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Incorporation of a RB approach in MS testing at OMCLs

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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 and to stress the importance of involvement of the OMCLs in the market surveillance testing process. Different types of possible risks are listed in the document, and sampling and testing strategies are proposed. Moreover, alternative risk-based strategies to market surveillance testing approaches are discussed. 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. The HMA pre-authorisation risk assessment model has become compulsory as of 8 March 2020 for all new MRP and DCP product registrations.

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

Position Paper for OMCLs

1. 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. Further, it discusses some of the general pratices for the involvement of OMCLs in the planning of drawing samples from the market for the purpose of surveillance testing. It is intendend to be of use to OMCLs and their associated inspectors or other colleagues who are involved in designing surveillance programmes. OMCLs are encouraged to discuss the content of this paper with their colleagues, as cooperative work in this area is important given the knowledge of the OMCL and the OMCL Network.

2. Introduction

The legal requirements for the sampling and testing of medicinal products are laid down in Directives 2001/83 Art 111 (Human medicinal products), Title XI, Supervision and sanctions and Directive 2001/82 Art 80 (Veterinary medicinal products), Title VIII, Supervision and sanctions.
Post-marketing sampling and testing is part of the overall supervision of medicinal products and is complementary to other important areas e.g. pharmacovigilance and inspection of manufacturers. The objectives of the post-marketing sampling and testing programmes are derived from the legal requirements:

- to supervise the quality of medicinal products placed on the market;
- to check compliance of the medicinal product placed on the market with its authorised specifications.

3. Purpose of a risk-based approach in market surveillance testing

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

Such risk analysis would be based on findings at assessment of applications for marketing authorisation and variations, GMP inspections, pharmacovigilance activities, or findings in similar products. Selection criteria could include risks identified for active substance, patient profiles, poor stability of product, production process, pharmaceutical form and data from previous controls. Thus, close collaboration with inspectorates, licensing assessors and the OMCL, including up-to-date information on variations etc. are necessary and invaluable for a risk-based approach to market surveillance.

4. 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.

Since the OMCLs are performing the testing, it is desirable that the OMCL has a role in the national surveillance programming strategy. If the OMCL is not involved in the planning, a good collaboration with the decision makers should be pursued so that the OMCL can contribute with experience and knowledge about identified risks.

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.

5. Existing Guidance

Guidelines for risk management systems for medicinal products in the field of pharmacovigilance and Quality risk management (ICH Q9) were drawn up a number of 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.

6. Risk-based approach in OMCL market surveillance testing

6.1. General considerations

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 and animal 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.

6.2. Different types of risk

6.2.1. 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.

6.2.2. Risks coming from the final product

- pharmacological or chemical 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, multicomponent finished products.

6.2.3. 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.

6.2.4. 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.

6.2.5. Pharmacovigilance

- product with frequent notifications;
- product under survey.

6.2.6. Manufacturer-linked risk

- 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.

6.2.7. 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.

6.2.8. 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.);
- 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.

6.2.9. Specific risk defined by the OMCL link to the experience/technical knowledge

An OMCL may focus its market surveillance activities according to its specific knowledge of relevant risks. The identified risks may concern products (e.g. nationally manufactured products, new dosage forms), or, they may relate to information gained from interactions with local police/customs or other sources. The OMCL may have specific analytical techniques (in-house screening methods, expertise in specific areas or the necessary instrumentation - e.g. biosafety L3 laboratory, NMR, Next Generation Impactor,…) which may be useful in investigating those risks.

6.2.10. HMA risk model

Risk-based surveillance planning will (in the future) be facilitated by the Pre-marketing Risk-based Model for Medicinal Product Testing which has been developed by a HMA working group. Since 8 March 2020 this model has become operative, currently focusing on MRP and DCP products. In a next step, post-marketing risk factors will be implemented in the model. The HMA model will on the long run become compulsory also for CAP products and optional for nationally registered products.

6.3. Other risk-based strategies for market surveillance testing

There are other strategies for surveillance testing that the OMCL Network could consider. The currently used risk-based approaches mainly involve product-based risk assessments. These allow the prioritisation of individual products for post-marketing surveillance, and while this is useful, it is also somewhat limiting. This is because no risk assessment tool or approach can ever be an ideal solution for risk-based surveillance work, given the limitations and subjective / probabilistic nature of risk assessment.

As part of continuous improvement work, the Network is therefore working to develop multiple other approaches when designing risk-based surveillance programmes, so that the full breadth of product quality risks can be managed. These strategies will be reflected in a future revision of this paper.

7. Sampling strategy

7.1. General considerations

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

It should be noted that "sampling" addressed in this position paper in context with market surveillance testing activities in OMCLs is not understood in the strict sense as for instance defined in chapter 7.3 of ISO/IEC 17025:2017 or the WHO guidelines for sampling of pharmaceutical products and related materials, No. 929, 2005, in particular with respect to sampling operation (e.g randomised sampling, use of sampling tools etc.).

According to Directives 2001/83 Art 111 and 2001/82 inspections shall be carried out by officials representing the competent authority who shall be empowered to take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State.

The legal requirement may be further elaborated in national legislation. For example, that samples shall be provided free of charge and all information and materials including reference standards necessary for the control must be supplied to the national competent authority.

The responsibility for sampling may vary between member states. The responsibility can lie with the OMCL, inspectors or others. However, when sampling is performed for the purpose of testing by an OMCL, a close collaboration with the sampler should be pursued. According to ISO 17025, the laboratory shall retain records of sampling data that forms part of the testing or calibration that is undertaken. This includes information on date and time of sampling and environmental or transport conditions.

7.2. 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. The sample size will depend on the number of pharmaceutical dosage units needed per test procedure, and also possibly retest in case of OOS result.

7.3. 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, falsified products, handling or tampering (e.g. repackaging and relabelling of parallel traded products).
For the sampling of active pharmaceutical ingredients, please refer to PA/PH/OMCL (12) 51, *API surveillance – position paper for OMCLs*, in its current version.

7.4. 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). At the same time, the OMCL should be able to test the product within the shelf life of a particular batch.

When products are not requested from the MAH, it is advisable to have a voucher system in place to ensure rapid sample replacement and avoid challenges at the point of sampling. The vouchers should be signed by the MAH and exchanged at the point of sampling; the vouchers will then entitle to obtain from the manufacturer a quantity of product that corresponds to the units sampled.

8. 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.

8.1. 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.

8.2. 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.

9. 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.