's owner, or of which the marketing authorisation holder can reasonably be expected to have knowledge from scientific literature or safety studies, immediately and in any case no later than 15 days of the day on which the holder concerned gained knowledge of the event.

(2) The marketing authorisation holder of a medicinal product for human use must report to the Danish Medicines Agency all non-serious suspected adverse reactions seen in Denmark and which are reported to the marketing authorisation holder by a healthcare professional, a patient, a relative, or of which the marketing authorisation holder can reasonably be expected to have knowledge from scientific literature or safety studies, no later than 90 days after the marketing authorisation holder concerned gained knowledge of the reaction.

(3) The marketing authorisation holder of a medicinal product for veterinary use must also report the suspected serious adverse reactions mentioned in subsection 1 to the competent authority in the EU/EEA country acting as reference member state at the times agreed, as regards medicinal products which:

- (i) are mutually recognised under the procedures in article 21, article 22 and article 32(4) of Directive 2001/82/EC, see Directive 2004/28/EC, or
- (ii) fall within the procedures in article 36, article 37 and article 38 of Directive 2001/82/EC, see Directive 2004/28/EC.

(4) Subsection 3 does not apply if Denmark acts as reference member state under the provisions of the mentioned subsection and a report was made subject to subsection 1.

(5) In addition to the information mentioned in subsections (1) and (2), the marketing authorisation holder must inform the Danish Medicines Agency immediately about any other important new information, which might influence the evaluation of the benefits, and risks of the medicinal product, see section 25(1) of the Danish Medicines Act. In particular, the marketing authorisation holder must forthwith inform the Danish Medicines Agency of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information, which might influence the evaluation of the benefits and risks of the medicinal product concerned.

7.-(1) The marketing authorisation holder of a medicinal product for human use must report to the European Medicines Agency all suspected serious adverse reactions seen in a country outside the EU/EEA (third country) and which are reported to the marketing authorisation holder by a healthcare professional, a patient or a relative, immediately and in any case no later than 15 days of the day on which the holder concerned gained knowledge of the event.

(2) The marketing authorisation holder of a medicinal product for veterinary use must report to the Danish Medicines Agency and the European Medicines Agency all suspected serious and unexpected adverse reactions and all suspected exposure reactions seen in a country outside the EU/EEA (third country) and which are reported to the marketing authorisation holder by a healthcare professional, a patient, a relative or the animal's owner, immediately and in any case no later than 15 days of the day on which the holder concerned gained knowledge of the reaction. Reports from relatives and the animal's owner shall only be reported to the Danish Medicines Agency.

8.-(1) The marketing authorisation holder of a medicinal product for human use must submit periodic safety update reports to the Danish Medicines Agency in accordance with the obligations and the frequency specified in the marketing authorisation. The periodic safety update reports must be submitted to the repository of periodic safety update reports of the European Medicines Agency.

(2) Holders of marketing authorisations which were granted before 21 July 2012, and for which the frequency is not laid down as a condition to the marketing authorisation, must submit periodic safety update reports to the Danish Medicines Agency immediately upon request and at the following data lock points:

- (i) every six months after the marketing authorisation was issued in Denmark and until the placing on the market,
- (ii) every six months in the first two years following the initial placing on the market,
- (iii) once a year for the following two years, and
- (iv) at three-yearly intervals thereafter.

The update must cover the period since the most recent periodic safety update report and must be submitted no later than 70 days after the most recent data lock point, if the periodic safety update report covers a period of up to 12 months. If the periodic safety update report covers a period of more than 12 months, the report must be submitted no later than 90 days after the most recent data lock point. The periodic safety update reports must be submitted to the repository of periodic safety update reports of the European Medicines Agency.

(3) For generic medicinal products and for medicinal products comprised by section 18(1)(i) of Danish executive order no. 1239 of 12 December 2005 on marketing authorisation for medicinal products, etc., the marketing authorisation holder must submit periodic safety update reports to the Danish Medicines Agency, if it has been specified in the marketing authorisation in connection with the authorisation of the medicinal product and when requested by the Danish Medicines Agency on the basis of concerns relating to information about pharmacovigilance data or due to the lack of periodic safety update reports relating to the medicinal product's active substance(s). At the same time, the Danish Medicines Agency specifies the frequency for the submission of the reports. The periodic safety update reports must be submitted to the repository of periodic safety update reports of the European Medicines Agency.

(4) Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports may be amended and harmonised by the Committee for Medicinal Products for Human Use or by the Coordination Group, see article 107c(4) of Directive 2001/83/EC, to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure, as described in Articles 107e and 107g of

Directive 2001/83/EC, and to set a Union reference date from which the submission dates are calculated. In connection with the harmonisation, the Union reference date is either the date of the first marketing authorisation in the Union of a medicinal product containing this active substance/this combination of active substances or, if this date cannot be specified, the earliest of the known dates of marketing authorisations of medicinal products containing this active substance or this combination of active substances. The European Medicines Agency publishes decisions about the harmonised frequency and dates for the submission of periodic safety update reports. All amendments become effective six months after the publication. Following the European Medicines Agency's publication of the decision, the marketing authorisation holder must submit an application for a variation to the Danish Medicines Agency, see section 26 of the Danish Medicines Act.

(5) A periodic safety update report must contain the following:

- (i) a summary of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation,
- (ii) a scientific evaluation of the risk-benefit balance of the medicinal product, and
- (iii) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

(6) The marketing authorisation holder of a medicinal product, for which the frequency and the dates of submission of the periodic safety update reports have been amended and harmonised under subsection 4, can request to the Committee for Medicinal Products for Human Use or the Coordination Group to change the Union reference date or the frequency of submission of periodic safety update reports on one of the following grounds:

- (i) for reasons relating to public health,
- (ii) in order to avoid duplication of assessments, or
- (iii) in order to achieve international harmonisation.

Such requests must be submitted in writing and must be duly justified. The Committee for Medicinal Products for Human Use or the Coordination Group must, following the consultation of the Pharmacovigilance Risk Assessment Committee, either approve or deny such requests. If the Committee for Medicinal Products for Human Use or the Coordination Group approves the request to amend the reference date or the frequency of submission of periodic safety update reports, the marketing authorisation holder must accordingly submit an application for a variation of the marketing authorisation to the Danish Medicines Agency, see section 26 of the Danish Medicines Act.

(7) The marketing authorisation holder is allowed to submit a request to change the frequency of submission of periodic safety update reports laid down in subsections 1-3 in accordance with the procedure in Commission Regulation (EC) No 1234/2008, as amended by Commission Regulation (EU) No 712/2012.

(8) The Danish Medicines Agency may change deadlines for submission of periodic safety update reports where required by special circumstances.

9.-(1) The marketing authorisation holder of a medicinal product for veterinary use must submit the reports mentioned in section 5 to the Danish Medicines Agency in the form of periodic safety update reports as soon as the Danish Medicines Agency so requests and at the following data lock points:

- (i) every six months after the marketing authorisation was issued in Denmark and until the placing on the market,
- (ii) every six months in the first two years following the initial placing on the market,
- (iii) once a year for the following two years,

(iv) at three-yearly intervals thereafter, and

(v) in connection with the submission of an application to renew the marketing authorisation.

(2) The marketing authorisation holder may synchronise the submission of periodic safety update reports in Denmark with the submission in other countries. The marketing authorisation holder may use the anniversary date of the authorisation in another country as the basis for the calculation of data lock points provided that the deadlines in subsection 1 are not extended. The marketing authorisation holder must inform the Danish Medicines Agency if synchronisation is used.

(3) The periodic safety update report must include a scientific evaluation of the risk-benefit balance of the medicinal product. The update must cover the period since the most recent periodic safety update report and must be submitted no later than 60 days after the most recent data lock point.

(4) After the granting of the marketing authorisation, the marketing authorisation holder is allowed to submit a request to change the periods mentioned in subsection 1 in accordance with the procedure in Commission Regulation (EC) No 1234/2008, as amended by Commission Regulation (EU) No 712/2012.

(5) In connection with the granting of the marketing authorisation and subsequently, the Danish Medicines Agency can define other deadlines for submission of periodic safety update reports than those mentioned in section 9(1).

10. Marketing authorisation holders for parallel import of a medicinal product, see part 4 of the Danish executive order on marketing authorisation for medicinal products, etc., are not comprised by sections 8 and 9 but must forward all enquiries received pursuant to section 4(6) that are not reported to the Danish Medicines Agency pursuant to section 6 or 7. Enquiries must be forwarded as soon as the Danish Medicines Agency so requests, however, at least every six months in the first two years after the medicinal product was placed on the market, then once a year for the following two years and at three-yearly intervals thereafter.

11. The Danish Medicines Agency can lay down specific rules on the form of the reports mentioned in sections 5-9.

Use of adverse reaction data

12.-(1) The Danish Medicines Agency must promptly and in any case within 15 days of the receipt of reports of suspected serious adverse reactions and reports of suspected exposure reactions seen in Denmark forward these reports to the European Medicines Agency, the other EU/EEA countries and the marketing authorisation holder.

(2) The Danish Medicines Agency forwards all reports of suspected adverse reactions arising from an error associated with the use of a medicinal product to the Danish Patient Safety Authority. The Danish Medicines Agency can also forward reports of suspected adverse reactions arising from off-label use and misuse of medicinal products to the Danish Patient Safety Authority. Reports are forwarded in anonymised form.

13.-(1) The Danish Medicines Agency compares the information concerning adverse reactions and exposure reactions reported to the Danish Medicines Agency with the available information about:

- (i) medicine consumption,
- (ii) lack of efficacy,
- (iii) non-prescribed use,
- (iv) misuse and abuse,
- (v) evaluation as to whether the withdrawal period is sufficiently long,
- (vi) potential environmental problems in connection with use of the medicinal products, and

(vii) other data, which might influence the evaluation of the benefits and risks of the medicinal product.

(2) If the Danish Medicines Agency, as a result of an evaluation of adverse reaction data, finds that a marketing authorisation should be varied, suspended or revoked, the Agency must promptly inform the European Medicines Agency, the other EU/EEA countries and the marketing authorisation holder, see sections 17a and 17b of the Danish Medicines Act.

Penalties

14.-(1) Any violation of sections 4(1)-(2) or (4)-(6), 5, 6(1)-(3), 7 as well as 8(1)-(5), 9(1) and (3) and 10 is punishable by a fine.

(2) Companies, etc. (legal entities) will be held criminally liable under the provisions of Part V of the Danish Criminal Code.

(3) Provisions laid down pursuant to section 11 may provide for the imposition of a fine.

Commencement and transitional provisions

15.-(1) This executive order enters into force on 1 July 2016.

(2) Executive order no. 822 of 1 August 2012 on monitoring of adverse reactions from medicinal products is repealed.

Danish Ministry of Health, on 23 June 2016

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