DECISION

No. 11/23.05.2008

on approval of the Guideline on set up of risk based planning for inspections of pharmaceutical manufacturers

The Scientific Council of the National Medicines Agency,
set up based on Order of the Minister of Health No. 1027/22.05.2008, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 23.05.2008 in accordance with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, with further changes and completions, agrees on the following

DECISION

Single article. – The Guideline on set up of risk based planning for inspection of pharmaceutical manufacturers is approved, according to the Annex which is integral part of this decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on set up of risk based planning for inspections of pharmaceutical manufacturers

CHAPTER I
Introduction

Art. 1. – This Guideline is a translation and adaptation into Romanian of Guideline EMEA/INS/GMP/85283/2008 on the elaboration of the inspection programme at the manufacturers' sites, based on risk assessment, issued by the European Medicines Agency (EMEA) .

Art. 2. – (1) According to Law No. 95/2006 on healthcare reform, Title XVII-The medicinal product and to the Minister of Public Health Order No. 904/2006, through repeated inspections and, if necessary, through unannounced inspections, the National Medicines Agency (NMA) should grant compliance with legal requirements concerning medicinal products.

(2) The NMA may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing practice.

Art. 3. – (1) A risk based approach to inspection planning will enable the frequency, depth and breadth of inspections to be determined accordingly.

(2) This will allow flexible and effective administration, whilst maintaining a high level of patient safety.

Art. 4. – The NMA need to develop a systematic and risk-based approach to make the best use of their surveillance and enforcement resources while maximizing the impact of those resources on the public health.

Art. 5. – (1) The NMA should have a written procedure that covers the preparation, realization and supervision of an annual inspection programme.

(2) This programme should ensure that the extent and frequency of inspections can be adhered to as planned.

(3) Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner.

CHAPTER II
Purpose

Art. 6. – This Guideline contains provisions for a risk based planning system according to which sites that fall under NMA supervision are subject to inspection.

CHAPTER III
Scope

Art. 7. – This Guideline covers the field of inspection of manufacturers of medicinal products, investigational medicinal products included, biological substances and sterilisation of active substances.

Art. 8. – This Guideline covers medicinal products for human use.

CHAPTER IV
Procedure

IV.1 **Principle**

Art. 9. – Planning and scheduling of inspections is realised as follows:

a) compile all relevant sites/facilities in a list;
b) establishing the necessary amount of time for inspection at each site;
c) establish the inspection frequency;
d) prioritise inspections by calculating individual inspection dates per site;
e) establish risk ranking;

IV.2 Inspections-site list

Art. 10. – All sites/facilities that are subject to inspection are to be listed in an appropriate up to date list. This list could include the following information:

a) Name and address of inspectorate;
b) Name of the competent inspector;
c) Name and address of each site;
d) Pharmaceutical forms manufactured per site;
e) Date of the last inspection per site
f) Number of inspection days required per site;
g) Inspection frequency per site
h) Date of the next inspection.

IV.3 Expenditure of time needed for inspection at each site

Art. 11. – (1) The following table presents guidance values for the required inspection time per type of site; the type of manufacturing site is

classified by the relevant dosage form and the manufacturing process, respectively.

(2) The risk ranking of the type of manufacturing site is based on the assessment of the risk severity, probability of occurrence and probability of detection with respect to product quality defects and process safety issues.

(3) This risk ranking assumes that critical processes and products (e.g. sterile products) would have a higher public health consequence than less critical products and processes; hence these products are given a higher weight.

Classification of manufacturing or importation sites according to the type of product/process		**Overall inspection days[1]**
1.1	**Sterile Products**	
	1.1.1 Aseptically prepared (list of dosage forms) 1.1.1.1 Large volume liquids 1.1.1.2 Lyophilisates 1.1.1.3 Semi-solids 1.1.1.4 Small volume liquids 1.1.1.5 Solids and implants	**≥ 10**
	1.1.2 Terminally sterilised (list of dosage forms) 1.1.2.1 Large volume liquids 1.1.2.2 Semi-solids 1.1.2.3 Small volume liquids 1.1.2.4 Solids and implants	**≥ 8**
	1.1.1 Batch certification only	**≥ 1**

1.2	**Non-sterile products**	
	1.2.1 Non-sterile products (list of dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.2 Capsules, soft shell 1.2.1.3 Chewing gums 1.2.1.4 Impregnated matrices 1.2.1.5 Liquids for external use 1.2.1.6 Liquids for internal use 1.2.1.7 Medicinal gases 1.2.1.8 Other solid dosage forms 1.2.1.9 Pressurised preparations 1.2.1.10 Radionuclide generators 1.2.1.11 Semi-solids 1.2.1.12 Suppositories 1.2.1.13 Tablets 1.2.1.14 Transdermal patches	**≥ 4**
	1.2.2 Batch certification only	**≥ 1**
1.3	**Biological medicinal products**	
	1.3.1 Biological medicinal products 1.3.1.1 Blood products 1.3.1.2 Immunological products 1.3.1.3 Cell therapy products 1.3.1.4 Gene therapy products 1.3.1.5 Biotechnology products 1.3.1.6 Human or animal extracted products	**≥ 7**
	1.3.2 Batch certification only (list of product type) 1.3.2.1 Blood products 1.3.2.2 Immunological products 1.3.2.3 Cell therapy products 1.3.2.4 Gene therapy products 1.3.2.5 Biotechnology products 1.3.2.6 Human or animal extracted products	**≥ 1**

1.4	**Other products or manufacturing activity** (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials, herbal or homeopathic products, bulk or total manufacturing, etc).	
	1.4.1 Manufacture of: 1.4.1.1 Herbal products 1.4.1.2 Homeopathic products 1.4.1.3 Biological active starting materials	**> 3**
	1.4.2 Sterilisation of active substance/excipients/finished product: 1.4.2.1 Filtration 1.4.2.2 Dry Heat 1.4.2.3 Moist heat 1.4.2.4 Chemical 1.4.2.5 Gamma irradiation 1.4.2.6 Electron beam	**>1**
1.5	**Packaging only**	
	1.5.1 Primary packaging 1.5.1.1 Capsules, hard shell 1.5.1.2 Capsules, soft shell 1.5.1.3 Chewing gums 1.5.1.4 Impregnated matrices 1.5.1.5 Liquids for external use 1.5.1.6 Liquids for internal use 1.5.1.7 Medicinal gases 1.5.1.8 Other solid dosage forms 1.5.1.9 Pressurised preparations 1.5.1.10 Radionuclide generators 1.5.1.11 Semi-solids 1.5.1.12 Suppositories 1.5.1.13 Tablets 1.5.1.14 Transdermal patches	**> 2**
	1.5.2 Secondary packaging	**> 1**

1.6	**Quality control testing**	
	1.6.1 Microbiological: sterility 1.6.2 Microbiological: non-sterility 1.6.3 Chemical/Physical 1.6.4 Biological	**<u>> 2</u>**

[1] The overall inspection days are guidance values and include the necessary time for preparation and report of the inspection; they represent the total personnel expenditure (e.g. 10 overall inspection days equals in 2 inspectors inspecting for 5 days or 4 inspectors inspecting for 2½ days, preparation and report time included).

(4) The required inspection time may be adjusted accordingly depending on the:

a) type of inspection (full vs. partial inspection);

b) complexity of the site (size, variety of facilities);

c) complexity of the manufacturing process (type and sequence of operations, process controls applied);

d) the complexity of the product and its therapeutic significance and

e) patient exposure

IV. 4 **Frequency of inspections**

Art. 12. – (1) Large companies may be inspected department by department, a full general GMP inspection being completed at least every five years.

(2) Generally the interval between inspections should not exceed 3 years as lack of continuity may give rise to lower awareness of current GMP or allow significant deficiencies to develop.

(3) The necessity to carry out immediate inspections (e.g. due to product quality defects or significant changes of building, equipment or processes) is not affected.

Art. 13. – (1) Companies representing a low risk and meeting the expectation of GMP at a high level do not have to be inspected as often as the ones that manufacture products or perform activities representing great risk and operate with great GMP deficiencies.

(2) It should be stressed that the activities of the individual company (e.g. products and dosage forms manufactured, materials and substances handled and personnel, premises and equipment involved in the manufacture) and its past record of GMP compliance should be taken into consideration when planning the frequency and duration of inspection; accordingly a review of the observations arising from the last inspection including all deficiencies will form

a major precondition for the subsequent decision on an adequate inspection frequency.

Art. 14. – To define the frequency of inspections the NMA should take into account, amongst others, factors such as:

a) The agency's knowledge of the company (overall compliance status and history of the company or facility);

b) Results of product testing by OMCLs;

c) Number and significance of quality defects (e.g. recalls);

d) Results of previous inspections;

e) Compliance information from agencies/bodies outside the EU;

f) Major changes of building, equipment, processes, key personnel;

g) Experience with manufacturing of a product (e.g., frequency, volume, number of batches).

Art. 15. – Generally the frequency of inspections can be categorised as follows:

Category	**Description**[2]	**Inspection interval**
Compliance factor I Poor compliance	The last inspection revealed critical and/or more than/equal to six (> 6) major deficiencies	1 year
Compliance Factor II Acceptable Compliance	The last two inspections revealed no critical and less than six (< 6) major deficiencies	2 years
Compliance Factor III Good Compliance	The last two inspections revealed no critical and major deficiencies	3 years

[2] Deficiencies are categorised according to the Definition of Significant Deficiencies laid down in the NMA Scientific Council Decision No. 21/28.09.2007 on approval of the GMP Inspection report - Community format.

IV. 5. **Calculation of the next inspection date**

Art. 16. – The calculation of the next inspection date results from the last inspection date and the risk assessment process conducted by the NMA Pharmaceutical Inspection Department.

IV.6. **Responsibility and supervision**

Art. 17. - (1) The Pharmaceutical Inspection Department elaborates and supervises the annual inspection programme, which is approved by the NMA President.

(2) A periodical review of the inspection programme should ensure that serious deviations from the inspection time plan are noticed and corrective actions taken as necessary.