

# OMCL Network of the Council of Europe GENERAL DOCUMENT

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### Incorporation of a RB approach in MS testing at OMCLs

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| <b>Concerned Network</b>                                       | GEON                                                                                                   |

## **Introduction to the document**

*The aim of this position paper of the GEON is to underline the great importance of using risk analysis for selection of products for market surveillance testing at OMCLs. Different types of possible risks are listed in the document, and sampling and testing strategies are proposed. This paper may be read in connection with other documents on risk assessment for targeting Market Surveillance by OMCLs, which have been developed over time in the GEON and by other bodies such as the EMA, the HMA Working Group on Product Testing and its successor, the HMA Drafting Group for Risk based Approach to Product Testing.*

## **Incorporation of a risk based approach in Market surveillance testing at OMCLs**

### **Scope of the document**

This document describes potential areas, where risk assessment may be used in the market surveillance testing conducted by OMCLs, to define priorities before establishing a test programme.

### **Purpose of a risk based approach in market surveillance testing**

The OMCLs have a unique mission within the medicines regulatory network to protect public health by detecting defective medicinal products on the market. Adoption of a risk based approach to market surveillance would allow the OMCLs to concentrate their limited resources on those areas considered most likely to pose a risk of quality defects.

### **Role of OMCL**

In general the surveillance of medicinal products on a national level includes inspection, pharmacovigilance and the post-marketing OMCL laboratory testing. This supervision is aimed at giving consumers a higher guarantee that medicines are of good quality. A genuinely global risk management strategy involves improved regular interaction between, and coordination of, assessment, inspection, pharmacovigilance and laboratory control activities.

The manufacturing pharmaceutical company carries out quality release testing of production batches of medicines according to quality systems required by the authorities. In order to fulfil its role within the global medicines regulatory network, the OMCL performs post-marketing laboratory testing by small size oriented or random sampling (a) to check that the quality control carried out by the manufacturers is functional and reliable, (b) to verify that the analytical methods used by the manufacturer are appropriate (only in cases where the MAH method is used) and (c) to confirm that the quality of medicines is maintained along the distribution chain.

The analytical work of many OMCLs has changed over the years. The number of samples provided for legal/suspicious and enforcement analysis has increased. In some cases, OMCLs may have limited involvement in the risk evaluation process but have to perform the analyses for the competent authority. As a consequence, and in order to optimise the use of OMCL resources for surveillance studies, a risk based approach in choice of products to be included in market surveillance studies is appropriate, and is already in use in OMCLs within the Network.

### **Existing Guidance**

Guidelines for risk management systems for medicinal products in the field of pharmacovigilance and Quality risk management (ICH Q9) were drawn up some years ago. In the ICH Q9 document it is clearly indicated that risk management regarding quality of medicines includes both manufacturing and use of a drug, i.e. the quality should be maintained throughout the life-cycle of the product and should remain constant compared to the product used in clinical trials. Risk assessment includes risk identification, risk analysis and risk evaluation, and there are a number of models available for this purpose.

## **Risk based approach in OMCL market surveillance testing**

Several criteria have to be considered to define a risk based programme of control. Laboratory test strategies have to consider different types of risks in relation with either the manufacture of the product (API, finished product), or its impact on patients' and target population's safety and care. The evolution and change of therapeutic protocols or regulatory environment can also have an impact on defined medicinal products or categories of medicinal products. Some of these changes can have major consequences for public health. Due to these different factors, different types of risk have to be considered to incorporate a risk based approach in OMCL programmes of control.

### **1. Different types of risk**

#### **1.1. Risks connected to the raw materials (in particular the API)**

The risk can come from:

- origin (geographical, or origin from vegetable or animal source...);
- weak stability, poor solubility – polymorphology, meta-stable modifications (etc.) of API;
- complicated manufacturing process;
- manufacturing process susceptible to producing harmful impurities (risk of residual solvents, elemental and/or genotoxic impurities; viral risk coming from the use of columns coated with monoclonal antibodies during purification steps; possible viral contamination of the cell substrate used to produce a recombinant therapeutic protein etc.);
- novelty of the active substance and high technology of quality control;
- multiple API manufacturers for a single medicinal product.

These categories of risks should be identified during the evaluation phase of the marketing authorisation process.

#### **1.2. Risks coming from the final product**

- pharmacological class subject to non-conformities;
- generic status leading to diverse production by manufacturers not necessarily known by the national authorities;
- product likely to be falsified;
- just-in-time production due to sales levels and/or therapeutic use;
- very low frequency of production (rare diseases);
- special pharmaceutical forms with their specific risks;
- applications for new or innovative products;
- new production process, major variations occurring during the life of a product or changes of specifications;
- new ingredient combinations;
- new formulations (ex: removal or changes of stabilising products);
- compounds with potential stability problems e.g. products with short shelf-life;
- possible harmful process-impurities;
- narrow therapeutic window (e.g. phenytoin);
- problematic bioavailability;
- biological standardisation of potency;
- complicated manufacturing process of the formulation;
- critical life-saving products (e.g. adrenaline)
- low dose or low concentration of API in the finished product.

### 1.3. Risks associated with target population

- specific or vulnerable populations suffering from severe diseases, that should not be exposed to other risks: neonates, children, aged people, cancer, HIV patients;
- products used for long-term treatment.

### 1.4. Regulatory environment, therapeutic protocol

- batch release performed by national authority or not;
- coordinated programme of market surveillance or not;
- new version of pharmacopoeia monographs concerning the product/raw material or active substance;
- pharmaceutical questions raised during the marketing authorisation process;
- new therapeutic indications with change in posology, route of administration (parenteral, ocular, pulmonary) and/or patient types;
- high dispensing level;
- high daily intake;
- ethnic medicines, e.g. TCM (Traditional Chinese Medicines);
- change and evolution of therapeutic protocols (new indications);
- complaints reported;
- market withdrawals.

### 1.5. Pharmacovigilance

- therapeutic class or product with frequent notifications;
- therapeutic class or product under survey.

### 1.6. Manufacturer-linked risk<sup>1</sup>

- specific issues related to a manufacturer (GMP issues and OMCL testing results);
- manufacturer not well-known by national authority;
- location of production site authority;
- new manufacturing site.

### 1.7. Specific public health plans

- specific screening of target products: biotox, piratox, cancer plan...

Screening of these specific risks does not necessarily require that all planned controls (indicated in the dossiers or monographs) should be performed. The most pertinent tests could be selected for the analytical test protocol. Risk management can be conceived as control campaigns targeted both on products to be sampled and/or testing parameters to be controlled.

### 1.8. Specific risk linked to veterinary products

The veterinarian domain generally takes inspiration from human medicine but has to take into consideration its specificity, as do the VICH versus ICH and CVMP versus CHMP.

Here are some examples that are to be considered when establishing a market surveillance programme for an OMCL in the veterinary field:

- Risk tied with target population: food producing animals are prioritised because of the problem of residues in food, and the possibility of inducing resistance in humans to some active substances (antibiotics, anti-parasitic substances etc.);

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<sup>1</sup> See also item 1.1.

- Risk for the users (vet, farmers etc.) in case of accidental injection, inhalation, skin contact...;
- Products used for mass/flock treatment;
- Products used in disease eradication campaigns;
- Products used for treatment of zoonotic disease (that can be passed between animals and humans);
- Vaccination of wildlife;
- Product which may pose a risk to the environment.

## **2. Sampling strategy**

The sampling should focus on the questions: what, where, when and how to sample and on known or suspected risks as listed above.

### **2.1. Products to be sampled**

Detailed information on the APIs and/or final products are needed and close co-operation with inspectorates, licensing assessors, including up-to-date information on variations, and other OMCLs etc. are necessary and invaluable for the pertinence of the programme of control.

### **2.2. Points of sampling**

Depending on the type of product and the type of risk to be anticipated, sampling can occur at any step of the production or distribution chain. For finished medicinal products, the further down the distribution chain the sampling is performed, the higher is the chance of detecting inadequate storage, handling or tampering (e.g. repackaging and relabelling of parallel imported / parallel distributed products).

### **2.3. Frequency and time of sampling**

This addresses on the one hand the frequency of the sampling and testing of a particular product, which should be in line with the risks defined under items 1. On the other hand this also addresses the aspect of stability: the nearer to the end of shelf-life of a particular batch, the higher the risk of a quality defect (either batch or generally product related).

## **3. Testing strategy**

The testing should focus on the questions how and what to test, and on the type of anticipated or suspected risk as listed above.

### **3.1. Testing method**

Testing can be performed according to the MAH's method or according to other methods. A survey of the product quality in a risk based approach may prompt the OMCL to make use of specifically defined methods/techniques including for example methods/techniques such as GC or HPLC coupled with MS or MS/MS, NIR or NMR. The use of Process Analytical Technology in pharmaceutical manufacturing may require the use of different analytical methods in the OMCL in comparison to the routine manufacturer's release test. In this context the methods used for stability studies might be appropriate.

Applying the MAH's method allows the OMCL to check the robustness of the method. Using other methods may also allow checking whether the MAH's method is capable of adequately describing the quality of the product.

### **3.2. Parameters to be tested**

Usually at least identity and assay are tested. Impurity testing might be justifiable for reasons related to the quality of the MA dossier. The selection of further parameters to be tested depends also on the dosage form. Further parameters with a higher risk may be identified from:

- the general chapter of the pharmacopoeia on dosage forms;
- market surveillance studies;
- the experience of the OMCL or reports from other OMCLs;
- the specifications of the product described in the product's dossier of the MAH.

### **Demands on OMCLs**

To set up a market surveillance programme using a risk based approach is a challenge for the OMCL. For some OMCLs this may introduce a new type of job i.e. to collect, structure and evaluate information. In order to obtain the necessary information, contacts with e.g. assessors and inspectors will be required. The risk based approach means that a risk evaluation must be made prior to the decision to perform testing and the decision is made based on the information available. Beside internal information it is also appropriate to cover available information on the evolution and development of regimentation, therapeutic monitoring and public health plans.