Guidance on scientific principles for regulatory risk assessment of biotherapeutic products

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization. Publication of this early draft is to provide information about the proposed WHO guidance on scientific principles for Regulatory Risk Assessment of Biotherapeutic Products to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 30 January 2015 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

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This guidance document published by WHO is intended to be scientific and advisory in nature.
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1. Background and Scope

This document sets out scientific principles to be considered by national regulatory authorities (NRAs) and manufacturers in the process of licensing biotherapeutic products used in human medicine. It covers the regulatory expectations for innovative biotherapeutic products, and for so called copy products including similar biotherapeutic products (also call biosimilars) (see the section of Glossary). The document also considers the regulatory risk assessment needed for dealing with situations where, for various historical reasons, products were licensed using a pathway which did not follow globally agreed and relevant regulatory expectations for these biologicals as set out in this document and for which there may be concerns of safety and efficacy, e.g. biotherapeutic products licensed through a generic approach/pathway with little or no clinical data (1). The International Conference of Drug Regulatory Authorities (ICDRA) discussed such situations at its meeting in Singapore in 2010 (2) and requested the WHO to assist in developing approaches to evaluating these already licensed products according to WHO guidelines thus enabling them to remain on the market or for phasing them out in a reasonable period of time. More recently, the World Health Assembly adopted two resolutions, one on the critical needs in the biotherapeutics area, that is to promote access to these products as well as to ensure their quality, safety and efficacy (3), and the other on regulatory systems strengthening, where WHO is requested to provide guidance on strengthening regulatory systems, especially those dealing with increasingly complex biological products (4).

The scope of products covered by this WHO guidance note includes:

- All biologically active protein products used in the treatment of human diseases and which are prepared by rDNA technology;
- Protein product used for in vivo diagnosis, such as monoclonal antibody products used for imaging and products used for ex vivo treatment;
- Protein products intentionally modified by e.g. pegylation, conjugation with a cytotoxic drug or modification of rDNA sequences.

Although the document deals primarily with biotherapeutic protein products, some aspects are also relevant to polysaccharide based medicines, such as heparins.
2. Regulatory Expectations for Biotherapeutic Products

Special considerations apply to the production and control of biological medicines, including biotherapeutics, which do not apply to chemical drugs. This is because of the biological nature of the starting materials, the manufacturing processes and the test methods needed to characterize batches of the product. For example, production of many biotherapeutics involves the culture of cells and microorganisms. Others, such as heparins, are isolated directly from biological materials. Also, biologicals are highly complex products in molecular terms. Even with the great progress made in the ability to purify and characterize biologically active macromolecules with respect to their protein and post-translational components, such as lipid and oligosaccharides, it is still not possible to fully predict their biological properties and clinical performance from their physicochemical characteristics alone. Changes, such as deamidation, oxidation or N- and C-terminal differences, can also occur in the polypeptide chain. Details vary depending on the production process and may or may not affect clinical performance. Nonclinical and clinical evaluation are therefore key components of the regulatory assessment of all biotherapeutics.

Furthermore, biological systems are known to be inherently variable, a feature which has important consequences for the safety and efficacy of the resulting product (5). Although comprehensive analytical characterization of the drug substance and/or drug product is expected, considerable emphasis must also be given to the manufacturing process, including process validation and in-process control. Understanding the production process and monitoring consistency of production are, therefore, critical since even slight variations in the manufacturing process can impact the clinical safety and efficacy of the product and occasionally lead to major adverse effects, such as immunogenicity, with potentially serious safety implications. The demonstration that batches of product do not differ in clinically relevant quality attributes from those of lots shown to be safe and effective in clinical studies is a crucial component not only of product evaluation and licensing but also of ongoing regulatory oversight.

Regulatory expectations for biotherapeutic protein products can be found in the WHO Guidelines on the Quality, Safety and Efficacy of Biotherapeutic Protein Products Prepared by Recombinant DNA Technology which were adopted by the WHO Expert Committee on Biological Standardization (ECBS) at its meeting in October 2013 (2).
These extensive guidelines provide NRAs and manufacturers with guidance on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology and intended for use in humans. They are based on over three decades of experience in this technically demanding field and replace “WHO Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology” (6). They are the result of several reviews and consultations during the period 2012-2013 and are considered to be a replacement and not a revision of the original WHO guidelines. This is because they contain new sections on nonclinical and clinical evaluation of rDNA-derived protein biotherapeutics which were lacking in the original document. In addition, a section on issues related to manufacturing changes both during development and once the product is on the market also has been briefly introduced. WHO guidelines on evaluating the impact of manufacturing and other changes on marketed vaccines were adopted by the WHO ECBS at its meeting in October 2014 (7). The general principles set out in this document could also apply to biotherapeutic products.

3. Regulatory Expectations for Similar and Other Copy Biotherapeutic Products

Following considerable international consultations at the global level since 2004, WHO Guidelines on evaluation of similar biotherapeutic products were adopted by the WHO ECBS in 2009 (8). These emphasize the need for a head to head demonstration of the “similarity” of a copy biological product’s characteristics, with respect to both physicochemical, immunochemical and biological properties to a defined and already licensed reference product in order to justify a reduced non-clinical and clinical package for licensing a candidate product. This is expected to reduce overall development costs and time to marketing authorization. Only an originator product that was licensed on the basis of a full registration dossier can serve as a reference product, as defined in the WHO Guidelines (8). Critically, the head to head comparability exercise involves not only evaluation of quality attributes but also of non-clinical and clinical aspects with the same reference biological product throughout. Clinical studies should be designed so as to specifically demonstrate comparable safety, efficacy and immunogenicity between the products in sensitive
populations in order for the candidate product to be called a similar biotherapeutic product (SBP).

These WHO Guidelines are intended to provide a globally acceptable set of basic principles regarding the evaluation of similar biotherapeutics although it was recognized that, by themselves, they will not resolve all issues. Several countries or jurisdictions have now developed their own guidelines but there are some differences in detail between them. Furthermore, other regulatory pathways, such as a stand-alone approach based on a full registration dossier as described in the WHO Guidelines (5), may also be appropriate for licensing copy biologicals (9). However, it was reaffirmed at a WHO Consultation in Seoul (9, 10) in 2010 that only copy biotherapeutic products licensed on the basis of a full comparability package involving head to head comparative evaluation of quality, nonclinical and clinical aspects with one defined reference product should be called SBPs, i.e. biosimilars. It was suggested that copy products appropriately licensed by other pathways might be called “non-innovative biological products” (9) but this has not yet been universally accepted and several names are being considered. Nevertheless, there is full agreement that the approach to licensing small-molecule generic medicines, involving only product analysis and the demonstration of bioequivalence to a reference product, is not appropriate for the development, evaluation and authorization of copy biological products. As already mentioned above, clinical performance of biologicals is highly dependent on the manufacturing process and slight changes can lead to adverse clinical effects. Beside the comprehensive comparison at the quality level, appropriately designed clinical studies with sufficient statistical power are therefore essential to demonstrate the safety and efficacy of copy biological products since it is currently not possible to predict all aspects of the clinical performance from measurable and detectable physicochemical characteristics alone. Consistency of production is also critical since unintentional changes during production may impact product performance.

4. Regulatory Situation regarding Copy Products

As patents and data protection measures for innovative biotherapeutic products expire, or near expiration, there has been considerable interest in producing copies of these
highly successful medicinal products. Indeed, copies of biotherapeutic protein products have been produced in some developing countries even before patents had expired globally. For example, under trade-related aspects of the Intellectual Property Rights (TRIPS) Agreement of the World Trade Organization, the pre-1995 product patents did not apply in India and this left copies of many biological products that were patented before 1995 marketable in India. Moreover, due to regulatory gaps at the time, some copy biotherapeutic products may have been approved for marketing without undergoing adequate regulatory evaluation consistent with WHO Guidelines (5, 8). Furthermore, innovators have not sought patent protection for some drugs in India thereby creating an opportunity for Indian companies to influence the domestic market and to supply other countries where these products had not been patented (11). The emphasis of many Indian pharmaceutical manufacturers has been directed more toward the development of copies rather than original molecules because of much lower development costs including reduced time to market (12).

Much of the interest in this pharmaceutical area has been driven by the possibility that copy products would be more affordable than the innovative ones and thus potentially improve access to much needed biotherapeutic medicines globally. The major question that arose was how copies of the innovator products should be licensed, and whether there could be a reduction in the nonclinical and clinical package submitted, bearing in mind that these medicines are highly complex products, manufactured by equally complex and sophisticated processes, a situation compounded by the challenges of dealing with biological variability. It was recognized that copying biologicals would be much more complex than copying small molecules. Quite clearly some clinical data are required for licensing such copy biological products, and quite clearly too, a traditional generic pathway as used for small molecule drugs is not appropriate (1, 13). The concept of “similar but not necessarily identical biological products”, with a designated comparative regulatory pathway as described in the section 3, was developed by the WHO (8) and other countries, following the lead of the European Medicines Agency (14). Accordingly any new product referencing an innovator product and using the designation SBP (or equivalent) should be developed and licensed in accordance with the WHO standards (8). Copy products not meeting these criteria can be evaluated by other regulatory pathways,
such as a stand-alone approach based on a full registration dossier as described in the WHO Guidelines (5). These should not be referred to as SBPs.

5. Risk Assessment Considerations

A serious problem has been identified in some countries where, for historical reasons, biotherapeutic products have been licensed on data which did not meet present regulatory expectations as agreed on a global level regarding quality, nonclinical and clinical data (1). Sometimes, copy products have been licensed as simple generics. Often, little is known about the safety and efficacy of the individual products, since in many cases pharmacovigilance in the countries concerned is weak and sometimes non-existent. In addition, the nomenclature for these products is confusing and traceability poor (13, 15). In some countries, the coexistence on the market at the same time of copy products licensed inappropriately by a generic pathway, or without sufficient nonclinical and clinical data, and true biosimilars is a matter of concern. The lack of terminology for products developed as copy products with only partial or no comparability to a reference product has compounded the problem and led to a great diversity in evaluating as well as naming these products (10).

Slight differences between the biotherapeutic product of one manufacturer and that of another, or between an innovator and copy biotherapeutic product, could have unintentional effects on their clinical performance and safety and need to be handled carefully from a regulatory perspective. NRAs should undertake a regulatory risk assessment of biotherapeutic products already on the market but known to have been licensed with data which do not meet globally agreed and relevant regulatory expectations. A risk based approach to dealing with this problem would allow licensed biotherapeutic products to remain on the market for a specified period during which time manufacturers would be required to submit first a risk management plan for regulatory approval and subsequently appropriate quality, nonclinical and clinical data, as necessary, for regulatory evaluation to support the continuation of the license. This plan should consist of an analysis of available and missing data in accordance with WHO guidelines on SBPs (8) as well as a description of measures intended to fill the identified data gaps.
The timeline for completing such a review exercise would depend on the risk assessment of each individual product on the market (see the section of Points to Consider in a Stepwise Risk Based Assessment). Products from manufacturers who did not submit a risk management plan or appropriate data, or submitted data which were considered insufficient to support continued licensing, would be automatically removed from the market.

In adopting a risk based approach, product supply would not be compromised and authorization would be regularized after the defined time period when all products would have undergone further regulatory evaluation and found to meet internationally accepted standards of quality, safety and efficacy. Should a problem be identified with a particular product before the end of the specified time period, the implicated product’s license could be withdrawn immediately or the labelling modified as appropriate. A product claimed to be a SBP but failing to meet WHO Guidelines (8) could be given the opportunity to be re-submitted as a stand-alone product on the basis of a full registration dossier as described in the WHO rDNA Guidelines (5) or be withdrawn from the market in a period as defined by the local risk-based assessment.

In the third implementation workshop on WHO SBP guidelines held in Seoul in 2014, it was stated that some NRAs require manufacturers to submit reports to re-evaluate and continue regulatory approval 3-5 years following licensing (e.g. Brazil, Europe, Egypt, India, Indonesia, Iran, Japan, Korea, Peru, Russia, Singapore). Some of the considerations for a stepwise risk based assessment described below maybe helpful in such reviews.

Traceability is a key element in monitoring the performance of biotherapeutic products since some problems maybe product specific (e.g. product specific safety issues) and/or batch related. An adequate nomenclature system is essential to ensure specific identification. This should include all important indicators such as brand (proprietary) name, manufacturer’s name, country of origin and, critically, the lot number.

6. Points to Consider in a Stepwise Risk Based Assessment

A stepwise risk-benefit and prioritization assessment, based on product-specific considerations, should be carried out in order to decide the appropriate action and the time a particular inappropriately licensed product should be allowed to remain on the
market prior to finalization of the review. Initially, this will depend upon the time
needed to generate and provide the missing information, the risk associated with
removing the product from the market and the risk of keeping the product on the
market, and could be between say 6 months and 4 years. However, manufacturers
should first be required to submit a risk management plan to the NRA within a short
time period detailing their proposals for dealing with the situation including the
generation and provision of quality, non-clinical and clinical data as appropriate. An
example of a risk based plan for dealing with a particular regulatory situation can be
found in the actions of Health Canada. In 2009, Health Canada initiated a risk based
plan of action to deal with changes in the regulatory oversight of heparins to reflect
the fact that in future they would be regulated in Canada as biologicals (biologics) and
not pharmaceutical drugs. While both unfractionated heparins and low molecular
weight heparins are administratively controlled as drugs in some administrations, they
are essentially biologicals and the importance of their biological origin is increasingly
recognized by the global regulatory community. Health Canada set a 12 month
transition period to allow manufacturers to update their files to reflect data required
for biological drugs. Manufacturers were also required to identify immediately after
the official date of transfer of regulatory authority how much of their licensed product
was sold in Canada per year. In addition Health Canada announced that any biosimilar
heparin submissions should follow Health Canada’s regulatory framework for
subsequent entry biologics and not the generic pathway used for small molecule drugs
(16).

Consideration should be given to the following in deciding appropriate actions:

a) The number of products on the market which have been licensed using
inappropriate regulatory pathways and whether there are any therapeutic
alternatives on the market which have been licensed also by an experienced
NRA meeting the standards of the relevant WHO Guidelines (see b, below).

b) Whether the product in question is manufactured and licensed in a country
with a jurisdiction which has and follows well established regulatory
frameworks including all principles for SBPs according WHO (8), as well as
considerable experience in the evaluation of biotherapeutic products, SBPs,
and post marketing surveillance activities. If a product is manufactured and
licensed in such a country, then this provides confidence regarding its quality, safety and efficacy. However, it would be important to ascertain whether the actual product on the market in the country with limited regulatory experience is identical, including site of manufacture (process validation and in-process control), and conditions of use especially the labelling to that licensed, supplied and used in the manufacturing country with the more experienced jurisdiction;

c) The extent to which the registration dossier of the biotherapeutic product meets the recommendations of the WHO Guidelines on the Quality, Safety and Efficacy of Biotherapeutic Protein Products Prepared by Recombinant DNA Technology and the WHO Guidelines on evaluation of similar biotherapeutic products (5, 8). Attention should be paid to any important differences between national requirements and WHO Guidelines, such as mandatory requirement for viral validation and human immunogenicity studies and data needed to allow extrapolation of biosimilars to other indications (12). In this case, the NRA should recommend critical data set for re-registration of such products;

d) The level of actual use of the biotherapeutic product (market share or number of patients impacted);

e) Whether the product is essential for treating certain patients. This assessment should cover: What is the disease being treated?; Is the condition life-threatening?; What are the consequences of treating or not treating or stopping treatment in patients already under the product? What is the risk of switching between therapeutic alternatives?; What is the nature of the affected patient population (paediatric, adult, senior/elderly);

f) The likelihood and the potential consequences, if any, of supply problems on clinical outcomes should the product be taken off the market;

g) The seriousness of a potential lack of efficacy, as well as possible safety issues that may result from the continued use of the product under review. This should include an assessment of the severity of the potential impact on a patient of an immunogenic effect arising from the use of the product (e.g. 17);

h) The ability of the pharmacovigilance system in place in the country to monitor and determine adverse reactions and/or efficacy problems, such as reduced clinical effectiveness, associated with the biotherapeutic product, should they
exist. With poor pharmacovigilance systems in many countries, as well as
nomenclature difficulties, it may be impossible to obtain sufficient data to
demonstrate that a particular product was the cause of an adverse reaction or
that patients may be at risk from the use of clinically inadequate products.
Traceability is a key element in monitoring the safety performance of
biologics by enabling pharmacovigilance measures.

i) As already mentioned, the expertise and capacity of regulators responsible for
licensing biotherapeutic products is critically important for the appropriate
evaluation of these products. Capacity building will be needed where
resources and expertise is considered inadequate. Where the number and
experience of persons available to undertake an overall review is limited,
consideration could be given to the possible mentoring, through the WHO, of
the NRA needing support by an experienced authority that has established and
follows guidelines according to WHO SBP guidelines. Work sharing
agreements with other NRAs including joint reviews should also be explored.

j) Consideration should be given to transparency with respect to informing
healthcare professionals, pharmacists and patients of the review process and
its time lines. This could be done through website posting, as in Canada (16),
or via a symbol and some text in the product information and referring to the
need to align the licensing process with current international expectations.

7. Conclusions

Although discussions on how best to license copy biotherapeutics on the basis of a
reduced nonclinical and clinical data package continues, there is increasing alignment
between jurisdictions on key issues (see 18). Since the publication of the WHO
*Guidelines on evaluation of similar biotherapeutic products* (8), several activities
such as implementation workshops (10), development of case studies (19-21), and
other publications (18) have been undertaken by the WHO at both global and regional
levels. It has become clear that much investment in the development of biosimilar and
copy biotherapeutic products is taking place worldwide, including in countries with
emerging economies. It is also becoming clear that the regulatory agencies of many
countries need to be strengthened with respect to their regulatory oversight of
biotherapeutic products in general and biosimilars and copy products in particular.
The expertise and continuous training of regulators responsible for licensing is
critically important for the appropriate evaluation of these sophisticated products
which should be understood to be biologicals and which may include proteins,
polysaccharides and DNA molecules. These issues are reflected in the already
mentioned World Health Assembly resolution in 2014 which calls for the
strengthening of national regulatory authorities with respect to regulating increasingly
complex biological products (4). Regional initiatives to improve the awareness of
countries concerning these issues are already well underway in some areas, for
example in PAHO (22, 23), but needs may differ from region to region. It is expected
that this guidance document will contribute to these initiatives.
8. Glossary (alphabetical order)

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts.

**Biological medicine**
A medicinal product used in the treatment, prevention or diagnosis of disease, the production of which involves biological starting materials and manufacturing processes, as well as the use of biological test methods to characterize the product. It includes rDNA-derived medicines. In addition, biologicals are highly complex products in molecular terms and their clinical performance cannot be fully defined by physicochemical means alone. In some countries, biologicals are defined in regulations as vaccines, biotherapeutics, blood and blood products, genetic therapy products, cells, tissues and organs.

**Biotherapeutic product**
A biological medicinal product used in treating human diseases.

**Comparability exercise**
In the case of changes to an already licensed product, the activities – including study design, conduct of studies, and evaluation of data – that are designed to investigate whether a pre-change product and a post-change product are highly similar. In the case of a similar biotherapeutic product, the activities designed to compare the quality, safety and efficacy of a candidate biosimilar with the properties of a reference biotherapeutic product (RBP).

**Copy product**
A copy version of a previously licensed originator or innovative medicinal product. A copy biotherapeutic product may be licensed through a biosimilar regulatory pathway or as a stand-alone product on the basis of a full registration dossier.

**Generic pathway**
A regulatory pathway established for small molecule and chemically derived medicines. A generic medicine contains the same active pharmaceutical ingredient as, and is bioequivalent to, an originator (comparator) medicine. Since generic medicines are identical in the active pharmaceutical substance, dose, strength, route of administration, safety, efficacy and intended use, they can be substituted for the originator product. Biological products cannot be licensed through this pathway nor called ‘generic biologicals’ or ‘biogenerics’.

**Head-to-head comparison**
Direct comparison of the properties of the similar biotherapeutic product with the reference biotherapeutic product in the same study.

**Noninnovative product**
A copy biological medicinal product developed on its own and licensed through a stand-alone regulatory pathway possibly designed for abbreviated application, and not directly compared and analysed in a head to head comparability study of quality,
safety and efficacy against a licensed reference product. It may or may not have been
compared clinically, however, extrapolation of clinical indications is not acceptable in
any case, since quality or clinical comparison alone is not sensitive enough to justify
differences of potential relevance (13).

**Originator product/innovator product**
A medicine that has been licensed by a national regulatory authority on the basis of a
full registration dossier; i.e. the approved indication(s) for use were granted on the
basis of full quality, efficacy and safety data.

**rDNA-derived biotherapeutics**
Biotherapeutics prepared by recombinant DNA technology and developed as
described in the WHO Guidelines (5), i.e. all biologically active protein products
which are used in the treatment of human diseases and which are prepared by rDNA
technology.

**Reference biotherapeutic product (RBP)**
A reference biotherapeutic product is used as the comparator for head-to-head
comparability studies with the similar biotherapeutic product in order to show
similarity in terms of quality, safety and efficacy. Only an originator product that was
licensed on the basis of a full registration dossier can serve as an RBP. The selection
of the RBP is usually made at the national level by the national regulatory authority.
The term does not refer to measurement standards such as international,
pharmacopoeial or national reference standards.

**Recombinant DNA technology**
Technology that joins together (i.e. recombines) and possibly alters the sequence of
DNA segments from two or more different DNA molecules that are inserted into a
host organism to produce new genetic combinations. It is also referred to as gene
manipulation or genetic engineering because the original gene is artificially altered
and changed. These new genes, when inserted into the expression system, form the
basis for the production of rDNA-derived protein(s).

**Regulatory risk evaluation**
A systematic approach to evaluating information to support a benefit-risk decision
within a regulatory review and evaluation framework. It consists of an independent
evaluation of the risk assessment performed by the manufacturer, taking into
consideration all relevant and available information and data.

**Risk**
The combination of the probability of occurrence of harm and the severity of that
harm. In the context of pharmaceutical quality it is the probability and severity of any
kind of negative impact (hazard) on the quality of the product which may impact its
clinical performance.

**Risk assessment**
A systematic process of organizing information to support a risk decision to be made
within a risk management process. It consists of the identification of hazards and the
analysis and evaluation of risks associated with exposure to those hazards.
Risk evaluation
The comparison of the estimated risk to given risk criteria, using a quantitative or qualitative scale to determine the significance of the risk.

Risk management
A systematic approach to the assessment, control, communication and review of risks. Risk management in the context of pharmaceutical quality is often referred to as quality risk management – a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product across the product’s life cycle. A model for quality risk management is outlined in the WHO (24) and International Conference on Harmonisation guidelines (25).

Risk management plan
A detailed description of the activities that continuously ensure patients’ safety and their benefit from a medicinal ingredient. A risk management plan includes pharmacovigilance and many other elements.

Risk reduction strategy
A plan or method for decreasing the probability of occurrence of harm and/or the severity of that harm.

Similar biotherapeutic product (SBP)
Biotherapeutic product identified by its similarity in all characteristics to a chosen reference product in terms of quality, safety and efficacy demonstrated through a head-to-head comparability exercise, as described in the WHO Guidelines (8). It is licensed through a specific regulatory pathway. Any differences between biosimilar candidate and its reference product should be shown to be of no clinical relevance, and extrapolation of clinical indications may only be acceptable if scientifically justified. A similar biotherapeutic product is also called a ‘biosimilar’ and in some countries, a ‘subsequent entry biologic’.

Stepwise risk based assessment
A stepwise approach to the risk-benefit assessment based on product-specific considerations. It should start with initial assessment, addressing the question whether the risks of a product clearly outweigh the benefits or vice versa. Depending on a risk management plan submitted by manufacturers, the risk associated with removing the product from the market and the risk of keeping the product on the market can be estimated. Then it continues to decide the appropriate action and the time needed to generate and provide the missing information.
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