THE BOHEMIAN AND MORAVIAN UNION OF ORGANIZATIONS FOR AGRICULTURE SUPPLY AND PURCHASE

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Good Manufacturing and Distribution Practice in Manufacturing and Distribution of Medicated Feedingstuffs

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The principles of Good Manufacturing Practice and Distribution of the medicated feedingstuffs in cooperation with the Committee for Food Safety and Environment Technical and Committee for Commodities of Animal Origin of the Ministry of Agriculture were elaborated according to legal provisions for feedingstuffs and medicinal products manufacturing valid in the CR and relevant provisions of the European Community.

The Bohemian and Moravian associations of the organisations of agricultural supply and purchase in cooperation with the composite authors elaborated and discussed with the Ministry of Agriculture this issue on good manufacturing and distribution practice.

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Content

1. Introduction

The sphere of the manufacturing of an animal feedingstuffs is one of the pivotal links of manufacturing chain of foods of animal origin. The manufacturing of safe feedingstuffs and food is an essential requirement of the good manufacturing practice on every step of the chain of manufacturing of feedingstuffs and foods from the primary production to final processing. Therefore, consist in the responsibility of each manufacturer and distributor taking part in this chain, which ensures the safety of the marketed goods by the implementation of the principles of good manufacturing practice. The responsibility status for everyone, who takes part in food chain starting with the farmer, continuing with the supplier and importer of the feedingstuffs, manufacturer and shipper of feedingstuffs and ending with the food manufacturers and food dealer, is stipulated by the Regulation No 178/2002/EC of the European Parliament and the Council, which stipulates the general principles and requirements relating to food safety (so-called "European food law"). Simultaneously with creating of the EU legislative, which target is especially safety of the foods, the EU feedingstuffs industry also has created the quality assurance systems, which laid down the requirements on relevant implementation of the safety standards of the feedingstuffs and foods and, where need, created the own standards. These quality assurance systems on the safety of feedingstuffs either individually or collectively on national level were created. They rapidly reached such importance, that they were officially approved by national authorities or approved as the national technical standards.

FEFAC made up this European Feedingstuffs Manufacturers Codex (EFMC) in such a way, not to make the market barriers inside of the Community due to existence of the national quality assurance systems. The aim was also the facilitation of the mutual recognition of the national good manufacturing practice codices. Actual European Codex is created to provide practical information for benchmarking of national good manufacturing codices for manufacturing of the safe feedingstuffs with the aim to facilitate the mutual recognition of the contemporary national good manufacturing practice codices by the public institutions, the owners of national schemes and subjects involved in feedingstuffs and food chain. The certification rules establishing should be made under the auspices of the owners of national schemes and should be based on EN 45011.

The feedingstuffs manufacturers in the Czech Republic, which are the membership of the Bohemian and Moravian Union of Organisations of Agriculture Supply and Purchase (ČMSOZZN) in cooperation with the Ministry of Agriculture established, after the model of EFMC, the Principles of Good Manufacturing Practice for Premixes and Feedingstuffs Manufacturing using the Premixes or Supplementing Feedingstuffs intended for livestock. Observance of the principles of good manufacturing practice mentioned above will become obligatory for all feedingstuffs manufacturers in the Czech Republic after coming into force of the Regulation of the European Parliament and Council No 183/2005/ES on requirements of feedingstuffs hygiene. These manufacturers will have to implement, according to this Regulation, good manufacturing practice into their daily practice. These principles do however not contain good medicated feedingstuffs manufacturing practice, which keeps to the another legal EC and CR provisions, they however have to concur to each other. Good manufacturing practice of medicated feedingstuffs manufacturing is so direct continuing of the principles of good manufacturing practice used in the manufacturing of medicated premixes and feedingstuffs, issued in the previous time. **In this context is necessary to consider medicated premix and medicated feedingstuffs to be same as medicinal product** and by the reason of that, their manufacturing and distribution have to fulfil very strict requirements, which are unambiguously stipulated by the provisions. The medicated feedingstuffs manufacturer thus has to observe both the requirements according to the **Act No**

91/1996 Coll. on Feedingstuffs in wording of the later amendments (into which has been transposed all EC provisions in the sphere of feedingstuffs issued before and after the accession of the CR into EC) and also the requirements of the Act No 79/1997 Coll. on Pharmaceuticals in wording of the later amendments (transposition of the Directive 2001/82/EC) and the Decree No.411/2004 Coll., on manufacturing and distribution (transposition of the Directive 91/412/EC). Medicated feedingstuffs manufacturing and their distributions breed the number of risks, which can be eliminated by observing of the good manufacturing practice. This guideline is essential material for elaboration of the own systems of good manufacturing practice and the system of the self-control of the critical points HACCP in the manufacturing and distribution of medicated feedingstuffs, which are created by the manufacturer according the specific manufacturing conditions. On the other hand medicated feedingstuffs are very efficacious and effective application of the medicament through the feedingstuffs used especially in the breeding with the high concentration of animals.

While the Central Inspections and Testing Agricultural Institute is the competent supervisory authority for the sphere of feedingstuffs manufacturing, the Institute for State Control of Veterinary Biologicals and Medicaments is the competent supervisory authority for the medicated feedingstuffs manufacturing. Both authorities closely cooperate in the discharge of the official control.

2 Contemporary regulation of veterinary medicinal products manufacturing

2.1 World

The medicinal product scope is one of the most regulated fields, the extent of the regulation and approach to regulation slightly differs in individual regions and these differences caused serious problems in free movement of this kind of goods. The main areas of the medicinal product manufacturing and trading represent the North America (especially USA and Canada), Europe and Japan.

The medicinal products manufacturing regulation (is the component part of the medicinal product market) is generally ensured by the relevant state authorities in all these parts both by the licensing of medicinal products manufacturing and by carrying out the repeated inspections at the manufacturing places by the inspectors from this institutions.

The USA is the main competitor of Europe in the sphere of the veterinary medicinal products manufacturing. The veterinary medicinal products manufacturing is regulated differently in the case of pharmaceuticals and biologicals. The FDA regulates both the veterinary pharmaceutical sphere and the human medicinal products according to the same principles and requirements. The sphere of biologicals (vaccines) is regulated by the USDA (US Department for Agriculture), which however does not have stipulated requirements in appropriate CFR (Code of Federal Regulation) in the same way as the requirements for the human biological medicinal products. The USDA requirements are significantly less strict in the sphere of requirements for premises and validations; on the other hand, USDA makes wide testing of each batch placed to the US market.

2.2 The Europe

The veterinary medicinal product regulation is within the EU ensured by the Directives, which regulate this sphere and which are transposed into the appropriate national legislative provisions. The main European Directive is recently the Directive 2001/82/EC (codified

directive joining and regulating several previous legal forms and directives), which was amended by the Directive 2004/28/EC. This amendment has to be transposed into national legislatives until 30.10.2005. Further Directive 91/412/EC is the most important directive for the sphere of the requirements for good manufacturing practice of the veterinary medicinal products. The sphere of medicated feedingstuffs is regulated by the Directive 90/167/EC.

Detailed good manufacturing practice requirements are published in the EU within the framework of the "Rules governing medicinal products", where, in the volume IV – Good Manufacturing Practice, are described in details the requirements of GMP via the form of fundamental document and its supplements (at present 18 supplements). All of the member states take part in the preparation and approval of these documents, which are prepared and approved on regular Ad Hoc GMP Services Meetings (four-time a year), where the delegates of individual competent authorities meet in the EMEA office.

Important part of the medicinal products regulation within the EU framework is EMEA, which has worked from the 1.1.1995. EMEA is responsible for management of marketing authorisation of medicinal products authorised by the centralised procedure and co-ordination of the expert activities in the EU and technical support for the working of expert groups.

Important document for harmonisation of approach of individual competent authorities is „Compilation of Community Procedures on Inspections and Exchange of Information". This document defines the rquirements for inspections quality system, information exchange procedure, the system of rapid warning, the inspection procedures and their recording etc.

National medicinal agency (competent authority), responsible for the appropriate regulation sphere has been established in each member state. Common human and veterinary agency is in some EU countries, or two individual competent authorities (one for human and one for veterinary medicinal products) are in another EU countries. Common agency works in Belgium, Austria, Ireland, Slovenia, Spain and Scandinavian countries. Separate agencies exist in Great Britain, France, Czech republic, Slovakia. Separate human agency and common agency ususually belong to the department of the Ministry of health, separate veterinary agency usually belong to the department of the Ministry of agriculture.

2.3 The Czech Republic

The European Directives are transposed into the Act No 79/1997 Coll., on Pharmaceuticals, as amended later (transposition of the Directive 2001/82/EC) and the Decree No 411/2004 Coll., on manufacturing and distribution (transposition of the directive 91/412/EC).

Two independent competent authorities are in the Czech Republic responsible for the regulation of the medicinal products: SIDC (State Institute for drug control, Šrobárova 48, Prague) – competent authority for the human medicinal products and ISCVBM (Institute for the State Control of Veterinary Biologicals and Medicaments, Hudcova 56A, Brno) – competent authority for the veterinary medicinal products.

Both medicinal agencies are responsible both for the sphere of manufacturing regulation (they grant licences for manufacturing and carry out the regular inspection) and for the sphere of authorisation of medicinal products. The EU inspectors several times inspected both competent authorities within the framework of the accession to EU and both authorities were recognised as equivalent to competent authorities of the other EU member states. Both agencies have taken part in activities of the EU since the entrance to EU and they have become the standard partners of the other EU medicinal agencies, EMEA and European Committee.

2.4 International organisations

Regarding to the permanent increasing demands in the sphere of medicinal product market regulation and to the continuous globalisation, the requirements harmonisation among the partial world areas becomes more and more important. Due to this fact, the ICH (International Conference on Harmonisation) was established in 1990. The parallel veterinary organisation VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) was officially established in 1996. Both the experts from the regulatory authorities and the industry experts from the USA, Europe and Japan participate in their activities. Both organisations elaborate the guidelines and detailed technical standards, which are used in partial spheres and facilitate mutual recognition of the obtained data. The sphere of harmonisation of manufacturing regulation is not however included so much in the programme of these conferences, both projects are targeted especially on harmonisation of technical requirements of marketing authorisation in individual key world regions.

In order to harmonise requirements in the sphere of inspections of the medicinal products manufacturing was, in 1970, founded the organisation PIC (Pharmaceutical Inspection Convention). At the beginning PIC has 10 members, the number of members increased, the new members were from Europe and Australia.

European legislature did further not allow concluding international treaties by the member states, it was not possible to accept new members from the 1993. Due to this the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme), which associates competent medicinal agencies of member states, was established in the 1995. PIC Scheme members are all current members of the PIC and further European countries (most of the members of current EU), Canada, Singapore and Malaysia. Both organisations work parallel under the abbreviation PIC/S. The 27 countries /medicinal agencies are presently active members, further members accede and some countries entertain the membership, including e.g. FDA. SIDC has been a member since 1997, ISCVBM since 2005. The main aims PIC/S are mutual recognition of the inspection results, harmonisation of the GMP requirements, unification of the quality system of inspection bodies, training of inspectors, and elaboration of the documents for conductions of inspections (so-called Aide Memoire), information exchange and establishment of mutual confidence.

Strong element of requirements harmonisation in the sphere of manufacturing and inspections is making agreements on mutual recognition of the certificates and results of inspections, e.g. among EU and the third countries, Canada and Australia etc. This agreements are called Mutual Recognition Agreements (MRA) and they are recently valid among EU and Australia, New Zealand, Switzerland, Canada (without veterinary biologicals) and Japan (only for non sterile human MP), also mutually among some countries out of the EU. The aim of these agreements is to obviate barriers of the free medicinal products movement among these countries, resp. remove duplication of some activities as testing and carrying out inspections.

3 Future of the manufacturing regulation

Medicinal products have to fulfil the high requirements for the quality, safety and efficacy. Moral, regulatory and economical aspects will conflict with in this sphere. Regulation disembarrassment in the sphere of medicinal products manufacturing will be impossible to assume in the nearest future, more probably an increase and a strengthening of the requirements according to increase of the requirements for medicinal products safety will

come. Increase of the requirements for medicinal substances manufacturing and some auxiliary substances, which will have to be manufactured according to GMP requirements, will come in Europe in 2005.

Ingoing trend of requirements convergence in partial key spheres will continue and will gradually include further spheres regarding the medicinal products regulation. Important role in the sphere of regulation of medicinal product manufacturing will play the EU, which harmonises the requirements for medicinal products manufacturing with the further states out of the EU by the making of international agreements on mutual recognition (MRA).

4 The legal provisions related to good manufacturing practice and distribution of medicated feedingstuffs

4.1 The legal provisions of the Czech Republic

The Act No 79/1997 Coll., on Pharmaceuticals in forced wording

The Decree No 343/1997 Coll., by which is stipulated the Way of Medicinal Products Prescription, Appurtenances of Medicinal Prescriptions and the Rules of their Use in wording of the Decrees No 157/2001 Coll., No 30/2003 Coll., No 34/2004 Coll. and 643/2004 Coll..
The Decree No 411/2004 Coll., by which is stipulated the Good Manufacturing Practice, Good Distribution Practice and detailed condition of manufacture licensing and medicinal product distribution, including the medicated feedingstuffs and veterinary autogene vaccines, variation of the granted licences, as well as detailed conditions of granting of licences of control laboratories (the "Decree on Manufacturing and Distribution of medicinal products").

The Act No 91/1996 Coll., on Feedingstuffs in wording of later amendments

The Decree No 451/2000 Coll., which execute the Act on Feedingstuffs in wording of later amendments

4.2 The legal provisions of the European Community

The Council Directive No 90/167/EEC stipulated the conditions relating to manufacturing, introduction to the market and use of medicated feedingstuffs

The Directive 2004/28/EC of the European Parliament and Council, which amends the Directive 2001/82/EC on Community code relating to veterinary medicinal product

EMEA and ER guidelines

The European Pharmacopoeia

The Regulation No 1831/2003/EC of the European Parliament and Council, on Use of the Additive Substances in Animal Feeding

The Regulation No 178/2002/EC of the European Parliament and Council, which stipulated the general principles and requirements on the Food law, established the European Food Safety Agency and stipulated the principles of the food safety

The Regulation No 183/2005/EC of the European Parliament and Council, which stipulated the requirements on the feedingstuffs hygiene

5 Terms and Definitions

Following definitions and terms are used for the purpose of the Good manufacturing and Distribution practice in manufacturing and distribution of medicated feedingstuffs:

Medicinal product is any medicinal substance or combination of such substances or medicinal product intended for administration to human or animals, if it is not additive substance.

Medicinal product

a) any substance or combination of substances, presented as having properties for treting or preventing disease in humans or animals; or
b) any substance or combination of substances, which may be used in or administered to humans; or used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Medicinal products are:

a) human medicinal products intended for use in or administer to humans,
b) veterinary medicinal products intended for use in or administered to animals,
c) veterinary immunological medicinal products administered with a view of establishing of active or passive immunisation or to making a medical diagnosis of the immunity status
d) herbal remedies, contained as an active substances at least one herbal substance or at least one herbal remedy or at least one herbal substance in combination with one herbal remedy,
e) dedicated medicinal products, which are defined as medicinal products, which can be according the authorisation decision soled without medical prescription out of the pharmacies

Substance is any matter irrespective of origin, which may be:

a) animal, e.g. micro organisms, toxins, whole animals, parts of organs, animals secretions, extracts or blood products,
b) vegetable or chemical

Medicinal substances are understood as:

a) medicinal substances intended to be the part of medicinal product, which is responsible for its efficacy; this efficacy is usually pharmacological, immunological or influences metabolism,
b) excipiens, which are in used amount without their own medicinal efficacy and
    1. allow or facilitate the manufacturing, preparation or storing of medicinal products or their administration, or
    2. influence positively pharmacokinetic properties of medicinal products contained in medicinal substances
c) herbal substances, which are understood as the whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, dried or fresh forms; as herbal substances are understood also the herbal exudates, which have not been subjected to any specific treatment; the herbal substances are precisely defined by the plant part used and the botanical name according the valid binomical nomenclature (genus, species, author, where is need the subspecies and variety).

Herbal preparation is preparation obtained by subjecting of herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. Herbal preparations included comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Premix for medicated feedingstuffs (further only medicated premix) any veterinary medicinal product subjected to authorisation, prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

Medicated feedingstuffs is any mixture of medicated premix or medicated premixes and feedingstuff or feedingstuffs, which is ready prepared for marketing and intended to be fed to animals without further processing or modification; medicated feedingstuffs are considered as veterinary medicinal product according the point "medicinal product b)".

Summary of product characteristic is a written summary of all information on medicinal product, which is a part of authorisation decision of medicinal product and contains the information important for the accurate use of this product.

Withdrawal period is the period between the last administration of the veterinary medicinal products to animals and under normal conditions of use and the production of foodstuffs of animal origin from such animals intended for human consumption. This period is established within the scope of the protection of public health by ensuring that such foodstuffs do not contain residues of pharmacologically active substances in quantities exceeding the maximum residual limits for active substances laid down pursuant to EEC Regulation.

Pharmacovigilance is supervision over the medicinal substances with the aim to ensure safety and as best as it possible ensure risk/benefit balance of the medicinal product. Pharmacovigilance includes especially collecting of information important for safety of medicinal product, including the information obtained via the clinical evaluation, their investigation and observation of appropriate measures.

Adverse reaction is a response to medicinal product administration which is noxious and unintended and which occurs at doses normally used for the prophylaxis, therapy or diagnosis of disease or for the restoration, correction or modification of physiological functions; in the case of clinical evaluation of medicinal product it is noxious and unintended response to any dose administration. This definition is not intended for transfusion products. The adverse reactions of medicinal products are divided especially into categories:

a) serious adverse reactions which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant health disability or incapacity or is a congenital anomaly or birth defects.
b) unexpected adverse reactions, the nature, severity or outcome of which is not consistent with the information in the summary of products characteristic in authorised medicinal product or is not consistent with the available information, e.g. with the summary of information for expert testing the evaluated veterinary medicinal product, which has not been authorised.
c) human adverse reaction which is nonxious and unintended and which occurs in a human being following exposure to a veterinary medicinal product.

Adverse event is adverse change of health status of patient or evaluated object which is the medicinal product was administered to, except the transfusion product, even if is not known that this event is in causal connection to the treatment by this medicinal product.

Serious adverse event is such adverse event which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant health disability or incapacity or is a congenital anomaly or birth defects, without the regard to dose of medicinal product used in the treatment.

Post-authorisation safety study is pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the authorisation decision and conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

Risk related to use of medicinal product

a) any risk relating to the quality, safety or efficacy of the medicinal product as regards human health, public health or animal health, or
b) any risk of undesirable effects on the environment

Risk/benefit balance an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 8. The balance of risk/benefit is positive, if the benefits from the use of medicinal products outweigh the risks related to its use.

Name of the medicinal product is name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark of the name of the marketing authorisation holder. Common name is international unauthorised name recommended by the World Health Organization or, in the case that such international unauthorised name does not exist, usual common name.

Strength of medicinal product the content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according the dosage form.

Immediate packaging is such form of packaging, which is immediately in the contact with the medicinal product. **Outer packaging** is packaging into which is placed the immediate packaging. **Labelling** is information placed on the immediate or outer packaging.

Package leaflet is written information for the user, which accompanies the medicinal product.

Batch is an amount of the product either manufactured or prepared together in a single production cycle (process) or homogenised during preparation or manufacture. The uniformity of all units belonging to the single batch is a fundamental principle of the batch.

Medicinal prescription is any medicinal prescription issued by a professional person qualified to do so.

Representative of the marketing authorisation holder is a person designated by the marketing authorisation holder to represent him in the all things laid down by this Law.

Handling with the medicinal products is their research, manufacturing, modifying, control, producing, distribution, storage and keeping, supplying and transport, supplying to sale, supplying, sale of the dedicated medicinal product, keeping in order to run a business, supplying of advertising sample, using of medicinal products in providing of health care and veterinary care and medicinal products disposal.

Pharmaceutical research is non-clinical safety evaluation and clinical evaluation of the products with the aim to demonstrate their efficacy, safety or quality.

Preparation of medicinal products is meant their formulation in pharmacy and in another workplaces, where is possible to make medicinal products.

Modification of medicinal product is meant such procedure, which is carried out in:

a) medicinal products are subjected to marketing authorisation before their supply or use in health care or veterinary care according the summary of the product characteristics or according the data provided by manufacturer,
b) evaluation of medicinal products before their use within the clinical trials, in accordance with the protocol and approved procedures of clinical trials;

Procedures according the a) or b) which are inadequately difficult or dangerous, whenever in other aspects they fulfil the marks defined in this paragraphs, are considered as preparation; their specification is defined by legal rules of practice.

Distribution of medicinal product is meant all activities including purveyance, storage, supply, including the supply of the medicinal product within the Community and export to the third countries, and relevant business transfers without the regard to fact, if it is the activity made free of charge or paid. Distribution is carried out in cooperation with the manufacturers, other distributors or pharmacies and other persons authorised to supply medicinal product to public, eventually authorised for use of the medicinal products. The supply of medicinal products, the sale of medicinal products by the dealer of dedicated medicinal products and the use of medicinal product in the providing of the health care and veterinary care are not considered to be a distribution of medicinal products. Import of the medicinal products from the third countries is also not considered to be a distribution of medicinal products.

Supply of medicinal products is meant their providing to personal entity or health care facilities. Also the mail-order providing is meant as supply of medicinal products.

The sale of the dedicated medicinal products is meant the sale, purchase and storage of dedicated medicinal products.

Use of the medicinal products in providing of veterinary care is meant their providing to breeder in order to following administration to animals or their direct administration to animals, and in conditions stipulated by the Act No 79/1997 in wording of later amendments and special provisions.

Circulation of medicinal products is supplying of medicinal products to persons defined in Act on pharmaceuticals, supplying of medicinal products, including the transfusion preparations, sale of the dedicated medicinal products and use of medicinal product in providing of health care or veterinary care.

Introducing of medicated feedingstuffs into circulation is meant the keeping of medicated feedingstuffs for the purposes of sale or any other way of providing to another persons or sale or providing of medicated feedingstuffs to another person without the regard to the fact, if it is the activity made free of charge or paid.

Use of the veterinary medicinal product out of range of authorisation decision is meant the use of veterinary medicinal product, which is not in accordance with the summary of the product characteristics. The use of the veterinary medicinal product out of range of authorisation decision is also meant the non-accurate use and abuse of medicinal product for the purpose of the control of use, prescription and supply of medicinal products in providing of veterinary care and pharmacovigilance.

The person providing the activities stipulated by the Act on Pharmaceuticals (further "operator") is meant:

a) a manufacturer of medicinal products, an importer of medicinal products from the third countries, a transfusion services facility, a control laboratory, a manufacturer of medicinal substances and excipients,
b) a distributor of medicinal products (further "distributor")
c) a distributor of medicinal products with the extended licence according to §77 sec. 4 or sec.5 c).
d) a person authorised for providing of health care according the specified legal provisions (further " heath care facility")
e) a person authorised for providing of veterinary care according the specified legal provisions
f) a person organising or carrying out the pharmaceutical research
g) a dealer of dedicated medicinal products

Good manufacturing practice is meant the set of rules assuring that the manufacture and control of medicinal products, eventually a manufacturing of the excipients, are accomplished in compliance with their quality requirements, with their intended use and in accordance with the appropriate documentation.

Good distribution practice is meant the set of rules assuring that the distribution of medicinal products, eventually a manufacturing of the excipients, are accomplished in compliance with their quality requirements, with their intended use and in accordance with the appropriate documentation.

Good laboratory practice is meant the system of quality assurance related to organising process and conditions, in which non-clinical studies of medicinal product safety are planned, performed, controlled, documented, proposed and archived.

6 The use of the medicinal products in providing of veterinary health care

1. A persons handling with the medicinal products are obliged:

a) to enforce of maximal benefit of medicinal product in their use and to reduce to the lowest possible degree of the adverse effect on the human health and public health, animal health and environment.
b) to observe the instructions for handling with the medicinal product in compliance with the summary of the products characteristic

2 Only the persons authorised for the certain activity according the Act on Pharmaceuticals should carry out the activities as handling with the medicinal products

3. Only following products should be prescribed, supplied or used in providing of veterinary care:

a) authorised veterinary medicinal products
b) medicated feedingstuffs, which is in compliance with the requirements of this Act
c) veterinary autogene vaccines which is in compliance with the requirements of this Act
d) medicinal products prepared in a pharmacy for individual patient in compliance with the veterinary surgeon prescription
e) medicinal products prepared in accordance with the monographs of the Pharmacopoeia Bohemica and prepared in the way stipulated by the legal rules of practice
f) veterinary medicinal products authorised in other member state in compliance with the Community provisions
g) authorised human medicinal products
h) medicinal substances and excipients

4. Following products should be further prescribed, supplied or used in providing of veterinary care:

a) medicinal product with exceptions issued by the State Veterinary Administration
b) unauthorised immunological veterinary medicinal products which use is approved by European Committee (further only "Committee") in compliance with the Community provisions related to some serious animal diseases.

5. Veterinary medicinal product, which use is restricted only for persons, which are authorised for use of veterinary medicinal product by the Institute for the State Control of

Veterinary Biologicals and Medicaments, and veterinary medicinal product which is possible to introduce to the circulation with placing of the foreign-language text on package after authorisation of the institute, should be used only by veterinary surgeon.

6 The only veterinary surgeon can administer medicinal products and authorised veterinary medicinal product used out of the authorisation decision range and is also entitled to assign another person for administering of medicinal product. The responsibility of veterinary surgeon for the harm due to using of medicinal product is not affect by assignation of such person.

7. Medicinal products containing thyreostatics, hormonal substances or beta-agonists should be prescribed, supplied or used for the veterinary treatment purposes, only when the conditions stipulated by specific legal provisions are observed.

8. Immunological veterinary medicinal products should be prescribed, supplied or used for the veterinary treatment purposes, only when their use is not in contradiction with the suppressive or protective measures laid down by the veterinary care institutions according the special legal provision.

9. The restriction laid down directly by the appropriate Community regulation is used in the case of animals produced the products of animal origin intended for human consumption.

10.The breeder of animals produced the products of animal origin intended for human consumption, have to observe, after the administration of medicinal product, the withdrawal period stipulated in authorisation decision or stipulated according the paragraph 10. Veterinary surgeons, that use, prescribe or supply medicinal products, are obliged to inform the breeder of animals produced the products of animal origin intended for human consumption about the withdrawal period, which has to be observed.

11. If the withdrawal period for certain species or category of animals is not established in the authorisation decision of certain medicinal product, the withdrawal period has to be established according the special legal provision. The withdrawal period for the products containing the substances established by Committee as necessary for the treatment of animals belonging to the family equidae, which belong, according the relevant Community provision, to the group of animals not intended for slaughter to be consumed by humans is established by the legal rules of practice according the control measures laid down in the relevant Community provision. The withdrawal period is not established in the case of homeopathic medicinal products.

12. Personnel that prescribes supplies or uses medicinal products in providing of veterinary care should record the prescription, supplying or using of the medicinal products according the requirements stipulated by the legal rule of practice. Legal rule of practice stipulated, with regard to persons that keep the records, the way of recording and the content of documents. The records should be kept for at least 5 years.

13. In providing of veterinary care can prescribe, supply or use medicinal products, if it is activities for the purpose of business, only the veterinary surgeon, who is acquainted in details with the health status of the animals and with the health and breeding conditions in certain breed and who fulfil the requirements for discharge of vocational veterinary activities according to the special legal rule (further only veterinary physician); it does not be valid in the special case of individual treatment of one animal or the group of animals in certain breed by another than veterinary physician (of certain breed)- the special cases are life threatening, health hazards or well-being of the animals. The veterinary physician is, in such case, obliged to acquaint oneself with the health status of the animal or animals in the extent necessary for the treatment. The medicinal product, which is on medical prescription only, should be only

prescribed in the amount, which is necessary needed for the appropriate treatment or therapy. The breeder should administer the medicinal products to the animals, that they own or that they take care or keep, if they are observed the conditions stipulated by the Act on Pharmaceuticals and Act on Veterinary Care.

14. Persons that have permanent address or they are settled in another member state than the Czech republic and that are authorised for providing of veterinary care in the area of the CR, are authorised for using medicinal products within the range stipulated by the legal rule of practice. The legal rule of practice stipulated the range of use medicinal products, which regarding to the marketing authorisation should be used, the way of transport, the packaging status and the requirements on the content of products, which should be used, for these persons. The records on the use of these products have to be kept according the sect. 11. These persons are, for this purpose, authorised for import of medicinal product to the Czech Republic in such amount, which do not exceed the daily need for the extent of provided veterinary care.

15. The only such technology equipment, which is the part of the farmsteading and for which the relevant District Veterinary Administration or Municipal Veterinary Administration in Prague (further "District Administration") established the veterinary conditions and measures according to Act on Veterinary Care should be used for use of authorised veterinary medicinal products, if they are not immunological medicinal products, in the form of administration via feedingstuffs in certain farmsteading; if such measures for appropriate technology equipment are not established, the breeder have to ask about the establishment of these conditions and measures on the relevant District Veterinary Administration and he can use such equipment for the purposes of medication use only after establishment of veterinary conditions and measures by the relevant District Veterinary Administration.

16. Breeders, who, as entrepreneurs, breed the animals, that products of animal origin intended for human consumption are obtained from, and who keep medicinal products intended for treatment of animals, are obliged for at least 5 years keep the records on way, how they get the medicinal products. This rule is also valid in the case, when the animals, which were the medicinal products intended for, were slaughtered or have not yet been in breeding of this breeder.

7 The Good Manufacturing Practice Requirements

7.1 The quality assurance system and GMP

7.1.1 General

The essential principle in the manufacturing of medicinal products is the assurance of the high quality assurance standard, which includes also the requirements of Good manufacturing practice (GMP). Individual GMP requirements are specified in the Decree No 296/2000 Coll., on Good Manufacturing Practice, Good Distribution Practice and detailed conditions of licensing of manufacturing and distribution of medicinal products, including medicated feedingstuffs, in the CR. Detailed instructions and recommendations are published in the form of binding rules in the ISCVBM Bulletin. The Volume IV Rules describes the GMP system in the EU; individual Annexes (see Modul I) give detailed instructions.

The general requirements on the Quality assurance system and GMP are divided into nine chapters:

- Quality management

- Personell
- Premises and equipment
- Documentation
- Production
- Quality Control (QC)
- Contract manufacture and a
- Complaints and product recall
- Self inspection

7.1.2 The Quality Assurance System (QA)

The aim of the quality control is to establish and fulfil the "quality assurance policy". The base elements of this system are:

- Relevant infrastructure of the "Quality System" including the defined organisation structure, procedures, processes and resources
- Systematic activities necessary for the achievement of sufficient certainty, that the products (activity) fulfil the quality requirements. The system of these activities is so called Quality Assurance.

The quality assurance system in pharmaceutical industry so represents the sum total of the organised activities and arrangements made to ensuring of adequate medicinal products quality includes also GMP and quality control (QC). The quality assurance system has to be documented and controlled.

The quality assurance system should include all elements, activities, which individually or together can influence the medicinal product quality. Therefore, QA is not only responsibility and duty of one subdivision of certain manufacturer, but responsibility of each employee, which could in any way influence the medicinal product quality.

The complex Quality Assurance system has to ensure minimally following requirements:

- Medicinal products are designed and developed in a way that takes account of the principles and requirements of GMP, GLP and GCP
- The responsibilities and competences of the managers have to be clearly specified, organisation structure of the company is defined, the personnel have their duties defined in detail in written job descriptions, an adequate number of personnel with the necessary qualifications and practical experiences is ensured
- All production and control operations are clearly defined and described, e.g. by the system of the Standard Operation Procedures (SOP)
- Actualised writing arrangement has to be made for supply and use of the starting and packaging materials
- Actualised writing arrangement has to be made for quality control of the starting materials, intermediate products, in bulk products
- QA system has to ensure the existence of the writing actualised SOP specifying production and checking of the finished product
- Finished product has not to be supply in distribution without appropriate checking by the qualified person (QP) (production and checking in accordance with the documentation, which is relevant to regulations on the production, control and release of medicinal products and with documentation of authorisation)
- Has to ensure, that the storage, distribution and handling with the medicinal products is made in that way and in conditions, which cannot influence the medicinal product quality

- There has to be created and used the functional system of Self-Inspection

7.1.3 GMP – Good Manufacturing Practice

GMP is that part of Quality Assurance, which ensures that products are consistently produced and controlled to the quality standards according to the approved regulated documentation and approved authorisation documentation. The standardised quality of the produce and control is the base premise. It can be ensured only on base of the accurate and clear specifications of all arrangements. Correctly operating GMP provide against non-compliance, which cannot be detected during the finished product checking, it is mainly:

- Cross contamination
- Confusion of products

The fundamental GMP requirements are:

- Clearly specified and regularly revised manufacturing procedures
- Validation of the critical steps of manufacturing procedure and their more significant changes
- The appropriate resources are ensured:
  - Qualified and trained personnel
  - Adequate premise and spaces
  - Suitable equipment and services
  - Suitable starting materials
- The manufacturing proceed according to clear, instructional and unambiguous SOP and instructions
- Personnel is trained to carry out procedures correctly
- Complete records of manufacturing, which demonstrate that all steps required by the defined procedure steps were in fact taken, that records make possible to completely reconstruct the manufacturing procedure; any significant deviations from specified procedures are investigated and recorded
- Appropriate storage spaces and ways of distributions
- The available system to recall any medicinal products from the market, in the case of quality defects after the releasing of the medicinal product for the market, is described and checked
- The system of complaints solving is specified, complaints are executed and examined appropriately, the appropriate corrective measures are taken

7.1.4 Quality control (QC)

The Quality Control (QC) is the part of GMP. Each manufacturer of medicinal products has to have Quality Control Department. The necessary condition of the correct QC function is independence on the manufacturing and other departments; the head of this department should be a person with appropriate qualification and sufficient experiences. QC should dispose of one or more control laboratories and sufficient following resources:

- Sufficient premises and equipment
- Trained personnel
- Approved procedures

The fundamental QC duties are:

- Sampling
- Analytical testing
- Monitoring of all materials and manufacturing conditions
- Approval and disapproval of the starting materials and finished products

The other QC duties are:

- Development, validation and introducing of all QC procedures
- Evaluation, keeping and saving of reference materials
- Ensuring of the correct labelling of packages of materials and finished products
- Stability testing of active substances and finished products
- Participation in complaints solving
- Concern in environment monitoring

The subjects of QC activities are starting materials, package materials, intermediate products, in bulk products, finished products, manufacturing conditions. The fundamental requirements for the control department are:

- Sampling is carried out by personnel and according to QC approved methods
- Testing assays are validated (accuracy, validity, linearity, reproducibility, robustness, selectivity)
- The records of all activities are kept
- Deviations are recorded and examined
- The starting materials released to manufacture fulfil the requirements for the quality and purity defined by the approved regulated documentation and authorisation documentation
- Appropriate package materials are used
- Correct labelling of the staring materials and finished products
- The finished product matches the specification, releasing to the distribution after the writing approval of QP, based on the fulfilment of output specifications of finished product, result of intermediate product testing, record of manufacturing process, including the evaluation of any deviations, the environment monitoring, finished product package control
- Keeping of sufficient amount of samples of both starting materials and finished products

7.2 Personnel

The manufacturer can invest and purchase buildings and equipment, the personnel is however the most important element in the GMP system. That is the reason, why the sphere of personnel care is greatly focused. Making and functionality of the Quality Assurance system and GMP is depending on people, who made the system, who use the system and who control the system.

The fundamentals for system function of the QA and GMP are:

- Sufficient number of personnel with necessary qualification and sufficient experiences
- The organisation scheme has to be established, which declares independence of the control department on the manufacturing. The established positions of the head of manufacturing and the head of Quality Control have to be independent. The Qualified Person has to be designed.
- The responsibilities of the heads have to be clearly specified; there should not be the responsibility gaps or overlaps. The responsibility should not be too much not to make the product quality risk
- The writing job descriptions, sufficiently detailed, in order to personnel clearly understand their duties and responsibilities, personnel should clearly understand their positions and their roles in the GMP system
- The functional system of the initial and continual trainings, motivation of personnel

7.2.1 Key Personnel

Three key persons are defined in pharmaceutical manufacturer – Qualified Person, the head responsible for production and the head responsible for quality control.

Qualified Person (QP)

- This person makes writing decision on releasing of each batch of finished product to distribution
- Controls the complete records of manufacturing, adjustment, environment, quality control and control the fulfilment of requirements of authorisation documentation, manufacturing licence and regulatory documentation
- Has competence to reject releasing of the product to distribution, when the requirements for quality was not met
- The requirements for education and experience are specified in the Act No 79/1997 Coll. on Pharmaceuticals, in wording of later amendments, which specified qualification requirements for Qualified person:

Qualified person of medicated feedingstuffs manufacturer has to have:
(§ 41 j Act No 79/1997 Coll.)

- an university degree in pharmacy – field of study pharmacy, in the field veterinary medicine and hygiene – field of study veterinary medicine, in the field of medicine, agriculture, in biological or technical fields, biology or chemistry.
- two years practical experience in manufacture or control of pharmaceuticals and passing of the specialised course in extension and in conditions stipulated by the Decree. Qualified person is obliged to improve practical and theoretical experiences according to the actual state of the scientific knowledge and technical progress. The manufacturer is obliged to ensure condition for further education of the qualified person.

The head of the Production Department

- Ensures that products are produced and stored according to approved documentation
- Approves and implements working instructions, SOP for interoperating control, controls their observance
- Evaluates manufacturing records
- Is responsible for the maintenance of spaces, premises and equipment
- Ensures that the appropriate validations and calibrations are done, ensures availability of the records
- Is responsible for initial and continuing training of personnel from manufacturing

The head of the Quality Control Department

- Approves or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products,
- Is responsible for carrying out all appropriate testing according to specifications
- Approves specifications, working instructions, SOP relating to QC (sampling, specifications, methods etc.)
- Approves and controls any contract laboratories
- Is responsible for maintenance of spaces, premises and equipment of the QC
- Ensures carrying out of validations of analytical methods and equipments, equipment calibration
- Is responsible for initial and continuing training of QC personnel

The head of the Production Department and the head of the Quality Control Department generally have some shared or jointly exercised responsibilities, as:

- The monitoring and control of the manufacturing environment
- The approval of suppliers of starting materials
- The approval of contract manufacturers
- The monitoring of compliance with the GMP requirements and observation of the hygiene
- Inspection, investigation of defects (this competence is assigned to independent Department of the Quality Assurance in major manufacturers
- The retention of records

7.2.2 Training

All the personnel, whose activities could affect, in any way, the quality of the product have to be included into the training system. The writing document (SOP) has to be defined for the training system, specifying the procedure and the training method of the new personnel and the system of continual education and training of the personnel appropriate to the duties assigned to them. The special training has to be given for personnel working in the clean areas, working with the high efficient, toxic, infectious, dangerous or sensitising materials etc. and in areas with the high contamination risk.

The writing plan of trainings has to be elaborated and approved by the responsible personnel within the framework of the training system. Appropriate training records have to be kept. The training should be repeated regularly and its efficiency should be investigated.

The training has to cover minimally two base fields, essential principles of QA and GMP and it should explain the importance of QA and GMP for pharmaceuticals manufacturing to all personnel. The second part of the training covers the specific trainings of specific procedures carried out by the appropriate personnel.

The training of the personnel, which takes part in the medicated feedingstuffs manufacturing, has to cover, except the points mentioned above, essential principles of QA and GMP, which are for this kind of manufacturing necessary.

7.2.3 Hygiene

Detailed hygienic programmes have to be established, specifying the requirements for the personnel health status, hygiene practices, clothing regimen for partial manufacturing fields, controls and distributions, the kind of movement in different areas and spaces of the factory.

7.3 Premises and equipment

7.3.1 Buildings and premises

Premises and equipment have to be located, designed, constructed, adapted and maintained to:

- Minimise the risk of errors and cross-contamination
- Permit effective cleaning, sanitation, decontamination and maintenance
- Minimise the dust nuisance and dirty
- Eliminate negative effect on the quality of the product

Buildings used for medicated feedingstuffs manufacturing should be situated in an environment with minimal risk of contamination, buildings should be maintained, and maintenance operations do not present any hazard to the quality of products. Cleaning, sanitation, disinfection of premises should be carried out in accordance with the approved writing procedures. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products

during their manufacture and storage, or the accurate functioning of the equipment. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals. The measures are taken in order to prevent the entry of unauthorised people.

Production Area. Three essential points is necessary to respect in design of production areas – flow of material, of personnel and sequence of the partial production operations. All points have to be in conformity and they do not influence each other negatively.

Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of operations and to the requisite cleanliness levels. The working spaces should be designed and constructed in such a way as to minimise the risk of confusion and to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing and control steps.

Where starting materials, primary packaging materials, intermediate products or bulk products are exposed to the environment, interior surfaces (walls, floors, ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and disinfection.

Storage areas should be sufficient capacity to allow orderly storage of the various categories of Materials and products: starting and packaging materials, intermediate products and finished products, products in quarantine, released, rejected, returned or recalled.

The materials have to be stored in appropriate conditions, protected from inadequate temperature, humidity, direct solar radiation, required storage conditions have to be monitored, checked and recorded.

The areas have to be unambiguously marked from the view of status of materials; controlled and limited admittance should be into the areas with recalled, cancelled or rejected materials. There should normally be a separate sampling area for starting materials; the sampling should be conducted in such a way as to prevent contamination or cross-contamination. The dangerous (flammable, toxic, narcotic and psychotropic) substances and materials) have to be stored in totally separated and in appropriate way safe and areas, with detailed records and controlled entrance.

Anciliary areas. Rest and refreshment rooms should be separate from other areas, should avoid contamination and should not directly communicate with production areas.

Quality control laboratories should be separated from production areas, should be located, designed, constructed, adapted and maintained to be appropriate for certain controlling activities. Control laboratories for biological, microbiological medicinal products and radioisotopes controlling should be separated from each other, equipped with self-ventilation.

Sufficient spaces should be given to avoid mix-ups and cross-contamination; sufficient spaces have to be detached for storage of samples. Specific spaces may be necessary to protect sensitive instruments from electrical interference, vibration, humidity etc.

Equipment – medicated feedingstuffs: required separate hopper place for medicated premix i.e. direct filling into homogeniser. (Do not use the micro machine intended for feeding ingredients).

Areas – medicated feedingstuffs: have to be approved for medicinal products manufacturing (in the approval competence of the ISCVBM) and for feedingstuffs manufacturing in the approval competence of the CITAI)

Areas: except the production areas the manufacturer has to have:

- storage area for the medicated premixes

- storage area for the medicated feedingstuffs samples
- storage areas for the finished medicated feedingstuffs
- storage areas with quarantine regimen or separated, delimited, marked area for returned, recalled medicated feedingstuffs.

7.3.2 Equipment for manufacturing of medicated feedingstuffs

Manufacturing equipment should be designed, constructed, located, maintained and operated in such a way to suit its intended purpose, should be easily and thoroughly cleaned. Cleaning and sanitation should be made according to previous approved and validated written procedures by standard way, and equipment should be stored only in a clean and dry condition. Cleaning equipment should be chosen and used in order not to be a source of contamination.

Equipment should be installed in such a way as to prevent any risk of error or of contamination; production equipment should not present any hazard to the quality of the product. The parts of equipment, which are exposed to the products, have not to be reactive, additive or absorptive to such an extent that will affect the quality of the product or present any hazard of quality of the product. During the maintenance, repairing has not to be endangered the quality of the product.

Balances and measuring equipment of an appropriate range and precision should be available for production and control operations. Measuring, balances, recording and measuring equipments should be calibrated and metrological checked at regular intervals by appropriate methods, adequate records of such tests should be maintained.

All equipments should be clearly marked from the view of status quo in which is in the moment (from the view of sanitation/decontamination, calibration, procedure step etc.). Fixed pipework and lines should be clearly labelled to indicate the contents and, where applicable, the direction of flow. Equipment not used for production and defective equipment should be removed from production and quality control areas, or at least be clearly labelled as defective /unusable.

For medicated feedingstuffs, manufacturing is required separate hopper place for medicated premix i.e. direct filling into homogeniser. The micro machine intended for batching of supplement substances intended for feed manufacturing.

7.4 Documentation

7.4.1 Pharmaceuticals a immunologicals

Good documentation constitutes an essential part of the quality assurance system and corresponding with all elements of GMP. The documentation should be unambiguously understandable and should permit complete reverse reconstruction of the manufacturing of medicinal product, or its batch. It has to exist:

- Written specifications for all materials
- Written descriptions for all production steps
- Written descriptions for control methods

The system of documentation has to ensure, that all of the workers know, what and when they have to do (provision documentation), on the other hand it has to provide to qualified person all information necessary for releasing of the medicinal product into distribution (recording documentation). Records have to describe the procedure of manufacturing of each individual batch of the medicinal product, including the data on distribution and another circumstances, which can affected the quality of the product.

The recording documentations should be proposed, elaborated, controlled, approved and distributed with care by the appropriate relevant way; they should comply with the relevant parts of the approved authorisation dossier. The title and contents of the document has to be unambiguous, they have not to permit inexplicit interpretation, and contents should be orderly fashioned and be easy to check. The appropriate and authorised person should approve, sign and date the documents. Documents should be labelled by appropriate way, should be regularly reviewed and kept up-to date. When the document has been revised, systems should be operated (cancelled and shredded) to prevent inadvertent use of superseded documents. The system of the document keeping and labelling of the copies has to be established.

The record documentation should be well arranged, should have a sufficient space for handwritten entries, which should be made in legible and indelible handwriting. Any alteration made to the entry on a document should be dated and signed, the alteration should permit the reading of the original information and the reason of the alteration should be recorded, where appropriate. The record documentation should be made or completed immediately after the action is taken and in such a way that all activities, which could affect the quality, safety and efficacy of the medicinal products, should have appropriate record, are traceable. There should not be any blank spaces in records. Data may be recorded by electronic data processing systems, photographic or other reliable means. Detailed procedures (SOP) relating to creating and use of that system should be available and the accuracy of the records should be checked, accuracy of the key records should be independently checked. The record documentation should be retained for at least one year after the expiry date of the certain medicinal product, minimally for five years from release the product to the circulation.

Types of the required documents:

- Specifications
  - Starting and packaging materials
  - Intermediate and bulk products
  - Finished product
- Manufacturing formula
- Instructions for processing, packaging, labelling, working instructions, SOP
  - Receipt of all materials
  - Labelling, quarantine and storage of all materials
  - Service, maintenance and cleaning of all equipments
  - Material sampling
  - Batching
  - Control of material in all steps of production
  - Release/reject of batches
  - Keeping of distribution records
  - Validation and classification of equipment
  - Calibration and service of analytical equipment
  - Maintenance, cleaning and sanitation
- Quality control procedures (QC)
- Batch processing and packaging records
- Batch control and distribution records
- Other documentation (validation, metrology, maintenance, personnel training and education, complaints investigation, returns, environment monitoring etc.

7.4.2 Documentation medicated feedingstuffs

The requirements are valid in appropriate way as mentioned above. **The Standard Operating Procedures (SOP)** for following procedures should be kept in disposal of manufacturer:

- taking over of raw material supply (especially taking over the medicated feedingstuffs)
- storage of raw materials (medicated feedingstuffs), material labelling
- releasing of the raw materials to the manufacturing including medicated feedingstuffs (weighing)
- device handling (records on proceed of manufacturing line, maintenance, activity in equipment breakdown)
- medicated feedingstuffs manufacturing
- medicated feeding stuffs packaging (bagging – package size, packaging material, loose granulated medicated feedingstuffs reservoir – reservoir labelling, the way of stopper blocking, labels – with requirements for medicinal products and feedingstuffs labelling
- storage
- release/ reject of the product to the circulation
- cleaning of stirring equipment (all manufacturing line)
- handling with the alarm, when is used
- medicated feedingstuffs sampling (procedure, regular active substance content analysis, sampling frequency
- samples storage (location, package, sample labelling, sample register)
- complaints processing (way, Qualified Person - QP position in recall processing)
- handling with returned medicinal products – medicated feedingstuffs
- recall of medicated feedingstuffs (customers data – database, findability of produced medicated feedingstuffs batches and also of used medicated premixes batches in medicated feedingstuffs)
- lorry cleaning – transporters of in bulk matter – where the cleaning proceeds, procedure and records
- manufacturing premises hygiene and sanitation
- obligatory documentation according to coherent provisions for medicated feedingstuffs manufacturing (ISO) –state supervision in the CITAI competency

The medicated feedingstuffs should have **orderly recorded documentation with data of medicated feedingstuffs manufacturing batch** – the record of batch manufacturing with the specifications of the key operations as – weighing, dispensing of the medicated feedingstuff/intermediate of medicated feedingstuff, the number of stirring machines, which are produced the manufacturing batch, granulation, the cleaning of the equipment before and after manufacturing, finished product sampling, packaging, material balance sheet, deviations from standard procedures and instructions, which was occurred in manufacturing (recording, investigation, approval), release/reject of the medicated feedingstuff batch to circulation.
Agreement on Contract Manufacture (with the licensed medicated feedingstuffs manufacturer according to the Act No 79/1997 Coll., on Pharmaceuticals) in the case of medicated feedingstuffs intermediate use for MF manufacturing. **The requirements on the agreement content** regarding to contract of the part of manufacturing are specified in part **7.7 Contract Manufacture and medicinal product checking**

Agreement on Contract Checking (with authorised control laboratory according the Act no. 97/1997 Coll., on Pharmaceuticals) – in the case, that manufacturer has not got any control laboratory equipped for medicinal products analysing (it is common practice in medicated feedingstuffs manufacturers – their laboratories has usually got equipment only for the routine analysis of the feedingstuffs). **The requirements on the agreement content** regarding to

contract of the part of manufacturing- checking, are specified in part **7.7 Contract Manufacture and medicinal product checking**

7.5 Production

7.5.1 Generally

Individual production operation must follow clearly defined and pre- approved procedures in accordance with the GMP requirements in order to obtain products of the requisite quality, which are in accordance with the relevant approved authorisation criteria, and the manufacturing to be in accordance with the conditions stipulated by the licence of manufacturing.

Production should be performed and supervised by competent people, trained in appropriate way. Entry to the manufacturing premises should be restricted and only authorised personnel should be there. All handling with the materials and products should be done in accordance with written procedures and instructions; critical procedures should be recorded. All incoming raw and packaging materials should be checked; containers should be cleaned and labelled with the prescribed data. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution. All materials and products should be stored under appropriate conditions, in an orderly fashion, separately individual batches, and with stock rotation, the FIFO system is necessary to use (first into the stock, first out of the stock).

Checks on yields, reconciliation of quantities of produced with the quantities of used starting substances should be carried out during the manufacturing. Operations on different products should not be carried out simultaneously in the same room unless there is no risk of mix-up or cross-contamination. At every stage of processing, products, intermediates and materials should be protected from any contamination. When working with dry materials, special precautions should be taken to prevent the generation and dissemination of the dust. This applies particularly to the handling of highly active or sensitising materials.

At all times during processing, all materials, bulk containers, major equipment and rooms should be appropriate labelled (including the active ingredient content, where applicable) with an indication of the product or material being processed, batch number and the stage of the production. Labels used for material labelling, bulk containers, major equipment and rooms should be well legible, their content should be unambiguous, labels should be in accordance with the company ´s agreed format. It is often appropriate in addition to the wording on the labels to use colours to indicate status, in which materials, bulk containers, major equipment and rooms are at present (e.g. quarantined, accepted, rejected material). Checks should be carried out to ensure that equipment links, conveyor-belts and similar equipment are connected in a correct manner.

Any deviation from instructions or procedures should be recorded in appropriate way, checked and approved by a competent person, with the involvement of the Quality Control Department when appropriate.

7.5.2 Cross-contamination

At all times during processing, contamination of a starting material or of the product by another material or product has to be avoided. The risk of accidental cross-contamination arises from the uncontrolled release of the dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from the clothing of operators. Amongst the most hazardous contaminants are highly sensitising materials,

biological preparations containing viable organisms, certain hormones, cytotoxic substances and other highly active medicinal substances. Very serious is contamination of products administered by injection, those given in large doses or over a long time.

Cross- contamination should be avoided by appropriate technical or organisational measures, for example:

- The production is done in segregated areas, or separate in time
- Providing appropriate air locks and air extraction
- Minimising of recirculation of untreated or insufficiently treated air
- Use of special protective clothing
- The cleaning and decontamination procedures of known effectiveness are used (the dirty of manufacturing equipment is the most common source of cross-contamination)
- Using of closed system of manufacturing
- Testing for residues is carried out
- Use of cleaning status labels on equipment with the indication of the cleaning status at this moment

7.5.3 Production validation

Validation studies should reinforce system GMP and should be conducted in accordance with written defined procedures. The proceeding, results and conclusions should be recorded. When any new manufacturing formula or method of preparation is adopted, validation should be taken to demonstrate its suitability for routine processing with achieving of appropriate product quality using the materials and equipments specified. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality or reproducibility of the manufacturing process, should be validated. Process and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

7.5.4 Starting materials

Starting materials should only be purchased from the approved and thorough known suppliers and, where possible directly from the producer. For each delivery, the containers should be checked for integrity of package and for correspondence between the delivery note and supplier's labels. Each batch should be sampled, checked and release to manufacturing individually. Materials in the storage area should be appropriately labelled after the receipt according to the company provision; the record should minimally contain:

- Name and internal company reference code
- A batch number given at receipt
- The status of material
- In quarantine
- Sampled (for each sampled package)
- Released, the number of releasing record and expiration, where is appropriate
- Rejected

Only starting materials, which have been released by the entry Quality Control, should be used in production, identity of each packaging unit should be checked. Designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers, should only dispense starting materials. Each dispensed material and its weight should be independently checked and the check

recorded. Starting materials dispensed for each batch should be kept together and conspicuously labelled as such.

7.5.5 Intermediate and bulk products

Before any processing operation is started, it is necessary to check, that the work area and equipment are clean and free from any starting materials, products, products residues or documents not necessary for the current operation. The correct storage and manufacturing condition should be kept during the production. All critical manufacturing processes and equipment should be validated. In-process control of appropriate steps and environmental monitoring should be carried out during the processing; all significant deviation from the procedures should be recorded and investigated.

7.5.6 Packaging materials

The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials. Particular attention should be paid to printed materials; their mixing-up has too serious consequence. Packaging materials should be stored in safe conditions and saved against the entry of unauthorised persons. Handling with these materials should be made in appropriate way to avoid their mixing-up, the appropriate detail records of their issue and use should be made. Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Medicated feedingstuffs have to be introduced to the market in original intact packaging, in the case of in bulk medicated feedingstuffs are transporters, which are they stored in, ensured according to the requirements on medicinal products (§ 41k section 12). The data that should be placed on the package are in this case the part of documentation in distribution of medicated feedingstuffs (41k section 9 of Act on Pharmaceuticals). Closed original packages have to be clearly identified and after its opening it is markedly evident, that they have been opened – their packaging or their seal (in the case of the transporters with in bulk medicated feedingstuffs) were permanently, irreversibly and markedly damaged.

The manufacturer declared on the packaging of medicated feedingstuffs or in accompanying documentation (if it is in bulk medicated feedingstuffs) the wording "MEDICATED FEEDINGSTUFF" and also declared the data stipulated in § 41k sect. 10 of Act on Pharmaceuticals. There are data, which have to always be declared on label of medicated feedingstuffs and data stipulated in § 43 sect.6 of the Decree No 411/2004 Coll. on good manufacturing and distribution practice including the notice "FOR ANIMALS ONLY".

Packaging, after using up of medicated feedingstuffs and medicated premixes used in the manufacturing of medicated feedingstuffs are disposed as hazardous waste according to the Act on Wastes.

7.5.7 Packaging operations

Normally, the labelling should be made immediately after the filling and sealing. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling could occur.

When setting up a programme for the packaging operations, particular attention should be given to minimise the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation. Before packaging operations are begun, steps should be taken to ensure that the working area, packaging lines and printing machines are clean and all steps of it should be recorded in appropriate check-list, all products and packaging materials to be used should be checked on

delivery for quantity and accuracy. The name and batch number of the product being handled should be displayed at each packaging station or line. Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly. Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

On/line control of the product during packaging should include at least checking the following:

- General appearance of the packages
- Whether the packages are complete
- Bottle (or package) the correct product into correct packages
- Whether any overprinting is correct
- Correct functioning of the monitors of the manufacturing line.

Samples collected from the production line should not be given back to the batch. Products, which have been involved in an unusual event, should only be reintroduced into the process after special inspection, investigation and approval by authorised person, record should be kept of this operation. Generally, any significant discrepancy observed during the bottling or packaging should be recorded, investigation and approval by authorised person should be made to evaluate their influence of the product quality and appropriate measures relating to the packaged batch should be taken. Any unused batch-coded packaging materials should be destroyed.

7.5.8 Finished products

The finished products should be held in quarantine until their final QP release under conditions established by the manufacturer for the finished product. Rejected materials and products should be clearly marked as such and should be stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate reprocessed or destroyed according to written provisions. The reprocessing of rejected product should be exceptional; it is only permitted if the quality, safety and efficacy of the product are not affected and if the product after reprocessing met the appropriate specifications. The reprocessing should be made in defined, approved procedure after the consideration of possible risks; the records should be kept on reprocessing.

Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory.

7.5.9 Medicated feedingstuffs production

The above specifying rules are valid for medicated feedingstuffs in connection with the following of the requirements of the Directive 90/167/EEC (Act. No 79/1997, on Pharmaceuticals).

The manufacturer should especially ensure that:

- the only feedingstuffs and their combination, which are in accordance with the Community provisions on feedingstuffs used in producing, should be used in producing
- the used feedingstuffs produced with authorised medicated premix will create the stabile and homogenous mixture
- authorise medicated feedingstuff will be used during the manufacturing process according the conditions stipulated in licence on placing on the market and especially that:

- any possibility of any adverse interaction does not exist among veterinary medicinal products, additives and feedingstuffs
- medicated feedingstuff will be keepable for appropriate period
- feedingstuff, which should be used for medicated feedingstuff production, does not contain the same antibiotic or anticoccidic substance as is the substance use in medicated premix
- the daily dose of medicinal product will be contain in the amount of the feedingstuffs, which is minimally the half of the daily feed dose of treated animals , or which is minimally half day need of non mineral supplement in ruminants
- the manufacturing procedure has to be in accordance with the good manufacturing practice principles
- medicated feedingstuffs should be regularly checked up – including the appropriate homogeneity tests
- medicated feedingstuffs should comply with the requirements of this Directive, especially concerned on the homogeneity, stability, shelf life and contamination
- premixes and medicated feedingstuffs should be stored in appropriate conditions, separately, in a special treated rooms or hermetic packages, determined specially for storage of such products
- medicated feedingstuffs should be placed on the market only in covers or packages with the seal or plug, which is destroyed when the package is opened to avoid the recurrent use
- when the road transport containers or similar container are used for transport of the medicated feedingstuffs to the market, they have to be cleaned before the next use to protect against any adverse interactions or contamination
- all activities are recorded by manufacturer
- the manufacturers are obliged to keep the daily records on kinds and amounts of authorised medicated premixes and feedingstuffs , used in production and on stored or distributed manufactured medicated feedingstuffs. Also the names and addresses of the breeder and animal owner, the name and address of the vet prescribing the treatment, if the medicated feedingstuffs is distributed by the licensed distributor, than the name and address of the licensed distributor
- the records have to be stored (in the CR for 5 years) and whenever available to competent institutions for checking

Validation

- the manufacturer carries out **the validations of the cleaning of manufacturing equipment after the produce of the medicated feedingstuffs** (estimation of the active substance content (medicinal product content) in manufactured product)
- **Validation of the manufacturing procedure** with the checking of the period of product miziny (be connected with the homogeneity evaluation of the finished product) – medicated feedingstuffs manufacturers usually made it on alternative substance (e.g. sodium salinomycinate)
- The manufacturer checked up in regular periods the **homogeneity** of the manufactured product
- Important **stability of the product** (see also the stability studies – medicated feedingstuffs – to observe the requirements for use of the medicated premix in the manufacture of medicated feedingstuffs – the shelf life of medicated premix after the mixing into the feedingstuffs)

7.6 Quality control (QC)

7.6.1 Pharmaceuticals and immunologicals

Quality Control Department is essentially concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out and that the starting materials and finished products are not released for use, or for distribution until their quality has been judged satisfactorily. The Quality Control Department activities are not confined to laboratory operations, but the department must also be involved in all decisions, which may concern the quality of the product. The independence of the Quality Control from Production is considered fundamental to satisfactory and disinterested operation of Quality Control; the manufacturing spaces should be accessible for QC personnel (sampling carry out, environment monitoring, investigation of deviations etc.)

Generally, each holder of manufacturing authorisation should have a Quality Control Department, independent from other departments, under the authority of the person with appropriate qualifications and experiences, who has at least one laboratory at his disposal.

The principal duties of the QC are:

- Specify, validate and implement the quality control procedures
- keep the reference samples of starting materials and finished products
- Ensure the correct labelling of the package units of the starting materials, intermediates and finished products
- Ensure the monitoring of the stability of the finished products
- Participate in investigation of complaints
- To monitor the manufacturing spaces

All activities should be carried out according the previously elaborated, approved and written procedures; the appropriate records of these activities should be performed, to allow their efficient reconstruction.

Finished product assessment should embrace all relevant factors, minimally:

- Assessment of production conditions
- Results of in-process testing
- Assessment of complete manufacturing (including packaging) documentation, assessment of any deviations
- Review of accordance with specification and authorisation documentation
- Checking of finished package

Control laboratory premises and equipments should meet the general requirements listed in Chapter 3. The number, qualification and experiences of the personnel should be appropriate to tasks imposed by the nature and the scale of the manufacturing procedures. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Laboratory documentation should follow the principles given in Chapter 4 and are valid for Quality Control Department documentation. The following documents should be available at the Quality Control Department:

- Specifications (all starting materials, intermediates and finished materials)
- Sampling procedures
- Testing procedures (according to authorised documentation)
- Testing records of carried tests

- Analytical records and/or certificates
- Data from environmental monitoring
- Validation records of test methods and equipment
- Procedures for and records of the calibration of instruments and maintenance of the equipment

Any quality control documentation relating to batch record and production record should be retained for one year after the expiry date of the expiry date of the batch and at least 5 years after the release the batch on the market. For some kinds of data it is recommended that records be kept in a manner permitting trend evaluation in longer time period.

The sampling provisions should contain:

- The way and method of sampling
- The equipment and instruments to be used
- The definition of the sample amount to be taken, relating to the material type, the number of packages sampled
- Instructions for any required sub-division of the sample
- The type and condition of the sample container to be used
- The identification of containers sampled and the way of the samples labelling
- Any special precautions with regard to specific materials (sterile, highly dangerous, flammable etc.)
- The storage conditions

Reference samples should be representative of each batch of materials or products from which are taken. Sample containers should bear a label indicating the full identification of material (name, strength, the batch number, the date of sampling, identification of the package unit, from which sample has been drawn). Reference samples from each batch of starting materials should be retained for at least two years after the release of the last released products, in which the starting material has been used (other than solvent, gases and water). Reference samples of the finished products are usually kept in final package at least till one year after the expiry date.

7.6.2 Quality Control (QC) – medicated feedingstuffs

The rules are valid in appropriate way as mentioned above for each manufacturer and the only differences are that the common quality tests for feedingstuffs are carried out in medicated feedingstuffs batch and **the manufacturer carries out the monitoring of the active substance (medicinal product) content in MF in appropriate intervals** (the Act No 79/1997 Coll, on Pharmaceuticals stipulated in regularly) only in selected batches of MF. It means that the results of tests are available only for selected batches of MF until their release by Qualified Person. The manufacturer in appropriate SOP determines frequency of the monitoring.

Medicated premixes

The production has to been carried out **in the full agreement with the principles of Good Manufacturing Practice for medicinal products manufacturing** according to **the product specifications** (important: the stability of the product in proceeding – e.g. use of the steam in pellets production- and consequently in the feedingstuffs, compatibility and homogeneity – appropriate mixing into feedingstuffs). The manufacturer has to avoid to cross-contamination in production. Due to dusty of the production should be used the closed transport system with respiration and the production should be placed in **restricted manufacturing space,** when is possible **separated from the other manufacturing spaces** by the protective (impact barrier) space to minimise the risk of contamination of other production spaces.

Information required for medicated premixes **incorporation** into medicated feedingstuff, **homogeneity, compatibility and stability:**

Incorporation:

- type, nature and quality of the feedingstuff – target animal
- amount of medicated premix (MP) in feedingstuff – it should be stated and in compliance with the European Pharmacopoeia monograph for MP (*really used minimal concentrations differ from the pharmacopoeia e.g. in France minimally 0,5 %, U.K. 0,2 % , in the CR 0,6 – 0,05%)* and also correspond with the Art. 14 of the Council Directive 90/167/EC i.e. daily dose MP must be contained the in the amount of the feedingstuffs, which is minimally the half of the daily feed dose of the animals under treatment, or which is minimally half daily need of non mineral supplement in the case of ruminants
- concentration of MP in the feedingstuffs should be given in mg/t and be conformed with the dose of mg/kg of bodyweight (EMEA/CVMP/080/95)

Homogeneity:

- the adequate incorporation of MP in final feedingstuffs should be demonstrated (use of the correct type of the feedingstuff) . Important role play the correct sampling place and a number of samples, method of analysis, particle size of the MP
- validated use of the analytic method
- demonstration, that there is not the physical separation during the transport

Compatibility:

- demonstrate biological and physically-chemical compatibility with the other compounds of the feedingstuffs (additives, vitamins, minerals, trace elements, binders, preservatives)
- list of known incompatibilities (e.g. ionophors and tiamulin)

Stability of medicated premix:

After the mixing into the common feedingstuffs:

- during manufacturing and processing (achieved temperatures about 110/10 min with the high pressure can destroy the antibiotic in conversion and granulation)

For storage in feedingstuffs:

- detail conditions and packages has to be specified
- type of feedingstuff – structure

7.7 Contract manufacture and analysis

Contract manufacture and analysis has to be correctly defined, agreed and controlled in order to ovoid misunderstandings, which could result in a product or work of unsatisfactory quality, eventually the risk for the complaints and recall solving system. There has to be a written contract between the Contract Giver and the Contract Acceptor that clearly establishes the duties of each party in technical sphere and in GMP, the way in which the Qualified Person releasing each batch of product for sale exercises his full responsibility has to be specified unambiguously. All agreements should be in accordance with the authorisation decision for certain product.

The Contract Giver duties are:

- The assessment of the competence of the Contract Acceptor to carry out in appropriate quality the work and to carry out the certain activity in accordance with the GMP requirements

- The Contract Giver should provide the contract Acceptor with all information necessary to carry out the contracted operations correctly in accordance with authorisation and any other provisions
- The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products
- The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that a Qualified Person has released the products.

The Contract Acceptor duties are:

- The Contract Acceptor has to have adequate premises and equipment, knowledge and experience, and competent personnel
- The Contract Acceptor has to be a holder of a manufacturing authorisation for appropriate production
- The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements.
- The Contract Acceptor ensures that all materials and products, which are supplied to him, are suitable for a certain purpose
- The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured

The Contract should contain so-called technical aspects supplement, which specify partial aspects of observation of GMP. The competent persons with suitable knowledge of the pharmaceutical technology, analysis and GMP should elaborate this supplement (the head of the Production department, Qualified person, the head of Quality Control Department). All agreements must be in accordance with the authorisation decision and authorisation documentation and agreed by both parties. Minimally should contain:

- The definition of the partial responsibilities relating to product manufacturing and control
- The specification of the way in which the Qualified Person releasing the product to the distribution
- The responsibility for the purchase, control and releasing of the starting materials, undertaking production and quality controls, including the in-process control
- The responsibility for sampling and analysis of the samples
- The way of elaboration of manufacturing, analytical and distribution records and their availability to Contract Giver and his QP; all records necessary for investigation of complaints or suspicion of adverse reaction should be available for Contract Giver
- The way of sampling and keeping of reference samples
- The responsibility for the complaints investigations and recall procedures
- The contract should permit the Contract Giver to do external audits in the premises of the Contract Acceptor.

7.8 Complaints and product recalls

The investigation of complaints and products recall is the sphere with the high priority and importance; they are the pilot elements of the Quality Assurance System and GMP. All complaints and other information relating to the non-complying products must be reviewed

and recorded carefully according to written procedures. In order to provide for all contingencies, a system should be designed if necessary to recall, promptly and effectively products known or suspected to be defective from the market.

7.8.1 Complaints

A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him, the effective system of the necessary corrective measures. If this person is not the Qualified Person, the QP has to be informed on each complaints regarding the quality of the product and on the way of its investigation, on each mandatory suspension of distribution and recall.

There should be elaborated written procedures describing the recording and investigation of the complaints and suspension of distribution and recall. The written record should be elaborated and should contain all details and document the investigation and decisions and measures taken as a result of the complaint of the quality. The Qualified Person should closely co-operate with the Quality Control Department, QP should dispose all relevant records and information, in the case of investigation of complaints. In all cases of complaint, regarding to quality of the product is necessary to assess in appropriate way, if a product defect is discovered or suspected in other products of the batch or in other batches to determine whether they are also affected. The results of the investigation should be used for repair and for prevention of the recurrence of this defect in future.

Complaints records should be reviewed regularly for any indication of specific or recurring problems of the quality requiring investigation and possibly the recall of marketed products and suspension of distribution, the trends of complaints should be evaluated retrospectively to allow the finding of latent causes of complaints/defects.

The State Institute for Drug Control, in the case of human medicinal products and the Institute for the State Control of Veterinary Biologicals and Medicaments, in the case of the veterinary medicinal products, as a state authority, should be notified of the complaint of the product quality and of the eventual mandatory suspension of distribution or recall.

7.8.2 Recalls

A person should be designated as responsible for the execution of suspension of distribution and recall of the product from the market and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation and should have available all appropriate records. The detailed written procedures should be elaborated for the suspension of distribution and recall procedures and they should be regularly checked and updated. The system of the suspension of distribution and recall should be capable of being initiated promptly and at any time. All competent authorities of all countries to which products may have been distributed should be informed promptly if product are intended to be recalled or distribution suspend.

The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers, e-mails, batches and amounts delivered), including those for exported products and medical samples. The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products. The effectiveness of the arrangements for recalls should be evaluated regularly.

Recalled products and products from the procedure of suspension from distribution should be identified and stored separately from released products in a secure area.

7.8.3 Defects classifications

The system of defect classification from the view of its seriousness is necessary to specify for the complaint investigation and due to decision on suspension of distribution or recalls. Usual classification is:

- I – Critical defects (potentially life endangering or can cause the serious health endangering)
- Immediately reaction by the all available means and ways is necessary (minimally in the form of suspension of distribution)
- II – Serious defects (can endangered the health, or can lead to wrong treatment, however not classified in category I)
- Rapid reaction is necessary (in the term maximally 48 hours)
- III – Other defects (represent limited health risk, the recall is directed from another reasons)

  Common term of decision is 5 working days

The signals for recall order are:

- Customers complaint
- Deviations from GMP discovered during investigation
- The stability studies result
- The Regulation of the state authority
- The result of the inspection
- Reveal of falsification or imitation
- Report on investigation of adverse reaction leading to the recall decision

7.9 Self inspection (Internal audits)

Internal (self) inspections (audits, controls) should be conducted in order to monitor the implementation and compliance with the quality assurance system, fulfilment and observing of principles GMP and to propose necessary corrective measures. The written instructions for the internal audits system, which specify who, what and in what way should done, should be elaborated (SOP). Internal audits are regularly made according the pre-determined plan, or in consequence of recognised defects (recall, repeated reject of material etc.). All parts of the Quality assurance system and GMP should be investigated in the internal audits:

- Personnel
- Premises and equipment and their maintenance
- Documentation
- Manufacturing procedures including interoperating control
- Adjusting
- Storage of starting materials and finished products
- Hygiene and sanitation
- Validation and revalidation, the system of calibration
- Quality control
- Distribution
- Complaint investigation and the system of suspension of distribution and recall from the market

Internal audits (self inspections) should be conducted in an independent and detailed way by designated competent person(s) from the company, independent audits by external experts may be also useful. All self inspections should be recorded in appropriate way. Reports should contain all observations made during the inspections and, where applicable,

proposals for corrective measures and the date of its completion. Proposed corrective actions should be controlled.

8 The good distribution practice

The effective Quality Assurance System including the Good manufacturing Practice requirements is necessary to be established during the medicinal products manufacturing and also to be produced and placed to the market only the products with the high quality. In addition, the product should be registered by the relevant national authority. This approach ensures that only medicinal products with the appropriate quality, safety and efficacy are released to the distribution.

Unless the quality, safety and efficacy has been affected during the distribution, it is necessary to apply such rules in the whole distribution chain to ensure protecting of relevant quality, safety and efficacy. These rules are summarised in "Recommended procedures of application of Good Distribution practice".

The only rules for distribution are established for human medicinal products in the EU (Directive 92/25/EEC, Guidelines on Good Distribution Practice of Medicinal Products for Human Use - 94/C 63/03). The requirements for Good Distribution Practice for veterinary medicinal products are not contemporary established in the EU.

The requirements for Good Distribution Practice for veterinary medicinal products are in the Czech Republic defined by the Act No 79/1997 Coll., on Pharmaceuticals, in wording of later amendments and by the Decree No 411/2004 Coll., on Manufacturing and Distribution of Medicinal Products. "Recommended procedures of application of Good Distribution practice" are issued as the Regulation of the ISCVBM.

The document "Recommended procedures of application of Good Distribution practice in distribution of mass produced veterinary medicinal products" was issued by the ISCVBM Brno according to §42b, section 1 g) Act No 79/1997 Coll. on Pharmaceuticals, in wording of later amendments. Related provision is the Decree No 411/2004 Coll., part 9 Good Distribution Practice.

The observation of the rules of Good Distribution Practice within the framework of the whole distribution chain and all its elements is ensured by the regulation of this chain, where the distributor has a duty to obtain the permission for the distribution of veterinary medicinal products from the ISCVBM. The observance of GDP requirements is investigated by the inspection GDP performed at the distribution place and by system of periodical inspections carried out by the ISCVBM inspectors before the granting of the permission (licence).

Good Distribution practice Recommended Procedures as were issued by the ISCVBM are divided into thirteen chapters:

- Quality Assurance
- Personnel
- Premises and equipments
- Documentation
- Procedures
- Control
- Complaints and recalls
- Import of medicinal products
- Export of medicinal products

- Counterfeits
- Internal audits
- Medicinal product distribution
- Medicated feedingstuffs distribution

8.1. Quality assurance

The requirements for the Quality Assurance System are defined in this chapter. The distributor should ensure that the quality of medicinal product would not be affected during all distribution activities. Distributor is obliged check up the efficacy of this system, e.g. within the framework of internal audit system.

Setting Quality Assurance System should ensure, that medicinal products have to be supply in undamaged original packages, have to be stored in relevant and controlled conditions to avoid of these contamination or larceny, have to be distributed only with valid expiration, have to be functional the system of distribution suspension and recall of medicinal product form the circulation. All procedures should be sufficiently described and recorded.

8.2. Personnel

Distributor should dispose of sufficient number of relevantly qualified and trained personnel with practical experiences with distribution of medicinal products. The organisation scheme with unambiguously defined relations, competences and responsibilities among the different departments and personnel subordination should be elaborated. Competences and responsibilities are clearly defined in written form and the personnel is acquainted with them.

The key worker is the Qualified Person, who is responsible for observation of legislative requirements according the §42a section 1 g) Act No 79/1997 Coll. on Pharmaceuticals. Qualified Person has unambiguously defined responsibilities and QP is responsible for implementation and observation of the Quality Assurance System.

The regular training system of each relevant personnel in GDP and subsidiary tasks should be established. Performed trainings are recorded. Personnel use appropriate working clothes and observe the principles of personal hygiene stipulated by writing provisions. Personnel observe the prohibition of smoking and eating in storage premises.

8.3. Premises and equipments

Premises and equipments intended for distribution of medicinal products are be designed, located, equipped and maintained to allow perform this activity reliably and to ensure required saving of the medicinal products quality at the whole distribution chain.

Premises should be of sufficient capacity, should allow proper, well arranged and separate storage according the established requirements, should be easily cleanable and good maintained. Premises should have the separate areas for receipt, expedition, quarantine and for storage of non-compliant medicinal products, e.g. in the case of complaints, recalls or counterfeits. Premises for discharge of consignments and receipt should be protected against unfavourable weather conditions, e.g. roofed or protected in another way. The arrangement of premises allows the consecution of particular procedures and protect against contamination or mixing-up.

Premises should be protected against the entrance of unauthorised persons; the entrance to the storage areas should be controlled. Adequate precautions should be taken against small animals and insect attack.

All products that needed the special storage conditions, as termolabile medicinal products or medicinal products with the content of narcotic or psychotropic substances are stored separately and in areas selected for this purpose.

The temperature and where is appropriate also humidity storage conditions should be monitored and checked by the relevant measure equipments. The storage premises should be classified i.e. should be documented, that the storage conditions are observed in the whole storage spaces – thermo-map. Measure equipment should be fitted with signalisation for the situations, when the temperature range is exceeding, especially in the case of storage of thermolabile products, where the variation of condition can affect the quality of the product. All measuring equipment should be regularly and provable calibrated.

The transporters, which ensures keeping of specified conditions for the whole time of transport can be used for transport of thermolabile medicinal products.

8.4. Documentation

The perceptive and recording documentation, which contain all steps of the distribution chain, should be taken according the principles Good Distribution Practice. All key activities relating to the medicinal products distribution should be established in the perceptive documentation. Perceptive documentation should be in so called controlled regime, when each perceptive document is identified unambiguously, is signed and approved by the competent person, is valid for certain period, is actual and the register of such documents exists and allow the recall of all copies. Each document should be understandable, legible, easy to control, available and avoid double interpretation.

The sufficient records should be conducted on each key activity. The records are made at the time of performance of individual operations and allow tracing of the movement of each individual batch of medicinal product in the whole distribution chain from the supplier to customer. Recording documentation is stored minimally 1 year after the expiry of distributed batch of medicinal product, minimally 5 years from the record made. If it is stored via the computer systems the data have to be backed up in recoverably way, electronic system should be validated from the view of data protecting and their archiving and availability.

8.5. Procedures

Following procedures should be followed during the distribution activity:

- All medicinal products are stored according to specified storage conditions and in order to minimise their confusion, cross-contamination or damage.
- All medicinal products are orderly and well-arranged stored to be possible differentiate individual batches and ensure stock rotation according the time of storing (the system EEFO (ending expiration- first out).
- The medicinal products with special handling and storage demands are identified immediately after receipt and stored according to specified conditions.
- Rejected, suspend and recalled medicinal products and counterfeits or products with damaged packaging have to be stored separately, to avoid their redistribution or contamination of other medicinal products.
- Temperature of all storage areas is monitored and controlled and the records, which are evaluated, are elaborated and kept. The written procedure is elaborated for the temperature checking, which includes the measures, which have to be taken in the case of exceeding the temperature range.
- Stored medicinal products have to be delivered in clean, appropriately marked packages, which adequately protect the products before unfavourable conditions
- Medicinal products requiring special storage conditions have to be transported by the specified way and by a special means, to avoid their quality damage.

8.6. Controls

The control of each delivery should be made in receipt according the documentation of the delivery, the control of the quality certificate of each batch of delivered medicinal product (in the case of import), the control of the entireness of the package, control of the expiry date, control of the batch number and control of the authorisation number of medicinal product in the Czech Republic.

Medicinal products should be delivered only to competent customers, only authorised medicinal products or medicinal products with granted exemption according to the Act No 79/1997 Coll., on Pharmaceuticals, medicinal products not exceeding the expiry date and those in entireness packaging should be expedited.

8.7. Complaints and recalls

There has to be elaborated writing procedure for investigation of complaints and recalls and established and assert the system of registration or complaints and recalls according to the Decree No 411/2004 Coll.

There has to be elaborated writing procedure for handling with the returned products, according to this procedure, returned products have to be immediately put into quarantine, where they remain until the decision of their next destiny. Returned medicinal product can be redistributed only in the case:

- The product is in original package and in good condition
- Distributor is sure, that the product has not been exposed any conditions, which could unfavourably affect its quality
- Time to expiry is for customer acceptable
- The product has been investigated by Distributor's Qualified Person

The distributor is obliged to inform all of his customers in the case of recall of certain product and actively cooperate on the recall of the medicinal product from the market.

The way of disposal (usually incinerator) and the record of disposal should be made in the case of disposal of certain batch (medicinal products with exceeded expiry date, medicinal products with quality defect).

8.8. Import of veterinary medicinal products

Import of veterinary medicinal products within the EU is according the requirement of § 3 sect. 5 Act No 79/1997 Coll. defined as a distribution and the permission granted by the ISCVBM is necessary for this activity according the §42 sect. 2 of this Act. Import of medicinal products from the third countries is not considered as distribution and has respect to requirements stipulated for manufacturers of medicinal products.

Imported medicinal products should be documented, including the date, amount, name, pharmaceutical form, content of active ingredient, package size, batch number, expiry date and number of registration (in the Czech republic) of imported medicinal product, the name and address of the supplier.

Distributor's Qualified Person (distributor, which import medicinal products and place them to the market in the Czech Republic), beside the duties mentioned in chapter 5.5, is responsible for the controlling of the facts, that all necessary tests certifying the quality of the medicinal product according to the condition of manufacturing licence and authorisation decision (analytical certificate) was performed in each batch of imported medicinal product in the country, where the product was made. The part of this control is also checking if the

package materials of each batch of imported medicinal product match the approved authorisation documentation of certain medicinal product.

The distributor should have the writing form of the certificate on quality of the medicinal product and eventually approval for their manufacturing granted by the relevant national authority to manufacturer of certain medicinal product, to check up this information. The distributor should have established the way of the checking of the conformity of printed packages with the authorisation requirements in the Czech Republic. In the case of medicinal products manufactured in the third countries and imported to the EU by the importer from the other EU country, the copy of relevant approval for importer of medicinal products from the third countries should been enclosed to the each delivery from these importer to the Czech Republic.

Qualified Person ratify before the placing the certain batch to the distribution, by the writing form, that checked, that the batch of medicinal product match the requirements stipulated in the Czech Republic provisions. Primary responsibility of the Qualified Person of the manufacturer, which produced the medicinal product, however remains.

8.9. Export of veterinary medicinal products

Export of medicinal products within the EU is according the requirement of § 3 sect. 5 Act No 79/1997 Coll. defined as a distribution and the permission granted by the ISCVBM is necessary for this activity according the §42 sect. 2 of this Act. Exported medicinal products should be documented by the similar way as the distributed products in the CR.

The distributor should dispose of certificate of quality in written form to the each exported batch of medicinal product.

8.10. Counterfeits

Counterfeits of medicinal products founded in a distribution network should be stored separately from the other products, not to avoid their distribution. They should be clearly labelled as not for sale. The holders of authorisation decision and the Institute for the State Control of Veterinary Biologicals and Medicaments are informed immediately about the ascertained counterfeits. The ISCVBM will inform the competent medicinal agencies by the system of the rapid warning.

8.11. Self inspection (Internal audit)

The main aim of the internal audit is to check the effectiveness of implement system of the quality assurance of certain distributor. The corrective actions based on the founded results are proposed.

Internal audits should be carried out according the established plan and further in the case of need. The records are made about the performed internal inspections, which include all findings, results, evaluations, proposals for corrective actions to relieve the finding shortage and actions carried out..

8.12. Distribution of medicinal products

The provision governing the distribution of medicinal products is valid in appropriate extension for distributors of medicinal products. Except the duties of distributors, they are obliged to observe following requirements:

- Distributors should ensure orders and deliveries according to the specifications of customer
- Distributor should elaborate and oblige the system of the approved supplier.

- Distributor can only supply medicinal substances with the Certificate of Quality containing the data according the Decree No 411/2004 Coll.
- Distributor can only supply medicinal substances with packages labelled with the name of substance, batch number, storage conditions, expiry date and the number of the Certificate of Quality of the substance, including the register number of control laboratory
- Distributor can only supply medicinal substance to person approved for preparation of medicinal products
- Distributor should have elaborated the effective system for assurance of the recall of medicinal or additional substance from the circulation

8.13. Distribution of medicated feedingstuffs

The following requirements, except the requirements valid for the distributors of medicinal substances, are valid for the distributors of medicated feedingstuffs

- To offtake of the medicated feedingstuffs only from the producers with the valid licence for manufacturing of medicated feedingstuffs
- Medicated feedingstuffs only distribute to persons, which are as the acceptors defined in prescription of medicated feedingstuffs
- Distributor has not to distribute medicated feedingstuffs of amount exceeding the amount specified in the prescription for medicated feedingstuffs
- Only the appropriate labelled medicated feedingstuffs in intact original packages is possible to distribute
- Medicated feedingstuffs should be only placed into circulation on the prescription drawn by the veterinarian. Distributor dispose of the prescription for medicated feedingstuff according the requirements stipulated in § 41j) sect 2 Act No 79/1997 Coll.
- Distributor ensures, not to avoid contamination of distributed medicated feedingstuffs. Medicated feedingstuffs have to be stored in appropriate separated and secured premises or in hermetically closed containers.

The manufacturer, in the case of import from the Community member states, has to have valid approval for the medicated feedingstuffs manufacturing from the member state and medicated feedingstuff should comply with the requirements for feedingstuffs stipulated by the special legal provisions. Medicated feedingstuff, in the case of import from the Community member states, has to have the Certificate issued by the relevant control authority according the relevant provision of medicated feedingstuff. Distributor is obliged to keep for 3 years the Certificate and its copy send to the ISCVBM until 7 days

The distributor has to have licence for veterinary medicinal products – medicated feedingstuffs manufacturing granted by the ISCVBM.