

COMMISSION DIRECTIVE 2000/38/EC**of 5 June 2000****amending Chapter Va (Pharmacovigilance) of Council Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products****(Text with EEA relevance)**

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

HAS ADOPTED THIS DIRECTIVE:

Having regard to the Treaty establishing the European Community,

Having regard to Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products⁽¹⁾, as last amended by Directive 93/39/EEC⁽²⁾, and in particular Article 29i thereof,

Whereas:

- (1) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress.
- (2) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.
- (3) The increasing use of the mutual recognition procedure established by Directive 75/319/EEC requires that current procedures for reporting and dissemination of suspected adverse drug reactions be amended to ensure better coordination between Member States.
- (4) The increasing use of electronic networks for communication of information on adverse drug reactions to medicinal products marketed in the Community is intended to allow competent authorities to share the information at the same time.
- (5) It is necessary to further define terms currently used within the pharmacovigilance systems.
- (6) It is the interest of the Community to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.
- (7) Holders of marketing authorisations should additionally be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.
- (8) The measures provided for in this Directive are in conformity with the opinion of the Standing Committee on Medicinal Products for Human Use,

Article 1

Chapter Va (Pharmacovigilance) of Directive 75/319/EEC is hereby amended as follows:

1. In Article 29a, the third paragraph is hereby replaced by the following text:

'This system shall also take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks.'

2. Article 29b is hereby replaced by the following text:

'Article 29b

For the purpose of this Directive, the following definitions shall apply:

- (a) *adverse reaction* means a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function;
- (b) *serious adverse action* means an adverse action which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect;
- (c) *unexpected adverse reaction* means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics;
- (d) *periodic safety update reports* means the periodical reports containing the records referred to in Article 29d;
- (e) *post-authorisation safety study* means a pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product;
- (f) *abuse of medicinal products* means persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

⁽¹⁾ OJ L 147, 9.6.1975, p. 13.

⁽²⁾ OJ L 214, 24.8.1993, p. 22.

For the interpretation of the definitions and principles outlined in this chapter, the marketing authorisation holder and the competent authorities shall refer to the guidance referred to in Article 29g.'

3. Article 29c is hereby amended as follows:

- (a) in the first paragraph the words 'person responsible for placing the medicinal product on the market' are changed to 'marketing authorisation holder';
- (b) in point (a) of the second paragraph the words 'at a single' are changed to 'in order to be accessible at least at one';
- (c) in point (b) of the second paragraph the words 'relevant national or Community guidance' are changed to 'guidance referred to in Article 29g';
- (d) to the second paragraph the following point (d) is added:
 - 'd) the provision to the competent authorities, 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.'

4. Article 29d is hereby replaced by the following text:

'Article 29d

- 1. The marketing authorisation holder shall be required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country.
- 2. The marketing authorisation holder shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a health care professional immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.
- 3. The marketing authorisation holder shall be required to record and report all other suspected serious adverse reactions which meet the reporting criteria in accordance with the guidance referred to in Article 29g of which he can reasonably be expected to have knowledge immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.
- 4. The marketing authorisation holder shall ensure that all suspected serious unexpected adverse reactions occurring in the territory of a third country and brought to his attention by a health care professional are reported immediately in accordance with the guidance referred to in Article 29g, so that they are available to the Agency and to the competent authorities of the Member States where the medicinal product is authorised, and in no case later than 15 calendar days following the receipt of the information.
- 5. In the case of medicinal products which have been considered within the scope of Directive 87/22/EEC, or which have benefited from the procedures of mutual recog-

inition foreseen in Articles 7 and 7a of Directive 65/65/EEC, Article 9(4) of this Directive, and medicinal products for which there has been a referral to the procedures foreseen by Articles 13 and 14 of this Directive, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions occurring in the Community are reported in the format and at intervals to be agreed with the reference Member State, or a competent authority acting as the reference Member State, in such a way so as to be accessible to the reference Member State.

6. Unless other requirements have been laid down as a condition of the granting of authorisation, or subsequently as indicated in the guidance referred to in Article 29g, records of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and at the time of the first renewal. Thereafter the periodic safety update reports shall be submitted at five-yearly intervals together with the application for renewal of the authorisation. The periodic safety update reports shall include a scientific evaluation of the benefit and risks afforded by the medicinal products.

7. Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in this article according to the procedure laid down by Commission Regulation (EC) No 541/95 (*).

(*) OJ L 55, 11.3.1995, p. 7.'

5. In Article 29e, second paragraph, the words 'medical practitioners' are changed to 'doctors and other health care professionals':

6. Article 29f is hereby replaced by the following text:

'Article 29f

1. The Agency, in collaboration with the Member States and the Commission shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community intended to allow all competent authorities to share the information at the same time.

2. Making use of the network foreseen in the first paragraph, Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the Agency and the other Member States, and in any case within 15 calendar days of their notification, at the latest.

3. The Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the marketing authorisation holder, and in any case within 15 calendar day of their notification, at the latest.'

7. Article 29g is hereby replaced by the following text:

'Article 29g

(a) In order to facilitate the exchange of information about pharmacovigilance within the Community, the Commission, in consultation with the Agency, Member States and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports, including technical requirements for electronic exchange of pharmacovigilance information in accordance with internationally agreed formats and shall publish a reference to an internationally agreed medical terminology.

(b) This guidance shall be published in Volume 9 of the Rules governing medicinal products in the European Union and shall take account of international harmonisation work carried out in the field of pharmacovigilance.'

8. Article 29h is hereby replaced by the following text:

'Article 29h

Where, as a result of the evaluation of pharmacovigilance data, a Member State considers that a marketing authorisation should be suspended, withdrawn or varied in accordance with the guidance referred to in Article 29g, it shall forthwith inform the Agency, the other Member States and the marketing authorisation holder.

In case of urgency, the Member State concerned may suspend the marketing authorisation of a medicinal product, provided the Agency, the Commission and the other Member States are informed at the latest on the following working day.'

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive no later than 5 December 2001.

When the Member States adopt the provisions set out in paragraph 1, they shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such references shall be adopted by the Member States. The Member States shall communicate to the Commission the provisions of national law which they adopt in the field covered by this Directive.

Article 3

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Communities*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 5 June 2000.

For the Commission

Erkki LIIKANEN

Member of the Commission