MINISTRY OF HEALTH

O R D E R

regarding the Pharmacovigilance Inspection at the Marketing Authorization Holder

Taking into consideration:

- the provisions of Art. 69 of the Government Emergency Ordinance No. 152/1999 on medicinal products for human use, approved with changes and completions through the Law No. 336/2002 with further changes and completions;

- the dispositions of Art. 10, paragraph (9) of the Government Ordinance No. 125/1998 regarding the setting up, organization and functioning of the National Medicines Agency, approved with changes and completions through the Law No. 594/2002 with further changes and completions

Seeing the approval report of the Pharmaceutical General Direction, Pharmaceutical Inspection and Medical Devices No. OB. 1.768/2004, in accordance to the Government Decision No. 743/2003 regarding the organization and functioning of the Ministry of Health with further changes

Minister of Health emits the following Order:

Art. 1. –The Model of the Standard File of the Pharmacovigilance Service from the Marketing Authorization Holder is approved in accordance with the ANNEX No. 1.

Art. 2. –The Plan for performing the Pharmacovigilance Inspection at the Marketing Authorization Holder is approved in accordance with the ANNEX No. 2.

Art. 3. –The Model of the Pharmacovigilance Inspection Report at the Marketing Authorization Holder is approved in accordance with the ANNEX No.3.

Art. 4. –The classification of deficiencies which can be found during the Pharmacovigilance Inspections at the Marketing Authorization Holder is approved in accordance with the ANNEX No. 4.

Art. 5. – (1) Each Marketing Authorization Holder will prepare the Standard File of the Pharmacovigilance Service by the 1st of March 2004.

(2) The Standard File of the Pharmacovigilance Service from the Marketing Authorization Holder has to be annually updated, or anytime modifications of the data written in the dossier occur.

Art. 6. – The Standard File of the Pharmacovigilance Service from the Marketing Authorization Holder will be sent to the National Medicine Agency, if asked, in order to prepare the Pharmacovigilance Inspections, or anytime is necessary.

Art. 7. – The ANNEXES 1-4 are part of the present Order.

Art. 8. – The present Order will be published in the Official Monitor of Romania, Part I.

Minister of Health,
Ovidiu Brînzan

Bucharest, 21 February 2004.
No. 179.

ANNEX 1

MODEL
of the Standard File of the Pharmacovigilance Service at the Marketing Authorization Holder

The Standard File of the Pharmacovigilance Service at the Marketing Authorization Holder (SFPSMAH) should present a short description for each chapter of the present ANNEX. Additional explanatory documentation will be attached, if necessary.

1. General Information

1.1. Short description of the Pharmacovigilance Service at the Marketing Authorization Holder

1.2. The products for which the respective holder has a Marketing Authorization (MA) in Romania

1.2. The investigational products of the respective holder which are included in clinical trials performed in Romania

2. **The description of the key-activities in the pharmacovigilance domain performed by the Marketing Authorization Holder:**

2.1. Way of collecting data concerning the suspected adverse reactions, reported to the company personnel and medical representatives

2.2. Way of transmitting suspected adverse reactions sheets to the National Medicine Agency (NMA)

2.3. Way of scientific evaluation of collected data and elaboration of reports for the National Center for Pharmacovigilance

2.4. Way of informing physicians and the NMA about the safety of the medicinal products authorized to be marketed in Romania

2.5. Way of preparing the Periodic Safety Updated Report, regarding the safety of the medicinal product

2.6. Way of putting in accordance of the Summary of Product Characteristics (SPC) with the information from the Periodic Safety Updated Report, regarding the safety of the medicinal product

2.7. Way of training of the involved persons in pharmacovigilance data collection

2.8. Way of collecting pharmacovigilance data in post-authorization phase (post-marketing safety studies)

3. Documentation

3.1. Instructions concerning the preparation, revision and distribution of the documents necessary for the pharmacovigilance activity

3.2. Short description of all documents concerning the pharmacovigilance activity (adverse reactions report sheet, different reports, recordings, standard operations procedures)

4. Personnel

4.1. The organizational chart of the Pharmacovigilance Service, presenting the organization, responsibilities and the relationships inside the organization

4.2. The qualifications, experience, and the responsibilities of the key-personnel:

- The qualified person in pharmacovigilance

- The contact person for withdrawal/blocking a product, in case there is a risk - safety problem/benefit-risk ratio insufficiently proved

4.3. General presentation of the training plans and of the way of keeping the records

5. Facilities and utilities

5.1. Short description of the facility

5.2. Short description of the archiving mode and of the place where the relevant documents for pharmacovigilance are kept

5.3. Short description of the computerized systems used in the pharmacovigilance activity, including their validation state

6. Contracts

The description of the co-marketing contracts, detailing the provisions concerning the pharmacovigilance in Romania (identifying the Marketing Authorization Holder, identifying the responsible person for pharmacovigilance, in the case of the products under co-marketing contracts)

7. The Quality System Management

The description of the quality system management (including a list of general and specific standard operating procedures, the organization of the internal audit and of the statistical analysis)

ANNEX No. 2

PLAN

for performing the Pharmacovigilance Inspection at the Marketing Authorization Holder

1. Inspection preparation

- Asking for the Standard File of the Pharmacovigilance Service at the Marketing Authorization Holder
- Establishing the date of inspection
- Establishing the inspection objectives
- Appointing the inspectors team
- Identifying the key-person(s) for the pharmacovigilance activity from the Marketing Authorization Holder (MAH)
- Inspection announcement
- Studying of the documentation with reference to the facility that is to be inspected:

• the Standard File of the Pharmacovigilance Service at the Marketing Authorization Holder

• The knowledge of the products of the respective holder with Marketing Authorizations in Romania

- The review of the reference documentation:

• the national legislation in the pharmacovigilance domain

2. Performing the inspection

- Pre-inspection meeting between the representatives of MAH, i.e. the key-person(s) for pharmacovigilance activities and the inspector(s) of the National Medicines Agency (NMA) :

• general presentation of the MAH activity in the pharmacovigilance domain

• reiteration of the inspection plan by the inspector(s)

- The inspection as such:

• discussion with the key-persons for the pharmacovigilance activity at MAH

• documents analysis, which the MAH should have in his possession, in conformity with the national legislation in the domain

• the inspection of the facilities, utilities

- The final meeting of the MAH representatives, with the key-person(s) for the pharmacovigilance activity and the NMA inspector(s):

• presentation of the relevant observations and of the deficiencies observed during in the inspection

• identification of possible remedies for the encountered deficiencies

• conclusions.

3. Issuing the inspection report

4. Transmission of one copy of the inspection report to the MAH

5. Following-up the way the deficiencies observed are solved by the MAH

ANNEX No. 3

MODEL

of the Pharmacovigilance Inspection Report at the Marketing Authorization Holder

The inspected facility:

- The name of the inspected facility
- The complete address of the inspected facility

The inspection data:

Inspector(s):

Reference documents for the inspection:

- The national legislation in the pharmacovigilance domain
- The Marketing Authorizations for medicinal products marketed in Romania by the respective holder

Introduction:

-Short description of the facility and of activities performed in the pharmacovigilance domain

- Specification if the Standard File of the Pharmacovigilance Service at the Marketing Authorization Holder (MAH) was available before the beginning of the inspection
- Date of the previous inspections
- Name of the inspector(s) that performed the previous inspection(s)
- Detailed presentation of the changes appeared until the last inspection

Short report on the inspection objectives:

- The purpose of the inspection
- The activity(s) inspected
- The personnel met during the inspection

Relevant observation made by the inspector(s) and the deficiencies observed:

The list of deficiencies classified as critical, major, others.

Each deficiency is presented taking into account the following:

- the deficiency identification
- explanation on the deficiency
- reference documents.

Recommendations:

Are made by the inspector(s) to the inspected facility, or to the National Medicines Agency – The National Center of Pharmacovigilance, if necessary.

Summary and Conclusions:

The inspector(s) has/have to specify if the inspected unit has an adequate pharmacovigilance system, as it is defined in the national legislation in this domain (the Decisions of the National Medicines Agency Scientific Council No. 12/2000 and No 24/2000)

Name of the inspector(s):

Signature:

Institution:

Date:

ANNEX No. 4

CLASSIFICATION

of deficiencies which can be found during the Pharmacovigilance Inspections at the Marketing Authorization Holder

Critical deficiency: system deficiency, of the pharmacovigilance practices or processes, which:

- endangers the rights, safety or the wellbeing of the patients, or:
- represents a potential risk for the public health; or
- represents a severe violation of the national legislation in this domain.

Needs immediate action.

Major deficiency: system deficiency, of the pharmacovigilance practices or processes:

- Which uncorrected may lead to endangering the rights, the safety, or the wellbeing of the patients; or
-Which uncorrected represents a potential risk for the public health; or
- Represents a violation of the national legislation in this domain.

Needs intensive follow-up. More major deficiencies of the pharmacovigilance system considered as a whole could lead to a critical deficiency.

Other deficiencies: deficiencies of the system, of the pharmacovigilance practices or processes, which cannot endanger the rights, safety or the wellbeing of the patients.

It might necessitate follow-up. More other deficiencies of the pharmacovigilance system considered as a whole could lead to a major deficiency.