Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)

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 (ECBS). Publication of this early draft is to provide information about the proposed Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) 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 5 April 2016 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 Kai Gao at email: gaok@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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1. Introduction

Monoclonal antibodies (mAbs) are a major class of recombinant deoxyribonucleic acid (rDNA) technology derived biotherapeutic products and as such have achieved outstanding success in treating many life-threatening and chronic diseases. Some of these targeted therapy products are ranked in the top ten lists of annual global pharmaceutical revenue successes. As patents and data protection measures on monoclonal antibody products have expired, or are nearing expiry, considerable attention has turned towards producing copies of the monoclonal antibody innovator products with a view to making more affordable products that may improve global access to these so called block buster products.

Structurally, monoclonal antibodies are highly complex biological macromolecules with size and charge variants, various post translational modifications, including different glycosylation patterns, N and C terminal heterogeneity, long half-lives and the potential for inducing immunogenicity. In addition, and importantly, they have several possible functional domains within a single molecule, depending on such as the antigen-binding region, the complement – binding region and the constant part interacting with Fc receptors. Each individual monoclonal antibody may therefore present a unique profile, a characteristic which needs to be taken into consideration during the evaluation of these products as biosimilars. Therefore, comparability studies of candidate biosimilar monoclonal antibodies and a biological reference product monoclonal antibody are quite demanding and challenging for developers of these products as well as for regulators.

WHO guidelines on evaluation of similar biotherapeutic products (SBPs) were adopted by the Expert Committee on Biological Standardization (ECBS) in 2009 (1). This document provided a set of globally acceptable principles regarding the regulatory evaluation of SBPs and served well as a basis for setting national requirements for SBPs in general. However, in 2014 WHO was requested to update these SBPs guidelines to take account of technological advances in the characterization of rDNA derived products. In response, WHO organized an informal consultation on the possible amendment of the 2009 SBP guidelines with an additional focus on similar biotherapeutic products containing monoclonal antibodies in 2015. The outcome of these discussions was that there was no need to revise the main body of the existing WHO SBPs guideline. All participants, including national regulatory agencies and industry, recognized and agreed that the evaluation principles described in WHO SBP guidelines are still relevant and applicable. However, it was also agreed that there was a need for additional guidance for the evaluation of biosimilar mAbs.

2. Aim

This product specific document is intended to provide special considerations for the evaluation of monoclonal antibodies developed as similar biotherapeutic products and to complement the
existing WHO Guidelines. This document should therefore be read in conjunction with the existing guidelines on biotherapeutics published by the WHO(1,2). Guidance on various aspects of rDNA-derived medicines, SBPs and mAbs are also available from several other bodies. These WHO Guidelines are not intended to conflict with, but rather to complement existing documents. It takes the form of WHO guidelines rather than recommendations since mAbs represent a heterogeneous class of products and the quality attributes of mAbs can vary from product to product. Furthermore, one mAb product may have multiple indications, therefore comparability study design of mAb SBPs will need to be adapted to suit the product in question, and follow case by case manner.

3. Scope
The scope of products covered by this WHO guidance includes all biologically active mAbs products used in the treatment of human diseases and which are prepared by rDNA technology.

4. Special considerations for characterization and quality assessment
Monoclonal antibodies for therapeutic use are preparations of an immunoglobulin or a fragment of an immunoglobulin with specificity for a target ligand and derived from a single clone of cells. Each molecule of monoclonal consists of two heavy and two light polypeptide chains which linked by di-sulfide bonds and form a Y-shaped protein molecule. The defined specificity of a monoclonal antibody is based on the binding region for an antigen that is located in the Fab part of the molecule. Within their Fc-region they have the ability to bind to specific receptors leading to immune effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), etc. Monoclonal antibodies are glycoproteins with glycosylation sites in the Fc-portion of the heavy chains, with further glycosylation sites possible dependant on the molecule.

From a regulatory perspective, mAb production and quality assessment is based on the same principles as used for the evaluation of other rDNA-derived biotherapeutic proteins. Therefore, the ‘WHO Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology’ (1) clearly apply applies to mAb SBPs. Biosimilar mAb products should also comply with WHO ‘Guidelines on evaluation of similar biotherapeutic products (SBPs)’ (2). A stepwise approach to the evaluation of mAb products in comparison with a reference biological product is indicated, comprising first of a thorough head to head comparability assessment of quality attributes, followed by head to head comparative nonclinical and clinical assessment. The demonstration of biosimilarity of a candidate biosimilar mAb product with respect to the RBP in terms of quality is a pre-requisite for moving forward into comparative nonclinical and clinical studies.

Although general principles for quality assessment of biosimilar mAbs are already described in existing WHO rDNA and SBP Guidelines (1,2), characterization of the biological activity of mAbs is not considered in detail. However, mAb products are complex and variable
glycoproteins which have diverse and variable effector functions. This implies that potency
assessment for mAb biosimilars is particularly important and has some unique characteristics.
Also, the expression system used for production of mAbs can, in some cases, considerably affect
the structure of the mAb product. Therefore, the quality part of this document will focus on
specific considerations for assessment of mAb potency and on the impact of expression system
selected for production.

4.1 Strategy for mAb biological activity assessment

Potency/biological activity of mAb products is an important parameter and needs to be measured
appropriately by in vitro, in vivo, biochemical (including immunochemical assays) and/or
physicochemical assays as appropriate. Since changes of higher-order structure in a mAb could
alter its bioactivity, the analysis of bioactivity is very useful as a means of evaluating the
comparability of higher-order structure.

An understanding of the mode of action of the mAb is important for considering the strategy for
biological activity assessment both in the characterization and the comparability study. MAbs
exert their action by various mechanisms ranging from simple binding to antigen, which alone
mediates the clinical effect, to binding antigen and mediating one or more immunobiological
mechanisms which combine to produce the overall clinical response. These immunobiological
properties may play a role in the mechanism of action and/or have an impact on product safety
and efficacy. Therefore, a detailed analysis of the biological activity of the mAb, demonstrating
the mechanism of action (e.g. ligand neutralization, ADCC, CDC, apoptosis), ability for binding
to Fc gamma and neonatal Fc receptors, as well as complement binding– should be provided as
appropriate. For example, Rituximab which is a chimeric mAb specific for CD20 requires Fc
function and especially ADCC for its clinical efficacy in all its clinical indications. Assessment
of Fc function (including ADCC) is therefore paramount for this mAb and biosimilar candidate
products should have comparable ADCC to the reference product. However Infliximab (a tumor
necrosis factor alfa (TNF alfa) antagonist) seems not to require Fc function for its clinical
efficacy in rheumatoid arthritis and psoriasis although this may be needed for effective treatment
of Crohn’s disease and inflammatory bowel disease (IBD).

Assays for measuring Fc function can be technically demanding. For example ADCC assays
require appropriately responsive target and efficient effector cells and identifying or producing
these can be difficult and arduous. The use of continuously growing cell lines may overcome this
is some cases. It is often necessary to engineer cells to obtain appropriate responses. Different
data may be generated with different assay formats and different cells/cell combinations.

If it can be shown that binding alone is the major mode of action of the mAb and
immunobiological activities are consistent, ligand binding assays may be used as a surrogate for
potency estimation for mAbs (for routine control) rather than classic bioassays. In some cases these non-cell based potency assays may show technical advantages compared to cell-based assays.

Although simple binding may seem to be the only mechanism operating to achieve clinical efficacy, other effects may also play a role in this. In some cases multiple functions of the mAb may be involved in an additive or synergistic manner to produce an overall combined clinical effect and this may be hard to dissect experimentally to allow a clear understanding of how the mAb mediates its clinical potency. Therefore, if intact mAbs are used, care must be taken not to assume that the Fc mediated immunobiological effects of the product are not involved in clinical efficacy, even when simple antigen binding is considered to be the primary mode of action. In this regard, use of a properly design cell based assay for measuring potency has an advantage.

4.2 Consideration of production cell line changes and resultant glycoform differences

The WHO SBP guideline allows for the use of different expression systems for production of the biosimilar and the reference product, if the manufacturer can demonstrate convincingly that the structure of the molecule is not affected or that the clinical profile of the product will not change. However, the use of a different host cell type may not be advisable for biosimilar glycoproteins because glycosylation patterns can vary significantly between different host cell types. Although mAbs are not highly glycosylated products, their molecular complexity and the importance of some post translational modifications requires as close as possible production processes (including the cells used to produce product) for the biosimilar and reference product to achieve acceptable biosimilarity. For instance, fucose bound by a α1-6 linkage to the trimannosyl core portion of N-linked carbohydrate chains or a non-reduced terminal galactose regulates the cytotoxic activity of antibodies. Therefore, the similarity of carbohydrate chains should be examined and compared for then SBP and reference biotherapeutic product (RBP). Also, it is useful to assess the relationship between the carbohydrate chain structures of mAbs (SBP and RBP) and their pharmacokinetics as glycosylation is known to potentially affect this.

In view of the above, the use of different cell lines can result in differences in glycoforms present on products, which may or not have clinical consequences. For example, production cells based on mouse cell lines, such as SP2/0 and NS0 secrete mAbs with the carbohydrate structure gal-alpha-1, 3-gal present on the carbohydrate moiety. Humans cannot produce the gal-alpha-1, 3-gal structure as they lack the necessary enzyme for its synthesis; however many humans produce antibodies against this. In a proportion of these individuals the antibodies are of the IgE class and this sensitization can result in anaphylactic reactions (often serious) if they are treated with mouse cell line derived, gal-alpha-1, 3-gal containing mAbs. This pre-existing antibody problem has been particularly evident for the mAb product Erbitux (Cetuximab; anti epidermal growth factor receptor receptor (EGFR)). The problem can be avoided by using human or some clones of Chinese hamster ovary (CHO) cells for production of mAb products as these cells cannot
synthesize the gal-alpha-1, 3-gal antigen. However this type of phenomenon can have important implications for biosimilar mAb development. For example, producing a copy of Erbitux in mouse cells could result in a biosimilar, but this would probably show the same gal-alpha-1, 3-gal related anaphylaxis problems as the reference product. However production of the mAb in CHO cells may avoid the anaphylaxis problem, as the gal-alpha-1, 3-gal structure would not be present on the mAb, but the differences in glycosylation, and possibly other post-translational modifications may disqualify the new mAb as a biosimilar, even though it has advantages over the Erbitux reference product.

Therefore choice of expression system for biosimilar mAbs needs careful consideration as various potential issues need to be assessed. Development of mAb products as biosimilars rather than as stand-alone products also needs thoughtful assessment, including a consideration of the clinical effects (beneficial and adverse) of the potential reference product(s).

4.3 Standards
International standards and reference preparations have been established for a wide range of biological substances prepared by rDNA technology. These standards and materials are used either to calibrate assays directly or to calibrate secondary standards or manufacturers’ working standards. A list of such materials is available on the WHO website. Each standard or reference preparation is held by one of the WHO custodian laboratories (e.g. the National Institute for Biological Standards and Control, Potters Bar, England).
Biological assays used to assess the biological activity of mAbs should be validated and traced to WHO IS or WHO reference reagents when available. The different uses of Reference Products and International Standards in biosimilar product development and evaluation are described elsewhere.

5. Special considerations for nonclinical evaluation of monoclonal antibodies
As regards nonclinical development, as for all SBPs, a step-wise approach should be applied to evaluate the similarity of biosimilar and reference mAb. Nonclinical studies should be performed before initiating clinical trials. In vitro studies should be conducted first and a decision then made as to the extent of what, if any, in vivo work will be required.
The following approach may be considered and should be tailored to the similar biotherapeutic product concerned on a case-by-case basis, also need to be fully justified in the nonclinical overview.

5.1 In vitro studies
SBP - general aspects
In order to assess any difference in biological activity between the similar and the reference biotherapeutic product, data from a number of in vitro studies, some of which may already be available from quality-related assays, should be provided.

As for all SBPs, the following general principles apply to similar biotherapeutic mAbs:

- The studies should be comparative in nature and should not just assess the response per se. To obtain unambiguous results, the methods used should be scientifically valid and suitable for their purpose. The studies should be sensitive, specific and sufficiently discriminatory to provide evidence that observed differences in quality attributes are clinically not relevant.
- Functional studies should be designed to be sensitive enough to detect differences in the concentration–activity relationship between the SBP and the RBP.
- They should be performed with an appropriate number of batches of the reference product and of the similar biotherapeutic product representative of the material intended for clinical use. Assay and batch-to-batch variability will affect the number needed. The number tested should be sufficient to draw meaningful conclusions on the variability of a given parameter for both the similar biotherapeutic and the reference product and on the similarity of both products.
- Together, these assays should cover the whole spectrum of pharmacological/toxicological aspects known to be of clinical relevance for the reference product and for the product class.
- The manufacture should discuss to what degree the in vitro assays used are representative/predictive for the clinical situation according to current scientific knowledge.

Since in vitro assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, these assays can be considered as paramount for the nonclinical biosimilar comparability exercise.

**Similar biotherapeutic mAbs - specific aspects**

For similar biotherapeutic mAbs, the nonclinical in vitro program should usually include relevant assays for the following specific topics:

- **Binding studies:**
  - binding to target antigen(s);
  - binding to representative isoforms of the relevant three Fc gamma receptors (FcγRI, FcγRII and FcγRIII), FcRn and complement (C1q);

- **Functional studies/Biological Activities:**
  - Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation or blockade);
  - Fc-associated functions (e.g. antibody-dependent cell-mediated cytotoxicity, ADCC; complement-dependent cytotoxicity, CDC; complement activation);

Together these assays should broadly cover the functional aspects of the mAb even though some may not be considered essential for the therapeutic mode of action. However, an evaluation of ADCC and CDC is generally not needed for mAbs directed against non-membrane bound targets.

**Additional notes**
As indicated in the ICH S6 (R1) guideline\(^{(4)}\), tissue cross-reactivity studies with mAbs are not suitable to detect subtle changes in critical quality attributes and are thus not recommended for assessing comparability.

As for all SBPs, if the comparability exercise using the above strategy indicates that the test mAb and the reference mAb cannot be considered biosimilar, it may be more appropriate to consider developing the product as a stand-alone.

### 5.2 In vivo studies

**Determination of the need for in vivo studies**

- As for SBPs in general, based on the totality of quality and nonclinical in vitro data available and on the extent to which there is residual uncertainty about the similarity of the proposed biotherapeutic mAb and the reference mAb, it is at the discretion of the National Regulatory Authorities (NRAs) to waive/not to waive the request for nonclinical in vivo studies. If the quality comparability exercise and the nonclinical in vitro studies are considered satisfactory and no issues are identified which would block direct entrance into humans, an in vivo animal study may not be considered necessary.

- However, some mAbs may mediate effects that cannot be fully elucidated by in vitro studies. Therefore, in such cases nonclinical in vivo studies may be necessary to provide complementary information.

**General aspects to be considered for all SBPs including similar biotherapeutic mAbs**

- If there is a need for additional in vivo information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered.

- If a relevant in vivo animal model is not available the manufacture may choose to proceed to human studies taking into account principles to mitigate any potential risk.

- Factors to be considered when the need for additional in vivo nonclinical studies is evaluated, include but are not restricted to:
  - presence of potentially relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures);
  - presence of potentially relevant quantitative differences in quality attributes between the similar biotherapeutic product and the reference product;
  - relevant differences in formulation, e.g. use of excipients not widely used for mAbs. Although each of the factors mentioned here do not necessarily warrant in vivo testing, these issues should be considered together to assess the level of concern and whether there is a need for in vivo testing.

- If product-inherent factors that impact PK and/or bio-distribution, like extensive glycosylation, cannot sufficiently be characterized on a quality and in vitro level, in vivo studies may be
necessary. The manufacture should then carefully consider if these should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers.

Performance of in vivo studies
The following explanations apply to all SBPs, including similar biotherapeutic mAbs.

General aspects
If an in vivo evaluation is deemed necessary, the focus of the study/studies (Pharmacokinetic, PK and/or Pharmacodynamics, PD and/or safety) depends on the need for additional information.

Animal studies should be designed to maximize the information obtained. The duration of the study (including observation period) should be justified, taking into consideration the PK behaviour of the reference mAb and its clinical use.

Effects of SBPs are often species-specific. In accordance with ICH S6(R1) and WHO “Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (2,4) , in vivo studies should only be performed in relevant species, i.e. (a) species which is/are pharmacologically and/or toxicologically responsive to the SBP.

PK and/or PD studies
When the model allows, the PK and PD of the SBP and the RBP should be quantitatively compared, including, if feasible, a dose-response assessment including the intended exposure in humans.

In vivo assays may include the use of animal models of disease to evaluate functional effects on PD markers or efficacy measures.

Safety studies
For safety studies a flexible approach should be considered, in particular if non-human primates are the only relevant species. The conduct of standard repeated dose toxicity studies in non-human primates is usually not recommended. If appropriately justified, a repeated dose toxicity study with refined design (e.g. using just one dose level of biosimilar and reference product and/or just one gender and/or no recovery animals) and/or an in-life evaluation of safety parameters (such as clinical signs, body weight and vital functions) may be considered. Depending on the endpoints needed, it may not be necessary to sacrifice the animals at the end of the study.

For repeated dose-toxicity studies where only one dose is evaluated, this would usually be selected at the high end of the dosing range and should be justified on the basis of the expected toxicity of the RBP.
The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended. Due to the different production processes used by the biosimilar and reference product manufacturers, qualitative differences of process related impurities will occur (e.g. host cell proteins). Such impurity level should be kept to a minimum to minimize any associated risk.

**Immunogenicity studies**

Qualitative or quantitative difference(s) of product-related variants (e.g. glycosylation patterns, charge variants) may have an effect on immunogenic potential and potential to cause hypersensitivity. In general, these effects are difficult to predict from animal studies and should be further assessed in clinical studies.

However, while immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for PK/toxicokinetics (TK) interpretation of in vivo animal studies. Therefore, adequate blood samples should be taken and stored for future evaluations if then needed.

**Local tolerance studies**

Studies on local tolerance are usually not required. If excipients are introduced for which there is no or little experience with the intended clinical route, local tolerance may need to be evaluated. If other in vivo studies are performed, evaluation of local tolerance may be part of the design of that study instead of the performance of separate local tolerance studies.

**Other studies**

Studies regarding safety pharmacology and reproduction toxicology are usually not required for nonclinical testing of SBPs.

In accordance with ICH S6 (R1) and WHO “Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology” (2,4), genotoxicity and (rodent) cancerogenicity studies are not required for (similar) biotherapeutic products.

### 6. Special considerations for clinical evaluation of monoclonal antibodies

#### 6.1 PK

**6.1.1 Aim of comparative PK studies**

Comparative PK studies should be used to further confirm the comparability of mAb SBPs that is established through comparative structural, functional and nonclinical studies. For instance, a mAb SBP may differ in its affinity for FcRn receptors from its RBP which may lead to could have a shorter or longer half-life. As a consequence of shorter half-life, drug exposure would be reduced which may lead to a lower of efficacy (5). Comparative PK studies may also be useful in
monitoring the impact of anti-drug antibody formation, and establishing evidence in support of indication extrapolation. It is not necessary to study the mAb SBP in every indication that is being sought. However, separate comparative PK studies may be required to bridge multiple distinct conditions that have been authorized for the reference mAb. The number of studies required depends both on the degree of similarity between the mAb SBP and the reference (ascertained from the data of chemical and manufacture control (CMC)) and on the indications for which the mAb SBP is proposed. The design of the comparative PK studies depends on various factors, including clinical context, safety profiles, and PK characteristics of the reference (target-mediated disposition, linear or non-linear PK, time-dependency, half-life, etc.).

6.1.2 Study design and population

A single-dose PK study in healthy volunteers is generally recommended, as it can be considered as a sensitive and homogenous population (6). A parallel group design is usually required for mAbs since a single-dose cross-over design is rarely appropriate due to the long half-lives of mAbs and the potential influence of immunogenicity on the PK profile. Regarding the use of healthy volunteers to study the PK of mAbs, there are some key considerations that should be taken into account. First, healthy subjects may exhibit a greater immunogenic response than a population with disease due to less target-mediated clearance and lack of concomitant medication, or background standard of care (e.g. immunosuppressive therapies) and other population factors (7).

Second, healthy subjects may not be appropriate if the disease relevant to the indication, or its treatment, is known to alter the PK of the reference product. For instance, receptor density, concomitant use of other therapeutic agents, disease type, degree of systemic inflammation, FcγR polymorphisms, the maximum concentration achieved in relation to antigenic mass are some of the situations where healthy subjects would not be appropriate. Third, a clinically relevant dose of anti-cancer mAb may not be considered as ethical in healthy volunteers due to safety concerns. Thus, a lower therapeutic dose or a dose below the therapeutic dose may be required.

It may be necessary to perform the PK study for mAb SBPs in a sensitive patient population rather than in healthy volunteers, if the likely risk/benefit ratio would be unfavorable in healthy volunteers as in the case of Rituximab. Unnecessary exposure to risk (safety, medical reasons) would be viewed as unethical. It is preferable that the chosen patient population be different from that selected to demonstrate the absence of clinically meaningful differences in safety and efficacy.

The choice of a particular population for PK analysis also depends on the range of therapeutic indications of the mAb under development. For example, if a reference mAb is authorized both as an anti-inflammatory agent and as an anticancer antibody (e.g. as with Rituximab) PK data in one therapeutic area may complement clinical data obtained in the other therapeutic area and thus can also strengthen the evidence for indication extrapolation. In addition, the most sensitive
population in whom PK characteristics is compared may not be the same as the population chosen for comparison of efficacy. To aid in selecting a sensitive study population, patient characteristics, such as the level of antigen/receptor and severity of disease, should be considered. Factors such as these may have an impact on the assessment of PK comparability.

### 6.1.3 Regimen

MAbs are often indicated for both monotherapy and as a part of combination regimens that incorporate immune-suppressants or chemotherapeutics. It may be sensible to study the comparative PK in the monotherapy setting in order to minimize the sources for variability.

### 6.1.4 PK characteristics of the reference mAb

The PK of the mAb may be affected by factors such as the antigen/receptor level (e.g. related to tumor burden in oncology), the existence of target-mediated clearance and/or receptor shedding. These factors may be indication specific and should be considered when selecting the dosage regimen and the population in whom to compare the PK of the SBP to the reference.

### 6.1.5 Doses

A dose should be selected that will enable the detection of potential PK differences between the mAb SBP and the reference mAb. MAbs generally possess a high degree of target selectivity, with many exhibiting nonlinear distribution and elimination, influenced by binding to their target. In general, it is recommended that the PK be compared using the lowest recommended therapeutic dose. For mAbs that are eliminated by target-mediated disposition, a low dose (i.e. one at which target-mediated disposition (TMD) is not saturated) may be particularly useful to detect differences in PK (8).

### 6.1.6 Routes of administration

Administration via a route that requires an absorption step is preferred. Where the route of administration requires an absorption step, such as the subcutaneous route (SC), standard comparisons of C\text{max} and AUCT may be used to assess PK comparability. It is also expected that the SC route is more immunogenic than the intravenous route (IV), which makes the SC route more appropriate for the investigation of potential immunogenic differences between the mAb SBP and the reference. However, many mAbs are only administered via IV injection or infusion, which may necessitate a more comprehensive comparative assessment of PK parameters that reflect clearance including half-life (t\text{1/2}), volume of distribution (Vd), clearance (CL) and the elimination rate constant (Kel).

If the application is envisaged with the use of auto-injector, it would be necessary to provide clinical data on that (e.g. third arm in the clinical study).
6.1.7 Sampling times

Primary PK comparability studies should include sufficient sampling to accurately characterize $C_{\text{max}}$ and should adequately characterize the late elimination phase such that the terminal disposition rate constant can be reliably estimated. In single-dose studies, optimal sampling should continue past the expected last quantifiable concentration (AUCT), and the concentration-time curve should cover at least 80% of AUC$_{0-\text{inf}}$.

In a multiple dose study, the primary parameters should be the truncated AUC after the first administration until the second administration (AUC$_{0,t}$) and AUC over a dosage interval at steady state. The proposed duration of the study typically corresponds to 5 half-lives of the mAb.

6.1.8 Specific assays for serum drug concentration

It is preferable to have a single, validated bio-analytical assay to detect both the mAb SBP and the reference mAb. The bio-analytical assay should be appropriate for the detection and quantification of mAbs and should be demonstrated to be bio-analytically comparable with respect to its ability to precisely and accurately quantify both the mAb SBP and the reference (9).

6.1.9 Parameters in PK

The PK endpoints necessary to demonstrate PK comparability may differ depending on the route of administration and the study design. In general, single-dose studies with an absorption step should compare AUC$_{t}$ and $C_{\text{max}}$ between the mAb SBP and the reference mAb. If a multiple dose study is performed in patients, sampling at first dose and at steady state should be performed. PK parameters that should be evaluated include AUC, $C_{\text{max}}$, and $C_{\text{trough}}$, clearance and half-life.

For mAbs that are administered only intravenously, the aforementioned parameters should be compared as well as parameters that reflect the clearance of the product.

Anti-drug antibodies (ADA) should be measured in parallel of PK assessment using the most appropriate sampling time points and a subgroup analysis by ADA status should be performed. If ADA is measured, characterization (neutralizing capacity) over time should be determined since this may add valuable information on observed PK parameters. The PK analysis on the ADA negative samples is of particular interest, providing the clearest picture on PK similarity.

6.2 PD

The overall objective of the development program is to establish comparability. Therefore, the selection of the primary patient population is driven by the need for homogeneity and sensitivity.

6.2.1 PD markers and PD assay

The effect of the mAb SBP/reference on exploratory PD markers (biomarkers) may be included as additional support for comparability. Formal inferential analysis is not recommended since reliable PD markers (i.e. those that are predictive of clinical outcomes) have not been identified
for most mAbs. If PD markers are considered relevant, manufacturers should pay attention to the following factors (6):

- sensitive enough to detect relevant differences, and if they can be measured with sufficient precision;
- the use of multiple PD markers, if they exist, is recommended;
- to study dose-concentration-response relationships or time-response relationships provided that the selected doses are within the linear part of the established dose-response curve of RBP;
- a clear dose-response relationship is shown;
- at least one PD marker is an acceptable surrogate marker and is related to patient outcome;
- the PD assay should at least be relevant to a pharmacological effect of the biological product (PD assay is highly dependent on the pharmacological activity of the product, the approach for assay validation and the characteristics of the assay performance may differ depending on the specific PD assay).

6.3 Primary clinical study

The purpose of the efficacy trials is to confirm comparable clinical performance of the SBP and the reference product. The comparative assessment of efficacy and safety is a key component of the clinical assessment for mAb SBPs. The extent and nature of the nonclinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and nonclinical in vitro data. It is important to note that clinical data cannot be used to justify substantial differences in quality attributes. If dose comparative and sensitive PD studies cannot be performed to convincingly demonstrate comparability in a clinically relevant manner for mAbs, evidence of comparability needs to be obtained by other studies. If there is residual uncertainty that remains based on comparative structural and functional characterization, animal testing and human PK/PD data, comparative clinical trials should be carried out to demonstrate clinical comparability between the proposed mAb SBP and the reference mAb. These clinical trials should be randomized, adequately powered, and preferably double blinded.

The primary clinical study is preferred to be conducted in a population that is different from the population for the PK/PD study. Manufacturer of a biosimilar product should perform a thorough analysis of the available clinical data in the public domain for the reference product in order to determine the population-endpoint combination that is likely to provide a relevant and sensitive model for detecting clinically meaningful differences in efficacy and safety. However, the choice of setting for the primary clinical study is dependent on many intrinsic and extrinsic factors, which may not always lead to the selection of the most sensitive/relevant population. The type and number of comparative clinical trials required for the proposed mAb SBP could be affected by several factors including a) the nature and complexity of the mAbs; b) the limitations of studies comparing structural and functional characteristics; c) the extent to which differences in
structure, function, nonclinical data and human PK/PD can predict clinical outcomes; d) the
degree of understanding of mechanism(s) of action of mAb and disease pathology; and e) the
extent of clinical experience with the reference mAb with respect to safety, efficacy, and
immunogenicity. The clinical data obtained from one or more clinical studies in the most
sensitive populations can also be used to support extrapolation to other indications in which the
proposed mAb SBP has not been tested.

6.3.1 Clinical trial design
Clinical trial design and statistical analysis of equivalence and non-inferiority trials that are
already addressed in the WHO “Guidelines on evaluation of similar biotherapeutic products
(SBPs)” clearly apply to biosimilar mAbs (1). The guidelines stress the importance of clearly
stating the specific design selected for a given study, and includes details on the determination of
the comparability margin, sample size determination, and statistical analyses. For biosimilar
mAbs, extrapolation to other indications is especially important, and additional considerations are
required in order to design a meaningful trial to support additional indications.

Although equivalence or non-inferiority studies would be acceptable for the comparative clinical
studies of the biosimilar mAb to the RBP, equivalence trials are generally preferred. Detailed
explanations regarding the advantages and disadvantages of equivalence/ non-inferiority design
for similar biotherapeutic products are provided in WHO Guidelines and also available from
several other bodies on SBPs (1,10,11,12). Special considerations for clinical trial design of
mAbs developed as biosimilars are provided below.

A demonstration of equivalence, as opposed to non-inferiority, is especially important given that
extrapolation to other indications is one of the goals of the development program for the
biosimilar mAb. Non-inferiority trials are one sided and hence do not exclude the possibility that
the biosimilar mAb could be found to be superior to the RBP. Such a finding would create
challenges in providing a justification for extrapolation to other indications of the RBP.

An important consideration during the planning and design of the equivalence trial for the
biosimilar mAb is that it should be conducted with a sensitive and well established clinical model
regarding both the study population and the study endpoints. Assay sensitivity is important to
provide some confidence that the trial, as planned and designed, will have the ability to detect
differences between the biosimilar mAb and the RBP if such differences exist (13). A trial that
lacks sensitivity could lead to the erroneous conclusion of equivalence of the biosimilar mAb to
the RBP. The selected study population should not only be representative of the approved
therapeutic indications of the RBP, but should also be sensitive to detect potential differences
between the biosimilar mAb and the RBP. Hence, historical scientific evidence should be
provided which shows that appropriately designed and conducted trials with the RBP against
placebo for the approved indication have reliably demonstrated the superiority of the RBP over
placebo. For situations in which relevant scientific advances make it necessary for the study
population or study endpoints to deviate from those leading to approval of the RBP for the specific indication, the proposed deviations should be discussed with the relevant regulatory authorities during the planning and design stage of the trial, and should include details on how the comparability margin(s) will be determined.

The selected study endpoints are also important determinants of sensitivity. Endpoints that are sensitive to detecting clinically meaningful differences between the biosimilar mAb and the RBP should be used. Although endpoints such as PD measures are expected to be more sensitive than clinical endpoints, there are few established PD endpoints for mAbs and clinical endpoints will likely have to be utilized. Effort should be made to use the same primary endpoint(s) as those that were used for establishing efficacy of the RBP. However, if that is not feasible, historical evidence to support sensitivity of the selected endpoint(s) as well as the determination of the equivalence margin(s) should be provided.

Since the efficacy of the RBP compared to placebo has already been demonstrated previously and it is also considered clinically important to ensure that the biosimilar mAb retains a substantial fraction of the effect of the RBP, an equivalence margin that preserves a fraction of the smallest effect size that the RBP can be expected to have relative to a placebo control is the most suitable margin. The fraction of the effect size of the RBP that must be retained by the biosimilar mAb should be clearly justified in each case, and should take into account the smallest clinically important difference in a given setting. A commonly used value is the 50 % rule in which 50 % of the effect size of the RBP is preserved, and its wide use appears to be historical. However, the 50 % rule is not expected to be justifiable in all cases as it could result in a margin that is larger than what is considered the smallest clinically important difference. Once the margin has been selected, the determination of the required sample size should be based on methods specifically designed for equivalence trials.

Statistical analysis of data from equivalence trials is typically based on the indirect confidence interval comparison which requires specification of the equivalence limits (14). Equivalence is demonstrated when the confidence interval for the selected metric of the treatment effect falls entirely within the lower and upper equivalence limits. If a p-value approach is used, then the p-values should be computed based on the Two-One Sided Test (TOST) procedure testing simultaneously the null hypotheses of inferiority and superiority. In using the TOST procedure, equivalence is demonstrated when the p-values obtained are less than the significance level used.

6.3.2 Study population
In order to detect differences between the mAb SBP and the reference mAb, clinical trials for mAb SBPs should be carried out in an appropriately sensitive patient population using endpoints that can accurately demonstrate both the similarity of the biosimilar to the reference product, and
its efficacy and safety in the indication (see Section 6.3.3). Rationale for the selected study population should be provided. In general, a homogeneous population of patients would minimize inter-patient variability and thus increase the likelihood of detecting differences between the mAb SBP and the reference mAb. Patients who have not received previous treatment, e.g. first-line therapy, are considered to be more homogeneous than patients who have previously received several or different lines of therapy. Ideally, the observed clinical effects should be triggered by the direct action of the mAb SBP/reference mAb without interference of other medications, as concomitant medications may affect or mask differences in PK/PD, efficacy, safety and/or immunogenicity of the tested products. To validate the effect of the reference mAb and the sensitivity of the study in the chosen study population, historical data should be used to justify the selection of the study population and equivalence margin. This could generally be done through meta-analysis or systematic review.

Monoclonal antibodies can function through various mechanisms of action, such as through receptor blockade or agonist activity (e.g. vascular endothelial growth factor (VEGF) and EGFR), induction of apoptosis, or delivery of a drug or cytotoxic agent, and immune-mediated cell killing mechanisms, e.g. CDC, ADCC and regulation of T cell function. Because the mechanisms involved in one disease may differ from those involved in another, extensive consideration should be given to the setting in which clinical comparability is to be tested, especially where it is known that extrapolation to other indications and uses will be sought.

In some jurisdictions, clinical studies in an unauthorized population (e.g. new indication, line of therapy, combined therapy, disease severity) may be acceptable to demonstrate “no clinically meaningful differences” for biosimilars. Manufacturers of biosimilar products should consult relevant regulatory authorities prior to conducting such studies.

### 6.3.3 Primary study endpoint

Clinically relevant and sensitive study endpoints within a sensitive population should be selected to improve the detection of potential differences between the mAb SBP and the reference product. In general, clinical outcomes, surrogate outcomes or a combination of both can be used as primary endpoints in mAb SBP trials. The same study endpoints for the innovator products may be used, as a large body of historical data is generally available in the public domain for setting the equivalence margin and calculating the sample size. The study endpoints may be different from those traditionally used or study guideline recommended endpoints for the innovator products, as these endpoints may not be considered as the most sensitive endpoints to detect clinically meaningful differences in an equivalent trial setting. A surrogate endpoint can be used as the primary endpoint, when the surrogacy to the clinical outcome is well-established or generally accepted, as seen with pCR in neoadjuvant treatment of breast cancer. The choice of the study endpoint should always be scientifically justified. A more sensitive clinical endpoint could be ones used as secondary endpoints for the innovator products, primary or secondary endpoints for the innovator products at different time points of analysis, and/or new surrogates.
For example, overall response rate (ORR) or complete response (CR) rate as endpoints for clinical efficacy studies of mAb SBPs in oncology trials are recommended, as these endpoints may be sensitive and are not time related. However, if progression-free survival (which is one endpoints recommended for clinical efficacy testing for innovator products) is more sensitive than ORR then this may be the preferred option. Likewise, in rheumatoid arthritis (RA), both continuous outcomes, e.g. changes in disease activity score of 28 joints (DAS28) over time, and dichotomous outcomes, e.g. American College of Rheumatology score 20 (ACR20), are considered acceptable in rheumatoid arthritis (RA) for determining clinical comparability (15).

When the primary efficacy endpoints that were used for the RBP cannot be used for SBP, it is advisable to include some common endpoints as secondary endpoints to facilitate comparisons between the mAb SBP and the mAb RBP. The role of these secondary endpoints in the overall interpretation of the study results should be clearly defined, particularly whether the secondary endpoints are used to support or to confirm equivalency or similarity.

National Regulatory Authorities (NRAs) may not always agree upon the choice of study endpoints. For a biosimilar manufacturer with a global development program that is guided or required by various NRAs to fulfil local regulatory or clinical practice requirements, it may be possible to pre-specify different primary study endpoints with the statistical power in the same trial to comply with various regulatory requirements.

6.3.4 Safety
6.3.4.1 General consideration
Comparative safety data should normally be collected pre-authorization, their amount depending on the type and severity of safety issues known for the reference product. Study population should inform safety events of interest and evaluate for overt new mAb SBP-specific safety findings. Care should be given to compare the nature, severity and frequency of the adverse reactions between the mAb SBP and the reference product in clinical trials that enrolled a sufficient number of patients treated for an acceptable period of time. Clinical safety issues should be captured throughout the clinical development during initial PK and/or PD evaluations and also in the primary clinical study establishing comparability. It is also useful to compare the safety profile of the mAb SBP with that of the reference product throughout the life-cycle of the reference mAb to ensure that there is no new safety signal elicited by the mAb SBP.

6.3.4.2 Immunogenicity
Recombinant DNA-derived biotherapeutics, including monoclonal antibodies, are recognized by the human immune system. This immune recognition may lead to an immune response that may have an impact on efficacy and safety. From the regulatory point of view, animal data are usually not sufficiently predictive of the human immune response. Thus, immunogenicity needs to be
investigated as part of the clinical trial program of a monoclonal antibody SBP. The analysis of the immunogenicity of DNA-derived biotherapeutics is outlined in the WHO Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology and Guidelines on evaluation of similar biotherapeutic products (SBPs). This general guidance should be taken into account in reviewing biosimilar mAbs. In addition, details regarding the advantages and disadvantages of particular assays as well as some considerations for interpretation of the results and decision making process are provided in several review articles (16,17,18,19).

**Immunogenicity of a SBP monoclonal antibody**

The basic data package contains the incidence, titer, neutralization capacity, and persistence of product antibodies determined by appropriate assays, as well as their pharmacokinetic and clinical correlations. The immunogenicity program needs to be tailored for each product. Thus, the manufacturer should present a summary of the immunogenicity program that justifies the selected approach. This summary should address the following topics as appropriate:

**Risk assessment**

- previous knowledge of the immunogenicity of the reference product, such as the presence of immunogenic structures in the active substance as well as the incidence, type, persistence and clinical correlations of the antibodies;
- findings of the physicochemical and structural comparisons between the similar mAb and its reference product, including process-related impurities and aggregates;
- differences in formulation and packaging, e.g. potential impurities and leachables;
- route and/or the mode of administration of the product;
- patient related and disease-related factors. Such as state of the immune system, concomitant immune-modulatory therapy, and potential pre-existing immunity.

**The risk-based immunogenicity program**

The manufacturer should present a risk-based immunogenicity assessment program:

- The basis of the immunogenicity assessment is the testing of patient samples pre-treatment, during treatment and post-treatment in an appropriate set of assays. The measurement of antibodies to monoclonal antibodies is methodologically challenging and as standard assay formats involving anti-immunoglobulin reagents are inappropriate for this product class, alternative methods should be used. Like other biotherapeutic products, a multi-tiered approach for assessment is needed. The developer has to validate assays for screening, confirmation, and neutralization capacity. Special attention should be paid to the choice of the control sera, determination of cut points and to the interference caused by the presence of matrix components and of the residual drug in the sample. To mitigate the potential interference, corrective measures should be implemented. For example, drug interference may be overcome by allowing time for clearance of the drug from the circulation prior to sampling
or by dissociating immune complexes or by removal of the drug. Inclusion of any of these measures must not compromise the detection of antibodies or patient treatment.

Integration of the product antibody testing in the comparative clinical trials: sampling schedule and duration of the follow up. It is particularly important to synchronise the sampling for product antibody determination and pharmacokinetic measurements as well for assessments of safety and efficacy.

- Special emphasis should be put on the potential association of product antibodies with loss of efficacy, infusion reactions as well as to acute and delayed hypersensitivity. The manufacturer should systematically use terminology and definitions to characterize potentially immune-mediated symptoms according to relevant publications (20).
- The manufacturer should take the dose, dosing schedule, intermittent of dosing into account.
- The vulnerability of the patient population(s) and the expected risks of immunogenicity should be taken into account in planning for the intensity of monitoring.
- The manufacturer should give a description and analysis of the use of pre-medication or de-immunization measures to mitigate acute infusion/injection-related reactions and other, possibly immune-mediated reactions.
- Product antibodies should be assayed post-treatment not earlier than 12 weeks in order to demonstrate the reduction of antibody titres or appearance of circulating antibodies possibly suppressed by the product.

Comparative immunogenicity

The lack of standardization and rapid evolution of the assay methodology makes it difficult to compare immunogenicity studies. Therefore, pre-licensing comparative immunogenicity studies are always needed in the development of SPBs (1,12). Immunogenicity testing of the SBP and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule. Parallel group design is recommended because of the long half-life of antibodies and because it may be difficult to interpret immunogenicity after a switch.

Assays and mAb characterization

Antibody assays should ideally be capable of detecting all antibodies against both the biosimilar and the reference molecule. Thus, assays can be performed with both the reference and biosimilar molecule as the antigen/capture agent in parallel in order to measure the immune response against the product that was received by each patient. The challenge of this assay is to develop two assays with similar sensitivity and specificity. Cross-testing all serum samples by both tests is useful to confirm the similar assay performance as well as similar antigen epitopes. The use of a single assay with the active substance of the biosimilar as the antigen/capturing agent for evaluation of all samples (including those from reference product treated patients) will be able, in
principle, to detect all antibodies developed against the biosimilar molecule, i.e. it is, in principle, conservative. However, this assumption needs to be justified by the manufacturer.

Following identification of confirmed antibody positive samples, characterization of the antibodies is required. Determination of their neutralizing potential is essential and deviation from this requires justification. Although a cell-based bioassay or a non-cell-based competitive ligand binding (CLB) assay can be used, the latter should only be used if relevant to the mechanism of action (MoA) of the product. For example, a CLB assay is appropriate in a scenario where a therapeutic mAb acts by binding to a soluble ligand thereby blocking it from interacting with its receptor thus inhibiting the biological action of the ligand. Since the assay procedure measures binding to the target and inhibition of the binding activity if neutralizing antibodies are present, it is reflective of the therapeutic's MoA. For intact mAbs where effector functions are likely to contribute to the clinical effect, cell-based bioassays are recommended as the mechanism of action cannot be adequately reflected in a non-cell-based CLB assay.

Cell-based assays are preferred for the assay of neutralizing mAb since they represent the more physiological situation. However, bioassays may not be sufficiently sensitive or measure neutralization effectively. In such cases, alternative functional methods including non-cell-based CLB assays could be explored to assess neutralizing antibodies. It such cases, it is recommended to seek advice from regulators.

Additional studies beyond the standard data package, such as immunoglobulin class and IgG subclass, will be necessary in special situations (e.g. occurrence of anaphylaxis). It may also be necessary to locate the antigenic sites (e.g. antigen-binding region vs constant region of antibody molecule). Banking of patient samples is necessary in order to have the possibility for re-testing in case of technical problems in the original assay.

Clinical immunogenicity study

The selected patient population should be sensitive for differences in immunogenicity. It is also important that the pivotal immunogenicity study includes PK measurements. Ideally, the repeat dose clinical trials should include sampling for immunogenicity and PK (trough levels) as well as simultaneous efficacy and safety assessments to establish the clinical impact of immunogenicity. If the study will include patients previously treated with the reference mAb a subgroup analysis of previously treated patients should be performed.

The sampling schedule should be optimized for the demonstration of similar onset and persistency of products antibodies to the test and the reference product.

The duration of the follow up of immunogenicity should be sufficient to demonstrate similar persistence and clinical impact of the product antibodies. In chronic administration, the minimum follow up is six months.
Immunogenicity should be followed after licensing by monitoring possible immune-mediated adverse effect. Special immunogenicity studies may be necessary in high risk situations, e.g. when the reference product is known to have serious but rare immune-mediated effects, such as anaphylaxis.

Evaluation of immunogenicity includes the incidence, titer, neutralization capacity and persistency as well as correlations to exposure, safety and efficacy. For time being, there is no generally accepted statistical methodology that could be used to define the limits of comparable immunogenicity. In general, excess immunogenicity of a SBP is not compatible with comparability unless the sponsor can convincingly show that the product antibodies have no clinical relevance and that the underlying difference between the SBP and the reference product does not signal an otherwise important problem.

Less immunogenicity may be acceptable if the manufacturer can justify that the clinical data of the reference product is still representative for the SBP. A subgroup analysis of antibody-negative patients should be performed to exclude the impact of immunogenicity.

6.4 Indication extrapolation

Indication extrapolation is the leveraging of efficacy and safety data from clinical studies in one indication to support the authorization of other indications in which the biosimilar has not been studied, but for which the reference product is authorized and well characterized. As part of guidance for biosimilar development, the WHO guidance document has provided recommendations regarding extrapolation of clinical data across indications. The principles recommended for indication extrapolation for biosimilars stated in the WHO guidance apply to mAb SBPs.

In addition to these principles, some special attentions should be paid to mAbs. Monoclonal antibodies have both Fab and Fc effector functions and may exert their clinical effect through a variety of mechanisms. These include, for example, ligand blockade, receptor blockade, receptor down-regulation, cell depletion (via ADCC, CDC, apoptosis), and signaling induction. A particular mAb may act through one or a combination of these or other mechanisms. Where a therapeutic mAb is indicated for a variety of diseases, various mechanisms of action may be important depending on the indication in question. In order to support extrapolation, the mechanisms that contribute to the efficacy of the mAb in each indication should ideally be well understood and clearly defined. It may not be possible to extrapolate when mechanistic differences are observed between the biosimilar and the reference product during the comparability exercise (e.g. in in vitro or ex vivo biological assays). This is especially true if the affected mechanism is not considered active in the studied indication since there would be no clinical data available to assess the impact of the difference on the indication to be authorized via
extrapolation. Due to their ability to exert effects through various mechanisms of action, extrapolation can be difficult when a mAb is indicated for a variety of diseases in which the important mechanisms of action are not well understood for each indication (21). Disease pathophysiology is another important determinant in the extrapolation assessment. Some mAbs hold indications for the treatment of diseases that bear little resemblance to each other. For example, if a reference mAb is authorized both as an anti-inflammatory agent and as an anticancer antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging. Since the pharmacokinetic characteristics of a mAb (e.g. linear vs. non-linear PK) may differ between various diseases, additional clinical data may be required to support extrapolation from one to the other. Also, posology may differ between indications (e.g. body surface area adjusted dosing vs. fixed dosing). In situations, such as the one described, manufacturers should consider performing clinical trials in the two unrelated settings if they seek to have a mAb SBP authorized for all indications held by the reference mAb.

The possibility of extrapolating safety including immunogenicity data requires careful consideration, and may have to involve more specific studies including PK/PD or immunogenicity studies. Immunogenicity is related to multiple factors including the route of administration (e.g. SC vs IV), treatment regimen (e.g. continuous vs intermittent), and patient-, disease-, and treatment-related factors (e.g. immune status). Therefore, extrapolation of immunogenicity data is not self-evident and always requires convincing justification (22).

6.5 Pharmacovigilance and post approval consideration
Pharmacovigilance measures should be in place once a mAb SBP is approved in order to ensure its long-term safety and efficacy. The general requirements for pharmacovigilance are the same as for any approved new drug. As described in WHO documents, including recording of product name, batch number, manufacturers’ name, and INN where exits are further detailed in the WHO guidelines (/1,2). Clinically important adverse events-induced by mAb SBPs occur at a relatively low frequency and the probability of them occurring during the time frame of the clinical trial is also low. Additionally, due to relatively small sample size, mAb SBP clinical trials may only have the statistical power to detect common adverse events. Thus, a targeted pharmacovigilance is essential for the identification and assessment of potential post-market risk for mAb SBPs.

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