MINISTRY of HEALTH

ORDER

regarding approval of Guidelines for classification of deficiencies observed during Good Manufacturing Practice inspections

Taking into account provisions of Government Emergency Ordinance No. 152/1999 regarding medicinal products for human use, approved with changes and completions through Law No. 336/2002, with further changes and completions,

Seeing the report for approval from the General Pharmaceutical, Pharmacy Inspection and Medical Devices Directorate No. O.B. 12.927/2004,

based on Government Decision No. 743/2003 regarding the setting–up and functioning of the Ministry of Health, with further changes and completions;

The **minister of health** hereby issues the following order:

Article 1. – The Guidelines for classification of deficiencies found during Good Manufacturing Practice inspections are approved, according to the Annex which is integral part of the present order.

Article 2. – On the date of the present decision entry into force, any contrary decision shall be repealed.

Article 3. – The National Medicines Agency shall fulfill provisions of the present order.

Article 4. – The present order shall be published in the Official Gazette of Romania, Part I.

Minister of Health,
Ovidiu Brînzan

Bucharest, 5 November 2004.
Nr. 1.442

ANNEX

GUIDELINES
for the classification of deficiencies observed
during Good Manufacturing Practice inspections

CHAPTER I
Purpose

Article 1. – The purpose of the present guidelines is:

– to classify deficiencies determined during Good Manufacturing Practice inspection for, according to risk;

– to harmonize classification of deficiencies determined by inspectors during inspections;

– to make public, for representatives of medicinal products and pharmaceutical substances industry, such situations as NMA inspectors consider unacceptable and which determine the classification of a company as not complying with Good Manufacturing Practice Rules (GMPR).

CHAPTER 2
Glossary

Article 2. – For the purpose of the present guidelines, definitions are applicable as provided in Minister of Health Order No. 1.058/2003 for approval of Good Manufacturing Practice Rules, as well as the following definitions:

– *deficiency* – any deviation from GMPR determined by an inspector during a Good Manufacturing Practice inspection (*GMP*) on a production site and which is mentioned in writing in the GMP inspection report; deficiencies are classified as ”critical “, ”major“ and ”other”;

– *critical deficiency (of risk 1)* – the deficiency which:

– presents a situation where the production of an inadequate good is highly possible;

– leads to occurrence of immediate or latent risk for the public health;

– involves fraud, misinterpretation or falsification of products or data;

Deficiencies considered ”critical“ by the inspector are listed under chapter 4.1;

– *major deficiency (of risk 2)* – a ”non–critical“deficiency which:

– has produced or may produce a product, which does not comply with its marketing authorisation (MA); or

– indicates a major deviation from GMPR; or

– indicates disregard of appropriate release procedures for the series or non–observance by the qualified person of obligations according to law; or

– a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such

Deficiencies considered “major“ by the inspector are listed under chapter 4.2;

– *other deficiencies (of risk 3)* – the deficiencies which, although cannot be classified as ”critical” or “major”, represent a deviation from GMPR; a deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as “major“ or “critical“.

In the present Guidelines, “other“ deficiencies are not listed as such. Under chapter 4.3 deficiencies are listed, which are considered “other“ by the inspector but which can be promoted to the status of “major“ deficiencies;

– critical product – the product to which any of the following criteria applies:

– narrow therapeutical index;

– high toxicity;
– sterile product;
– biological product;
– complex manufacturing process; a process during which any minor deviation from working parameters can lead to production of a non–uniform good or product not in accordance with its specification.

For example, the mixing of powders or granulation in case of solid forms with a low dose, products with prolonged/delayed release or sterile products; OTC medicinal products containing small doses of vitamines and minerals can be excluded from this category although their production involves a complex manufacturing process;

– *high risk product* – involving some risk for health, as a consequence of cross contamination; this category includes but is not limited to penicillines, certain cytostatics and certain biological products.

CHAPTER 3
General issues

Article 3. – During an inspection on a manufacturing site the inspector notes deviations from the GMPR which appear as deficiencies in the inspection report; based on them, the inspector evaluates the degree of GMPR implementation, presenting the general conclusion for the commencement or continuation of the manufacturing activity (classification as "GMPR complying") or for non–commencement or interruption thereof, respectively (classification as "GMPR non–complying").

Article 4. – (1) As it is impossible to identify all risk-generating situations, the seriousness attributed to deficiencies shall be according to the nature of deficiency and frequency of its occurrence.

(2) The general conclusion about GMPR compliance of an inspected manufacturing flow is based on the risk involved by the nature and extent of the deficiencies, reported to the category of manufactured product.

Article 5. – (1) The classification as "non–conforming" can have serious consequences for the company, ranging from implementation of important corrective measures, to temporary suspension or cancelling of manufacturing activity.

(2) For this reason, non–conformity situations shall be clear, well defined and directly supported by applicable regulations.

Article 6. – (1) The "GMPR non–complying" status attributed to a company based on deficiencies determined can be changed in the report with "GMPR complying" if, during inspection, the company immediately takes all necessary action to remove the reasons which have lead to the occurrence of deficiencies determined and supplies enough evidence regarding prevention of deficiencies reoccurrence.

(2) In such cases, the classification of deficiencies in the report remains the same.

CHAPTER 4
Classification of deficiencies

4.1. Critical deficiencies

Article 7. – (1) Generally, the company is declared as GMPR non–complying if at least one critical deficiency is recorded during inspection.

(2) Such situations shall immediately be reported to respective company management.

(3) The inspectorate management shall also be notified as soon as possible.

Article 8. – Whenever, in the inspector's opinion, the manufactured products present a high risk degree for health, appropriate sanction measures shall be taken.

Article 9. – Examples of "critical" deficiencies are given below.

(1) Sites:

a) no air filtering system in place to eliminate airborn contaminants possibly generated during manufacturing or packaging;

b) general inappropriate functioning of ventilation system/systems, leading to extended cross contamination;

c) inappropriate separation of manufacturing or control areas from other manufacturing areas for products of high risk degree.

(2) Equipment

The equipment used for complex manufacturing operations for critical products is not qualified and there is evidence of its inappropriate functioning.

(3) Staff

The person responsible for the activity of production or quality control, when manufacturing critical or high risk products, does not have a university degree in a field connected to the conducted activity and does not have enough practical experience in their responsibility area.

(4) Hygienization:

a) there is evidence of extended accumulation of waste or external materials, indicating inappropriate cleanliness;

b) there is evidence of massive microbian contamination;.

(5) Raw material testing:

a) there is evidence of falsification or wrong presentation of analytical results;

b) no record in place of tests carried out by the supplier/manufacturer of the raw material (analysis bulletin) and the manufacturer does not carry out the testing thereof.

(6) Manufacturing control:

a) there is No standard master formula;

b) the master formula or the manufacturing documents indicate major deviations or significant calculation errors;

c) there is evidence of the falsification or erroneous presentation of manufacturing and packaging files.

(7) Quality control department (QC):

a) there is no person responsbile for QC, available on the site;

b) the QC department is not a distinct and independent site, does not have real decision-making power and there is evidence that QC decisions are often cancelled by the production department or the management.

(8) Testing of finished products:

a) the final product is not tested according to its quality specification by the manufacturer, before series release for sale;

b) there is evidence of falsification or erroneous presentation of testing results / analysis certificates falsification.

(9) Records

There is evidence of falsification or erroneous presentation of records.

(10) Stability:

a) no available data for establishing the range of product valability;

b) evidence available of falsification or erroneous presentation of stability data/falsification of analysis certificates.

(11) Sterile products:

a) critical sterilisation cycles are not validated;

b) System of water production for preparations for injections is not validated and there is evidence of problems occurring, e.g exceeding of limits prescribed in specifications for the number of microorganisms/endotoxines.

c) No simulation tests have been carried out for filling with nutritive environment in order to validate the aseptical filling operations;

d) there is no environment control/monitoring of the viable particles during aseptical filling;

e) continuation of aseptical filling operations after unsatisfactory results of filling simulation test;

f) inappropriate series of sterility tests have been released for sale based on a second test without accurate investigation.

4.2. Major deficiencies

Article 10. – (1) Whenever no "major" deficiencies are determined during inspection, the company is declared generally considered GMPR complying.

(2) In the following situations however, the company shall be declared as non–GMPR complying:

– when several "major" deficiencies are determined during inspection, indicating that the site does not hold enough control on its processes and operations;

– whenever "major" deficiencies recorded during previous inspections are repeated, indicating lack of implementation of corrective actions on site as transmitted after previous inspections or lack of implementation of appropriate preventive actions to avoid repetition of such deficiencies.

(3) Certain deficiencies of this category can be promoted as "critical" deficiencies. These are indicated by (^).

Article 11. – Examples of "major" deficiences are indicated below:

(1) Sites:

a) deficient functioning of ventilation system, possibly leading to local or occasional cross contamination;

b) there is no regular maintainance/verification, e.g. air filters replacing, monitoring of pressure differences (^);

c) the facilities (steam, air, nitrogen, exhausting, etc.) are not qualified;

d) the systems for heating, ventilation, air conditioning (IVAC) and purified water are not qualified;

e) the temperature and humidity are not controlled or monitored when appropriate (e.g. the storing is not done according to requirements on the labels);

f) there are holes, fissures, worn out paint on walls/ceilings in the adjacent areas or over the manufacturing areas or equipments where the product is exposed;

g) surfaces which cannot be cleaned because of pipes, fixed accessories or pipes located over the products or manufacturing equipment;

h) surface finishing (floors, walls and ceilings) does not allow for efficient cleaning;

i) porous, non sealing finishings in the manufacturing areas, with obvious contamination traces (mustiness, powders from previous products etc.) (^);

j) insufficient manufacturing space which can lead to mixings (^);

k) physical and electronical quarantine accessible to authorized personnel / areas of physical quarantines not well marked and/or not observed (^);

l) there are no separate areas/enough precautions to prevent contamination or cross contamination during prelevation of raw materials.

(2) Equipment:

a) the equipment does not work according to specifications (^);

b) the equipment used for complex manufacturing operations is not qualified (^);

c) the cleaning “in place“ of an equipment is not validated;

d) the recipients for manufacturing of liquids and ointments are not equipped with fixing, easy to clean clips;

e) the stored equipment is not protected against contamination (^);

f) inadequate manufacturing equipment: porous surfaces which cannot be cleaned/materials releasing particles (^);

g) evidence of product contamination with other materials such as: grease, oil, rust and particles coming from the equipment (^);

h) there are no lids for the vessels feeding cone, recipients or similar manufacturing equipment;

i) lack/insufficiency of precautions taken when an equipment, such as a drier or autoclave, contains more than one product (possibility of cross contamination or mixing) (^);

j) the equipments layout does not prevent cross contamination or the possibility of mixing for operations carried out in shared areas (^);

k) the system for purified water is not maintained or does not work and supplies water of inadequate quality (^);

l) unsealing fittings;

m) there is no calibration program for the automatic, mechanical, electronical or measurement equipments/there are no records;

n) there are no records on equipment utilization.

(3) Staff:

a) the person responsible for the activity of quality control or production does not hold a university degree in a scientific field connected to the activity they are conducting and does not have enough practical experience in their responsibility area;

b) the delegation of responsibilities for the QC and production to persons who do not have the required qualification;

c) insufficient staff for QC and production, which leads to great error probability;

d) insufficient training of staff involved in the quality control and production, which might lead to GMP related deficiencies.

(4) Hygienisation:

a) there is no written hygienisation program, but the sites are maintained in an acceptable state of cleanliness;

b) there is no standard operation procedure (SOP) for the microbiological monitoring/of the environment, there are no action limits established for the manufacturing areas of the non–sterile vulnerable products;

c) the cleaning procedure of the production equipment is not validated (analytical methods included);

d) the cleaning procedure of the production equipment is not validated, in case non–dedicated equipment is used, for products with increased risk (^);

e) incomplete requirements regarding the staff health related to the working place.

(5) The raw material testing:

a) reduced testing program without adequate certification of the producers/suppliers;

b) quality of the water used in the manufacturing process is not acceptable;

c) the manufacturer does not carry out identification tests upon reception of raw materials on the site/ identification tests are not carried out on each recipient of active pharmaceutical substance (AFS) or after handling or packaging by third parties;

d) certificates of analysis indicating incomplete testing;

e) incomplete specifications;

f) the specifications are not approved through the QC department;

g) the testing methods are not validated;

h) the ASF utilization after retesting date without carrying out a new testing;

i) utilization of auxiliar raw materials after expiry date without carrying out retesting, if this is specified;

j) several series received only once are not sampled, tested and individually released;

k) there is no SOP regarding transportation and storage conditions;

l) certification of manufacturers/suppliers is allowed without correct documentation.

(6) Manufacturing control:

a) master formula prepared/verified by non–qualified staff;

b) the complex manufacturing processes are not validated (^);

c) incomplete validation studies/reports for complex manufacturing processes (absence of assessment/approval);

d) major changes not–approved/not documented compared with the standard manufacturing file (^);

e) the deviations from manufacturing instructions are not documented and approved;

f) the differences of yield or reconciliation after production are not investigated;

g) the release of the manufacturing line between different products is not object of any SOP and is not documented;

h) there is no regular check on the measurement instruments/there are no records;

i) the intermediary products and the manufacturing areas are not accurately identified, which leads to increased mixing risk;

j) the inadequate labelling/storage of the rejected materials and products, which leads to mixing;

k) after reception, the bulk or intermediary products, raw materials and packaging materials are not quarantined until release by the QC;

l) the production staff uses bulk and intermediary products, raw materials and packaging materials without prior authorization from the QC(^);

m) inadequate/inaccurate labelling of the bulk or intermediary products, raw materials and packaging materials;

n) raw materials weighing is not done by qualified staff, according to the SOP;

o) standard manufacturing file (standard master formula) is incomplete or has errors in the production operations;

p) changed size in the approved series are not prepared/verified by qualified staff;

q) incorrect/inaccurate information in the manufacturing/packaging documents of one series;

r) although documented, the utilization in manufacturing of a raw material coming from more than one series is done without QC approval/ this practice is not object to a SOP;

s) there is no written procedure for the packaging operations;

t) unusual events occuring during packaging are not investigated by qualified staff;

u) inadequate control of packaging materials, printed, coded and not coded (including storage, weighing, printing and removing);

v) the self-inspection program is missing or is inadequate/the program does not address all GMP chapters /records are missing or are incomplete;

w) withdrawal:

– absence of withdrawal procedure combined with distribution practices which do not allow for adequate withdrawal (distribution records are not available or are not preserved);

– inadequate quarantine and rejection practices, likely to allow for (re)sale of the withdrawn/rejected products;

(7) Quality control department:

a) inappropriate sites, personnel and testing equipment;

b) lack of authority which allows entry in production areas (^);

c) there are no SOPs or SOPs are not available for materials sampling, inspection and testing;

d) the products are distributed on the market without an analysis bulletin issued by QC (^);

e) the products are released by the qualified person without accurate verification of manufacturing and packaging documentation;

f) the deviations and the results close to the limits are not accurately investigated AND documented according to SOP;

g) in the manufacturing process raw material / packaging materials have been used without prior QC authorization;

h) reprocessing has been done without prior authorization of the QC department (^);

i) there is no system for handling complaints, claims and returned products;

j) SOP referring to the operations possibly affecting product quality as transportation, storing etc. are not approved through the QC Department/are not implemented;

k) absence of a system for change control;

l) in case of testing laboratories (internal or under contract) the existing systems and verifications for the qualification, use, calibration and maintainance of equipment, standards, solutions and records kept do not allow for guaranteeing the exactness, precision and accuracy of results and conclusions (^).

(8) Testing of packaging materials:

a) reduced testing program without appropriate certification by producers / suppliers;

b) packaging materials are not tested;

c) specifications are not approved through the QC;

d) there is no identification test made by those who pack/label after materials reception, at their working place;

e) certification of producers/suppliers is done without correct documentation.

(9) Testing of the final product:

a) non–complying products sold without adequate justification (^);

b) incomplete/inappropriate specifications;

c) finished products specifications are not approved through the QC;

d) incomplete testing;

e) testing methods are not validated;

f) there is no SOP regarding transportation or storage conditions;

g) using a unique identification criterion not including all acceptable options

(10) Records:

a) standard manufacturing file is missing;

b) documentation from suppliers is not available within an acceptable time frame;

(11) Samples

Counter–samples are not kept for the finished products

(12) Stability:

a) insufficient number of series/data for establishing validity date;

b) No measure is taken when data show product non-conformity with specification before expiration date;

c) there is no continuous program for stability assessment;

d) there is no stability study after changes in manufacturing (in forms)/of packaging materials;

e) testing methods are not validated.

(13) Sterile products:

a) the case when products in watery vehicle are not subject to wet sterilisation in final recipient, is not appropriately justified or approved through marketing authorization;

b) incorrect classification of rooms for the processing/filling operations (^);

c) aseptic manufacturing areas have negative pressure compared to clean areas (C–D areas). Clean areas (C–D) have negative pressure compared to areas not classified (^);

d) insufficient number of samples for determination of room cleanliness /inadequate sampling methods (^);

e) insufficient environment control/monitoring of viable particules during the process of aseptic filling (^);

f) the sites and equipment are not properly designed or maintained to decrease contamination/particle generation (^);

g) inadequate maintainance of purified water systems and water for injectables;

h) inadequate revalidation of the systems for purified water and water for injectables, after maintenance or improvement works, or a tendency determined to results outside the specifications;

i) personnel training is not appropriate;

j) the procedure of equipping staff for clean and aseptic areas is not appropriate;

k) inappropriate program for hygienization/disinfection;

l) inappropriate practices/cautions for minimizing contamination or prevention of mixing;

m) the time between cleaning, sterilisation and utilisation of components, recipients and equipment is not validated;

n) microbian contamination before sterilisation is not determined;

o) the time period between the start of the manufacturing or filtering is not validated;

p) inappropriate procedures for the test of aseptic filling simulation;

q) insufficient number of units filled during the test of "filling with medium";

r) the tests of "filling with medium" do not simulate real operations;

s) nutritive capacity of the medium is not demonstrated for a large spectre of microorganisms;

t) erroneous interpretation of the results for the "filling with medium" test;

u) the sealing test for phials is missing;

v) the number of samples for the sterility test is insufficient or not representative for the whole manufacturing series;

w) sterility testing is not done separately for each load of the steriliser;

x) purified water is not used as supply water for the water obtaining system for injectables and for the clean steam generator;

y) the presence of endotoxines is not tested in the water for injectables used to prepare parenteral products;

z) the presence of endotoxines is not tested in the water for injectables used for final rinsing of containers and components used for parenteral products, when these containers and components are not depyrogenated afterwards.

4.3. "Other deficiencies "

Article 12. – When only "other deficiencies" are recorded during inspection, the company shall be declared as GMPR complying.

Article 13. – In this article there are examples of "other deficiences" which, according to the circumstances, can become major.

(1) Sites:

a) the doors of the manufacturing or packaging areas with direct access outside are used by the personnel;

b) the leakage in the floor is not provided with a grate/gully;
c) the leakage outlets for liquids and gases are not identified;
d) the damaging of non-adjacent surfaces or over the exposed products;
e) non-production related activities are taking place in the manufacturing areas;
f) inappropriate spaces for personnel rest, equipment and washing;
(2) Equipment:
a) distance between equipment and wall is not large enough to allow cleaning;
b) the basis of fixed equipment is not well fixed at contact points;
c) use of temporary materials or means for repairs;
d) damaged or out–of–use equipment is not removed or accurately labelled;
e) minor equipment used for non critical products, is not qualified.
(3) Hygienization:
a) the hygienization programme is incompletely written but the sites have an acceptable cleanliness status;
b) the cleaning or hygiene programmes are not accurately implemented or observed by the employees.
(4) Testing of raw material:
a) the series proposed for retesting are used in production without prior QC authorization;
b) incomplete validation of testing methods;
(5) Manufacturing control:
a) incomplete SOP for materials and products handling;
b) access in the production area is not restricted to authorized personnel;
c) inappropriate verifications at product reception;
d) incomplete packaging procedures;
e) incomplete withdrawal procedure.
(6) Testing of packaging materials:
a) inappropriate procedures for transportation and storage;
b) inappropriate treatment of outdated or out of use packaging materials;
c) incomplete testing;
d) inappropriate specifications;
e) several series received at once are not sampled, tested and released separately.
(7) Final product testing:
Incomplete testing of physical parameters.
(8) Records:
a) incomplete records/documentation for a product;
b) incomplete plans and specifications for the buildings meant for manufacturing;
c) incomplete documentation concering the supervising personnel;
d) insufficient time of keeping the evidence and records;
e) missing charts/diagrams;
f) incomplete records for the hygienization programme.
(9) Samples:
a) raw material samples are not available;
b) insufficient amount of samples for the final product or active substance;
c) incorrect storing conditions.
(10) Stability:
a) insufficient number of series in the program of continuous stability testing;
b) incomplete testing of parameters;
c) insufficient amounts for complete testing.
(11) Sterile products:

a) steam used for sterilisation is not monitored so that its appropriate quality is ensured as well as the lack of additives;

b) inappropriate control as far as the maximum number of personnel is concerned, in clean and septic areas;

c) gases used for purging solutions or the solutions for pH adjusting are not subject to sterilising filtration;

d) inappropriate inspection for detection of particles and faults.