MEDICINES CONTROL COUNCIL

BIOSIMILAR MEDICINES
QUALITY, NON-CLINICAL AND CLINICAL REQUIREMENTS

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of biosimilar medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The Council is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to all the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and on the MCC website.

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MS M HELA
REGISTRAR OF MEDICINES

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1 PREAMBLE

Biological medicines that are manufactured to be ~~as follow-on~~ similar to registered originator medicines(unlike generic pharmaceutical medicines which are identical) ~~are similar, in principle to generic pharmaceutical medicines but~~ are known as *Biosimilar* ~~to distinguish them from generic pharmaceutical medicines.~~

The MCC practices for registration of multisource "generic" pharmaceutical medicines do not apply to biological medicines. This guideline outlines the specific information required for registration of ~~certain~~ biosimilar medicines. These types of biological medicines are similar to a reference product already registered in South Africa.

2 SCOPE

This guideline is applicable to biological medicines containing well-characterized recombinant DNA-derived therapeutic proteins that can be shown to be similar to a biological medicine registered in South Africa.

Vaccines ~~and monoclonal antibody products,~~ even if manufactured by recombinant DNA technology are excluded from the scope of this document. (Whereas requirements for monoclonal antibody are outlined in Annexure 1)

This guideline also does not address the comparability exercise required for changes introduced in the manufacturing process of a registered product, that is, changes during development and post-registration. These issues are covered in the current MCC Amendments guideline.

An application for a Biosimilar medicine that uses as reference a registered medicine classified as a pharmaceutical by the MCC, is not exempt from this guideline and should be submitted as described herein. The Council may decide to waive some or all of the requirements based on the circumstances and nature of the product comparability exercise.

This guideline should be read in conjunction with all relevant current guidelines pertaining to medicinal products ~~containing biotechnology-derived proteins as active substances~~.

See website http://www.mccza.com

3 INTRODUCTION

It is the policy of the MCC that all medicines containing, or derived from living materials including biosimilar medicines, are regarded as Biological Medicines and that applications for registration will require primary evaluation by the Biological Medicines Committee, in addition to other committees of the MCC.

~~An applicant may choose to submit an application for a Biosimilar as a new biological medicine with a full application dossier and supporting information~~. if the ~~Where this~~ new product is claimed to be similar in terms of quality, safety and efficacy to a reference medicine that has been registered in South Africa the applicant ~~required information~~ may submit ~~be modified~~ an application for registration of a biosimilar medicine according to ~~as described in~~ this guideline.

The information requirements for a biosimilar application primarily include defined requirements for physico-chemical and biological comparability, and reduced non-clinical and clinical evidence for safety and efficacy as outlined in this guideline ~~if defined conditions are met.~~

The original registered reference medicine is manufactured and controlled according to non-public proprietary methods that are not available to a "follow-on" developer; therefore it is necessary that the applicant for a biosimilar medicine (that may use alternative production technologies) provide evidence

that the biosimilar is indeed similar in quality, safety and efficacy to the registered medicine used as reference product.

If similarity cannot be demonstrated the products cannot be considered to be biosimilar and a full clinical submission application is required.

An appropriate comparability exercise is required to demonstrate that the biosimilar and the reference medicinal products have similar profiles in terms of physico-chemical properties, quality, safety and efficacy.

This guideline outlines the quality, non-clinical and clinical requirements for biosimilar medicines.

The quality section addresses the physico-chemical structural and functional requirements. The non-clinical section addresses the pharmaco-toxicological assessments. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, safety and efficacy studies as well as the pharmacotoxicological assessments with special emphasis on studying the immunogenicity of the biosimilar medicines. The section on pharmacovigilance addresses the in-use safety of the medicine as well as the risk management plan.

Product class specific annexes will supplement this guideline where a need is identified

4 LEGAL BASIS

Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended and the relevant Regulations.

5 QUALITY and NON-CLINICAL, and CLINICAL DATA

5.1 QUALITY AND NON-CLINICAL DATA

The objective is to establish the chemical and molecular nature of the Biosimilar active pharmaceutical ingredient [API] and drug product, and to show that it has no relevant differences in physico-chemical characteristics when compared to the API in drug product of the reference medicine.

~~The EMA guidelines[7.1, 7.2] describe suitable techniques and analyses that may be used to compare the molecular characteristics of the Biosimilar with the reference medicinal API. These also provide guidance on techniques for comparison of the final formulated medicines.~~

The relevance of observed differences in the physico-chemical characteristics must be explored using appropriate functional bio-assays, animal and clinical studies.

Validated analytical techniques that show the comparable functionality of the biosimilar and the reference medicine in appropriate *in vivo* and *in vitro* systems should be used. The functions that are selected for analysis should be shown to relate to the ~~clinical~~ biological activity of the molecule.All functions should be compared to the reference product activity and should be equivalent in those that are thought to be (major or minor) mechanisms of action, and no new activity is demonstrated that is not evident in the reference product

In vivo animal studies that show comparable toxicology and biological activity should be presented. Non-clinical studies should be performed before initiating clinical development, and should be comparative in nature, designed to detect differences in response between the biosimilar and the reference medicine and not just the response *per se*

The design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Results from the physicochemical and biological characterisation studies should be reviewed to assess the potential impact on efficacy and safety. A holistic approach is necessary to include all available information in the development of the non-clinical and clinical studies leading to a successful application for registration.

Ongoing consideration should be given to the use of emerging validated technologies.

The approach taken to establish the chemical and molecular nature of the biosimilar API, and to show that it has no detectable, relevant differences in physico-chemical characteristics, when compared to the API in the reference product, must be fully justified in the CTD non-clinical overview and/or the Quality Overall Summary.

Comparisons based on publications or pharmacopoeial monographs are not sufficient to establish similarities.

5.1.1 Pharmaceutical Quality

The application for registration of a biosimilar shall provide a full quality dossier detailing the source materials and inactive pharmaceutical ingredients (IPIs), manufacture, stability and control of the process in accordance with the MCC guidelines and compliant with the SA Guide to Good Manufacturing Practices (SA Guide to GMP) and other relevant guidelines[7.4, 7.5, 7.6, 7.7]

The basic requirement for a biosimilar is that it is demonstrated to be "similar" to the reference product. A lack of detectable, relevant differences between the biosimilar and the reference medicine is the basis for reducing non-clinical and clinical requirements for registration.

The applicant should carry out a comprehensive physicochemical and biological characterisation of the biosimilar API substance; each of these analyses must be conducted in a head-to-head comparison with the reference API substance.

Molecular characterization should be as extensive as possible within limits of current technology – these studies should, where possible be conducted in head-to-head comparison with the reference product. Primary, secondary and tertiary structure should be demonstrated as well as the composition and structure of post-translational modifications and additions – e.g. glycosylation. Techniques used should include a search for, analysis and comparison of antigenic epitopes that could lead to adverse reactions.

Examples of tests that may be used for physico-chemical characterization:

- Amino-acid sequence analysis of the purified product
- Peptide mapping
- Quantification of the active principle by ~~immunological~~ biological assays
- Molecular size analysis
- Characterization of higher order ~~secondary and tertiary~~ structure/s
- Identification of iso-forms
- Identification of post-translation modifications
- Quantification of truncated (extended) amino acid sequence impurities

OTHER FACTORS TO CONSIDER:

- Chemical modification (e.g. oxidation, deamidation, methylation)
- Aggregate formation
- Impurities (e.g. presence of host cell proteins)
- Glycosylation pattern

Structural differences which may be relevant ~~related~~ to immunogenicity or allergenicity

To evaluate similarity, all aspects of product quality and heterogeneity should be assessed. Differences may be due to differences in source materials, process, impurities or excipients, and should be assessed for their relevance and potential impact on clinical safety and efficacy of the biosimilar and a justification (e.g. own-study results or literature data) of the actions taken to assess the relevance of such differences must be provided.

Differences in critical product quality attributes (i.e. those that are known to have potential impact on clinical activity will add to the clinical testing required for the product ~~biosimilar~~. For example, if differences are found in glycosylation patterns that alter the biodistribution of the product and thereby change the dosing scheme, ~~dose-finding studies~~ additional clinical testing for the product would likely be required. Differences of unknown clinical relevance, particularly regarding safety, may have to be addressed in additional pre- or post-marketing studies [7.8].

Other differences between the biosimilar and reference substance may be acceptable, and would not trigger the need for extra clinical evaluation. For example, a therapeutic protein that has lower levels of protein aggregates could be thought to have a better safety profile than the reference and may not need added clinical evaluation.

Due to the unavailability of the API of the reference, the biosimilar manufacturer ~~may choose to~~ will typically use the commercially available reference medicine for the comparison, which will, by definition, be formulated with inactive pharmaceutical ingredients (IPI). It should be verified that these IPIs do not interfere with analytical methods and thereby impact the test results.

If the reference API needs to be purified from a formulated reference medicine in order to be suitable for characterisation, studies must be carried out to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process. The approach employed to isolate and compare the biosimilar active substance to the reference active substance should be justified as appropriate for the intended purpose. Where possible, the product should be tested with and without manipulation.

A similar comparison of the biosimilar medicine (final product) characteristics with the reference medicine should be undertaken.

5.1.2 *In vitro* biological studies

In vitro biological studies should be performed before initiating clinical development, and should be comparative in nature, designed to detect differences in response between the Biosimilar and the reference medicine and not just the response *per se*.[7.1]

Bioassays that show the comparable functionality of the biosimilar and the reference medicine in appropriate in *vivo* and *in vitro* systems should be ~~validated for~~ used. The biological endpoints that are selected should be shown to relate to the clinical activity of the molecule. Design of an appropriate non-clinical study program requires a clear understanding of product characteristics. Results from the physiochemical and biological characterisation studies should be reviewed to assess the potential impact on biological activity, efficacy and safety.

Comparative receptor-binding studies or cell-based assays, many of which may already be available from quality-related bioassays, should normally be undertaken in order to establish comparability in reactivity and the likely causative factor(s) if comparability cannot be established.

5.1.3 Non-clinical (animal) studies

In vivo animal studies to show comparable toxicology and activity should be presented.

Animal studies should be designed to maximise the information obtained and to compare the biosimilar and reference medicine intended to be used in the clinical trials. Such studies should be designed to detect differences in response between the biosimilar and reference medicine and should be conducted in a species known to be relevant, and sensitive using appropriately up-to date, validated methods.

Where the model allows, consideration should be given to monitoring a number of endpoints such as:

a) Pharmacodynamic effect/activity relevant to the clinical application. These data should usually be available from biological assays in the pharmaceutical modules of the dossier.

b) Non-clinical toxicity as determined in at least one repeat dose toxicity study, including toxicokinetic measurements.

Toxicokinetic measurements should include but not be limited to analysis of immunogenicity;

- Determination of relevant antibody titres,
- Where warranted due to biosimilar homology to endogenous proteins, analysis of anti-biosimilar antibody cross reactivity to endogenous proteins may be needed,
- Depending upon PK assay format and PD markers, the characterization of neutralizing antibodies may be needed to interpret the study.
- It may be relevant to analyse other forms of immune response.

The duration of the studies should be sufficiently long to allow detection of significant differences in toxicity and/or immune responses between the biosimilar and reference medicine.

If there are specific safety concerns, these might be addressed by including relevant observations (i.e. local tolerance) in the same repeat dose toxicity study.

Normally other routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar medicines, unless indicated from results of repeat dose studies or other information[7.9].

Animal immunogenicity studies may be of value in demonstrating similarity of immune responses to reference and biosimilar products, but cannot be an alternative to immunogenicity studies in humans.

5.2 CLINICAL DATA

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, PK/ PD studies may be sufficient for demonstrating clinical comparability [7.10].

Clinical studies should have the following characteristics:

- The biosimilar final product (formulation) is compared to a reference medicine that has been registered in South Africa. ~~on the basis of a complete application dossier, including evidence of Quality, safety and efficacy. (i.e. not another Biosimilar~~
- ~~The safety of the biosimilar must shown to be non-inferior to the reference medicine[7.11];~~
- ~~Non-inferiority margins must be pre-specified and justified as clinically relevant;~~

5.2 Clinical Data -continued

- In general, an equivalence design should be used for clinical studies
- The efficacy of the biosimilar must be equivalent to the reference medicine[7.12];
- There must be evidence for efficacy and safety for each indication
- A risk benefit analysis of the biosimilar product should be similar to the reference medicine

The requirements depend on the existing knowledge about the reference medicine and the claimed therapeutic indication(s). Available product/disease specific guidelines should be followed.

It is acknowledged that the manufacturing process will be optimised during development and before registration application. The required clinical data for the phase 3 comparability study should be obtained with the test product as produced with the final manufacturing process, formulation and specifications; and therefore representing the quality profile of the intended commercial batches. Any deviation from this should be justified and supported by adequate additional data.

For all clinical comparability trial designs, assay sensitivity has to be ensured[7.13]. Evidence must be presented to show that the end-point tests used have been validated and conducted by a competent and accredited laboratory.

5.2.1 Pharmacokinetic (PK) studies

Comparative PK studies designed to demonstrate clinical comparability of key PK parameters between the biosimilar and the reference medicine are an essential part of demonstrating similarity.

Specific considerations related to the inherent characteristics of proteins described in the EMA Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins [7.10] should be taken into account.

The design of comparative PK studies should not necessarily mimic that of the accepted “clinical comparability” design[7.10], and, differences in elimination characteristics between products e.g. clearance and elimination half-life should also be explored.

The choice of the design for single dose studies, steady-state studies, or repeated determination of PK parameters should be justified by the applicant. The crossover design is usually not appropriate for therapeutic proteins with a long half-life, e.g. therapeutic antibodies and pegylated proteins, or for proteins for which formation of specific antibodies is likely; parallel group designs should be considered

The acceptance range to conclude clinical comparability with respect to any pharmacokinetic parameter should be based on assessment of clinical data, considering all available efficacy and safety information on the biosimilar and reference medicine.

The accepted criteria used to assess clinical comparability studies initially developed for chemically derived, orally administered products are not always sufficient for biological medicines and the clinical comparability limits should be defined and justified prior to conducting the study.

5.2.2 Pharmacodynamic (PD) studies

The pharmacodynamic (PD) markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. The pharmacodynamic effect of the biosimilar and the reference medicine should be compared in a population where the possible differences can best be observed.

5.2.2 Pharmacodynamic (PD) studies

The design and duration of the studies must be justified. Combined PK/PD studies may provide useful information on the relationship between exposure and effect.

The selected dose should be in the steep part of the dose-response curve. The most appropriate dose level needs to be chosen. ~~Studies at more than one dose level may be required~~

5.2.3 Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

For biosimilar medicines, it is usual that comparative clinical trials of efficacy are required for the demonstration of clinical comparability. In certain cases, however comparative PK/PD studies between the biosimilar and the reference medicine may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

a) The PK of the reference medicinal product is well characterised.

b) There is sufficient knowledge of the pharmacodynamic properties of the reference medicine, including the binding to its target receptor(s) and intrinsic activity. Sometimes, the mechanism of action of the biological product will be disease-specific.

c) The relationship between dose/exposure and response/efficacy of the reference medicine (the therapeutic "concentration-response" curve) is sufficiently characterised.

d) At least one PD marker is accepted as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker is validated and well known. A PD marker may be considered a surrogate marker for efficacy if therapy-induced changes of that marker can explain changes in clinical outcome.

   Examples include absolute neutrophil count to assess the effect of *granulocyte-colony stimulating factor*, and early viral load reduction in chronic hepatitis C to assess the effect of *alpha interferons*. The choice of the surrogate marker for use in PK/PD studies should be justified.

If PK/PD studies are used to demonstrate comparability of the biosimilar, care should be taken to investigate a relevant dose range to demonstrate assay sensitivity[7.13].

The margins (limits) defining clinical comparability of PK and PD parameters must be defined *a priori* and justified[7.14].

5.2.4 ~~Efficacy~~ Clinical efficacy studies ~~trials~~

The physico-chemical, and non-clinical studies should be sufficient to establish molecular and functional similarity between the Biosimilar API and reference medicine API prior to any clinical studies of efficacy.

Comparative clinical trials will ~~usually~~ be necessary to demonstrate clinical comparability between the biosimilar and the reference medicine, and not the clinical efficacy de novo. Clinical comparability margins should be pre-specified and justified, primarily on clinical grounds. As for all clinical comparability trial designs, assay sensitivity has to be ensured.

If a clinical comparability trial design is not feasible, other designs should be explored.

Where the ~~various~~ clinical effects of the medicine have been shown to be related to ~~a single~~ the same mode of actions and the safety and efficacy of the biosimilar medicine and the reference product have been demonstrated for a particular clinical indication, it may be possible to extrapolate these data to other indications of the reference product that have not been independently and specifically studied for the biosimilar medicine in clinical trials. Such extrapolation for indications is however not valid if the

main clinical trial to demonstrate comparability is not designed to demonstrate non-inferiority of the biosimilar and is not able to detect potential differences between the biosimilar and reference products. The safety and immunogenicity of the biosimilar product must also be sufficiently characterised. The applicant should provide convincing motivation and in detail discuss the scientific~~. it may be acceptable that not all the clinical effects are addressed during efficacy trials , in order to support registration.~~

This approach needs to be justified and supported by published and pharmacopoeial evidence.

5.2.5 Clinical safety and pharmacovigilance requirements

Even if the efficacy is shown to be comparable, the biosimilar may exhibit a difference in the safety profile (in terms of nature, severity, or frequency of adverse reactions). Pre-registration safety data should be obtained in a number of patients sufficient to address the adverse effect profiles of the biosimilar and the reference medicine [7.15]. Care should be given to compare the type, severity and frequency of the adverse reactions between the biosimilar and the reference medicine.

Data from pre-registration clinical studies are normally insufficient to identify all potential differences. Clinical safety of the biosimilar medicine must, therefore, be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment. Within the registration procedure the applicant should present a risk management programme / pharmacovigilance plan[7.16]. This should take into account risks identified during product development and potential risks.

The applicant should give a risk specification in the application dossier for the Biosimilar medicine under review. This includes a description of possible safety issues related to tolerability of the biosimilar medicine that may result from a manufacturing process different from that of the originator and how these may be assessed in the post-marketing period. The applicant should propose possible activities to encourage the reporting of relevant adverse events, including events related to immunogenicity or loss of efficacy[7.17].

Following registration of the biosimilar, the holder of the certificate of registration (HCR) must comply with conditions of registration and the pharmacovigilance obligations will be closely monitored and reports of these activities, with defined timelines may be required. The routine Periodic Safety Update Reports[7.18] should also include information on adverse reaction reports, immunogenicity and any other information on tolerability or lack of efficacy that is applicable to SA and the registration conditions.

It will be required that safety update information applicable to the reference medicine (product class) will be applicable to the biosimilar. This safety information must be evaluated and assessed by the registration holder of the biosimilar in a scientific manner with regard to causality of adverse events or adverse drug reactions and related frequencies and should report to the MCC on the actions that will be taken to ensure the safety of patients.

5.2.6 Immunogenicity

All clinical studies should include assessment of immunogenicity of the product in comparison to the reference product. The assessment of immunogenicity requires ~~an optimal~~ robust antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and pharmacokinetics or pharmacodynamics, relevant for clinical safety and efficacy in all aspects.

5.2.6.1 Principles

- Assays used to assess immunogenicity should be relevant, sufficiently sensitive, and validated.

5.2.6.1 Immunogenicty Principles - continued

- The development of neutralizing antibodies and other types of specific immune response should be assessed in healthy individuals and in the different therapeutic indications.
- Immunogenicity data should be collected from a sufficient number of trial subjects to assess the development and variability of the immune response.
- The impact of these immune responses on the clearance/bioavailability of the biosimilar and on the continued safety and efficacy of the biosimilar ~~in healthy individuals and~~ in the different therapeutic indications should be assessed.
- Testing for immunogenicity should be performed by state of the art methods using assays with appropriate specificity and sensitivity. The screening assays should be validated and sensitive enough to detect low titre and low affinity antibodies. An assay for neutralising antibodies should be available for further characterisation of antibodies detected by the screening assays.
- Standard methods and international standards should be used whenever possible.
- The possible interference of the circulating antigen with the antibody assays should be taken into account.
- The periodicity frequency and timing of sampling for testing of antibodies should be justified.
- In view of the unpredictability of the onset and incidence of immunogenicity, long term results of monitoring of antibodies at predetermined intervals will be required. In the case of chronic administration, one-year follow up data will be required prior to registration.
- The applicant should consider the possibility of antibodies to process related impurities.
- Consideration should be given to allergenicity of the product.

5.2.6.2 Evaluation of the clinical significance of the observed immune response

If a difference in the immune response to the biosimilar is observed as compared to the reference medicine, further analyses to characterise the antibodies and their implications to clinical safety, efficacy and pharmacokinetic parameters are required. Special consideration should be given to those products where there is a chance that the immune response could seriously affect the endogenous protein and its unique biological function.

The applicant should consider the role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy. The applicant needs to propose activities to encourage the reporting of relevant adverse events, including events related to loss of efficacy.

5.2.7 Risk Management Plan

A suitable Risk Management Plan (RMP) should be in place (or planned) for the biosimilar medicine at the time of application for registration. This should be fully described in the CTD dossier in Module 1.13. It may be necessary to include South African and special population groups in these RMP activities. This RMP will form part of the conditions of registration.

Pharmacovigilance reporting procedures as defined in the current MCC guidelines should be adhered to. Additional conditions may be required as a condition of registration.

The HCR is responsible for ensuring that the product is traceable i.e. reflection of the proprietary name of the product on the adverse event reports.

Following registration, any specific safety monitoring requirement, safety update or package insert amendment imposed on the reference medicine or product class should be applied~~,~~ unless a waiver for such a requirement has been approved by Council.

5.2.8 Interchangeability

biosimilars are not generic products and cannot be assumed to be identical to the reference medicine. The API(s) may have different characteristics and formulations may be different resulting in differences in clinical performance or adverse effects.

Therefore, biosimilars are not considered to be interchangeable with the reference medicine or other medicines of the same class.

Equally, substitution in terms of Section 22F (Generic substitution) of Act 101 of 1965 (i.e. the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) does not apply to Biosimilars.

6 GLOSSARY OF TERMS AND ABBREVIATIONS

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

Biological Medicine
All medicines that contain a living organism, or are derived from a living organism or biological processes are considered Biological Medicines. They include, but are not limited to the following:

I. Plasma-derived and animal products, e.g. Clotting factors, Immunosera, Antivenoms;

II. Vaccines;

III. Biotechnology-derived medicines (rDNA products) e.g. rHu-antihaemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids;

IV. Products developed for Human Gene therapy.

Well-characterised, low-molecular mass, medicinal biological compounds, may be excluded by specific Council decision from biological medicine status, and in that case will not be reviewed through the biological medicines review process.

Biosimilar or Biosimilar medicine
This is synonymous with *follow-on biologics* and *similar biotherapeutic products* (SBP). A biosimilar is a biological medicine that is similar, but not necessarily identical, in terms of quality, safety and efficacy to an already registered reference biological medicine.

CTD (ZA CTD)
Common Technical Document, the format used for dossiers for application for registration of a medicine in SA.

DNA
Deoxyribonucleic acid

EMA
European Medicines Agency (Formerly EMEA)

Equivalence trial
An equivalence clinical trial is conducted to demonstrate that there is no clinically significant difference between a standard and an experimental treatment. The specified differences between the efficacies of the two treatments are shown to be no more than some pre-specified margin[7.11].

GMP
Good Manufacturing Practices – as defined in the current version of the SA Guide to GMP Guide,

Immunogenicity
The ability of a substance to trigger an immune response or reaction (*e.g.*, development of specific antibodies, T cell response, allergic or anaphylactic reaction) following administration to an animal or human.

IPI
An Inactive Pharmaceutical Ingredient, materials added during formulation that do not have any pharmaceutical activity.

MCC
Medicines Control Council of South Africa

Non-inferiority trial
Not inferior to a comparator in the parameter studied. A non-inferiority clinical trial is one which has the primary objective of showing that the response to the investigational product is not clinically inferior to a comparator by a pre-specified margin[7.11].

Originator medicine
This is the innovator product - A medicine which has been licensed by a national regulatory authority which Council aligns itself with 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.

PD
Pharmacodynamic – the biochemical and physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

PK
Pharmacokinetic – the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug.

Reference substance
The active ingredient from the reference medicine that will be used in comparisons of physico-chemical characterization, and other properties, of the biosimilar.

Reference medicine
The comparator for head-to-head comparability studies with the biosimilar product in order to show similarity in terms of quality, safety and efficacy. It is the originator medicine (innovator product).
Only an innovator product that was registered by MCC in South Africa on the basis of safety, efficacy and quality can serve as a reference medicine.
The reference product that is registered in South Africa must be sourced from a country that MCC aligns itself with.
It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

Similar
This is the absence of a relevant (or significant) difference in the parameter of interest.

7 REFERENCES

ICH Documents – see www.ICH.org
MCC Guidelines and Documents – See http://www.mccza.com

7.1 EMEA: Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005)
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003953

7.2 EMEA Guideline on similar biological products (CHMP/437/04), the 'overarching guideline'.
http://www.ema.europa.eu/pdfs/human/biosimilar/043704en.pdf

7.3 EMEA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: EMEA/CHMP/BMWP/42832/2005.
http://www.triskel.com/2%20Guideline%20biotech%20derived%20proteins.pdf

7.4 ICH Q7 Good manufacturing practice guide for active pharmaceutical ingredients

7.5. ICH Q8 Pharmaceutical development

7.6 Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs); WHO /BS/09.2110; 2009.

7.7 MCC Current Pharmaceutical and Analytical guideline

7.8 ICH Q9 Quality risk management

7.9 ICH M3 (R1) 2000: Note for guidance on non-clinical safety studies for the Conduct of human clinical trials for Pharmaceuticals (CPMP/ICH/286/95)

7.10 EMEA/CHMP/89249/04/ Guideline on clinical investigation of pharmacokinetics of therapeutic proteins

7.11 IK. Hwang, T Morikawa. Design issues in noninferiority/equivalence trials. In Drug Information Journal, Vol. 33, pp. 1205–1218, 1999

7.12 PJ. Atherton Skaff, JA Sloan, Design and Analysis of Equivalence Clinical Trials Via the SAS® System
http://www2.sas.com/proceedings/sugi23/Stats/p218.pdf

7.13 ICH E10 - Note for guidance on choice of control group in clinical trials. (CPMP/ICH/364/96)

7.14 ICH E9– Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)

7.15 MCC: Current Guideline for Reporting Adverse Drug Reactions in South Africa.

7.16 EMEA/CHMP 96286/2005: Guideline risk management systems for medicinal products for human use.

7.17 ICH E2E: Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)

7.18 ICH E2C (R1): Periodic Safety Update Reports

8 UPDATE HISTORY

Date	Reason for update	Version & publication
January 2010	First publication released for comment	Version 1, April 2010
15 July 2010	Deadline for comment	
March 2012	Comments considered and guideline finalised for implementation	Version 2, May 2012
With immediate effect	Date of implementation	
Aug 2013	ANNEXURE 1: Product specific for monoclonal antibodies released for comments	Version 3, Nov 2013
31 January 2014	Deadline for comments	
31 March 2014	Deadline for comments extended	
July/Aug 2014	Comments considered and guideline finalised for implementation	Version 3, Aug 2014
With immediate effect	Date of implementation	

ANNEXURE 1: Product Class Specific for Monoclonal Antibodies

1 Introduction

This product class specific annexure outlines the quality, non-clinical and clinical data requirements specific for registration of monoclonal antibody (mAb) containing medicines considered by the applicant as similar to a reference product already registered by the Medicines Control Council of South Africa.
While this Annexure 1 is specifically related to mAbs, the principles discussed can also be applied to related substances like for example fusion proteins based on IgG Fc (-cept molecules).

The annexure takes into account that different mAb products may share some properties, but may differ in other aspects such as mechanism of action and antigenicity. It is recognised that mAbs are complex structures with complex and multiple functional domains within the single molecule. mAbs may thus differ in terms of antibody-antigen binding regions and its secondary biological effects.

The quality aspects related to this class of biosimilar medicinal products should conform to those described in the principal document general biosimilar guide. The biosimilar and the reference product should be structurally, physicochemically and biologically similar. The clinical and non-clinical studies should be designed to detect any potential differences between the reference product and the biosimilar product and to clearly identify the relevance of any such differences if present.

2 Scope

This document is a supplementary to the South African Biosimilar Guidelines and should be read in conjunction with the said document.

The annexure provides acceptable principles for registering biosimilar mAbs that are claimed to be similar to reference products of assured quality, safety and efficacy that have been based on a full dossier, by the Medicines Control Council of South Africa.

3 Quality

The quality comparison showing molecular similarity between reference product and biosimilar is indispensable. The development of the biosimilar should involve extensive characterisation of a number of representative lots of the product that is shown to be similar to the reference product in all relevant quality attributes: structural, biochemical and biological properties.

As set out in the requirements for South African Biosimilars Guideline, the manufacture of the biosimilar should be based on a comprehensively designed production process taking all relevant guidelines into account. The manufacturing process should be consistent, robust and in compliance with the current Good Manufacturing Practices (SAGMP).

4 Non-clinical studies

Non-clinical studies should be performed before commencing clinical trials. In principle, *in vitro* studies should be performed first and the outcomes used to determine the *in vivo* studies required. The overall approach to the non-clinical and clinical studies must be fully justified in the non-clinical overview.

4.1 *In vitro* studies

Data from at least three independent batches of the biosimilar mAb product used in the *in vitro* studies one of which must be a production batch should be provided. The studies should specifically include:

- Binding of antibody to target antigen or antigens
- Binding to isoforms of the relevant Fc gamma receptors
- Fab-associated functions such as receptor activation or blockade
- Fc-associated functions such as antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and complement activation.

4.2 In vitro studies – continued

All such studies should be comparative and aim to detect differences between the biosimilar and the reference product. The studies should cover the functional aspects of the mAb, including those that may not be considered essential for the therapeutic action of the medicinal product.

The applicant should rather consider developing and registering the biosimilar as a new product if it is not possible with suitable non-clinical studies to demonstrate biosimilarity of the biosimilar and reference mAb products.

4.2 *In vivo* studies

When outcomes of the *in vitro* studies show that it is not possible to fully demonstrate biosimilarity of the biosimilar and reference products; it is necessary to further evaluate biosimilarity by *in vivo* studies. The applicant should consider the necessity of such *in vivo* studies after for instance, taking into account:

- Significant and relevant differences in formulation and the use of specific excipients.
- Quality issues such as different amounts of chemical or biochemical substances in the candidate and reference products.
- Availability and relevance of in vitro assays to the mechanisms of action

The scope of *in vivo* studies should consider whether additional information is needed on pharmacokinetics and safety issues. Animal models should conform to relevant ethical and scientific principles and guidelines.

~~In general repeat dose toxicity studies in non-human primates are not recommended~~. It is recognised that the different production processes used by the manufacturers of the reference and biosimilars may result in qualitative differences in levels of impurities and product-related substances. These differences may affect the biological effects of the mAb and have clinically important effects on the immunogenic potential of the biosimilars.

Studies on safety pharmacology and reproduction toxicology are not required for non-clinical testing of biosimilar mAbs. Studies on local tolerance are usually not required, but may have to be evaluated if excipients are present in the formulation for which there is insufficient clinical experience.

5 Clinical studies

Comparative clinical studies between the biosimilar and reference medicinal product should always be conducted. The number and type of such studies may vary and the design of such studies should be scientifically justified.

A step-wise approach should be utilised and the number of patients enrolled should be determined by the level of evidence obtained by the preceding steps that had been designed to support comparability.

6 Pharmacokinetics (PK)

The first step in comparing the biosimilar and reference mAb products is usually a study of their pharmacokinetic properties. The design of such studies depends on many factors including clinical context, safety and the PK characteristics of the antibody. The applicant should take into account the recommendations of the SA Biosimilar Guideline and cGCP. Assays should be appropriate for their intended use and adequately validated.

The study design should show comparability of the pharmacokinetics of the biosimilar and the reference product in an appropriate study population. The sample size should be appropriate to prove equivalence.

6 Pharmacokinetics (PK) - continued

Healthy volunteers are more homogeneous, have less target-mediated clearance, and therefore more likely to have uniform outcomes in PK studies. A single dose study in healthy volunteers is recommended. ~~this could provide important information on biosimilarity. It is, however, preferable to perform a cross-over study with characterisation of the PK profile.~~

The potential influence of immunogenicity of long half-life mAb may best be studied in parallel groups. It should be considered whether it will be more appropriate to perform the PK study in a different population from that selected to establish similar clinical efficacy. The choice of the patient and healthy volunteer population for the PK study should be fully justified; such justification may be based on a review of the scientific literature. It is recommended that in the instance where PK studies are performed in healthy volunteers, supportive PK data be obtained in clinical patients to support evidence of similar PK behaviour of the biosimilar and reference mAb.

The design of the studies to evaluate biosimilar PK/PD should amongst others, take into account:

6.1 Disease and patient characteristics: age range; number of previous treatments; concomitant treatments; and disease stage.

6.2 PK characteristics of the reference mAb: the PK of anticancer mAb may depend on the tumour burden that could be affected by multiple treatment doses; target and non-target mediated clearance mechanisms; and influence of potential receptor shedding.

6.3 If a mAb is registered for several clinical indications, it is usually not required to investigate the PK profile in all of these diseases. It is however necessary to do separate PK studies if the mAb is indicated in distinct therapeutic areas such as for instance, treatment for cancer and autoimmune disease. At least one of these studies should be adequately sized to prove the equivalence between the products, while the other PK study needs to be designed to provide supportive descriptive PK data in the other indication.

6.4 In principle, it is usually not required to test all the therapeutic dosage regimens; the applicant should select that dose most likely to detect potential differences in PK of the candidate and reference biosimilar medicinal products. It should be noted that a single dose study with the lowest therapeutic dose in patents is considered the best design to investigate differences in target-mediated clearance.

6.5 If there are different routes of administration (intravenous, subcutaneous), and both these are applied for, both should preferably be investigated. It may be possible to waive the evaluation of intravenous administration of comparability if both absorption and elimination have been demonstrated for the subcutaneous route using additional PK parameters such as AUC.

6.6 The sampling times should be selected to characterise the whole PK profile, including the elimination phase. It is important to characterise the full concentration-time profile at steady state in cases of non-linear PK of the reference mAb. This is particularly relevant if the anticancer mAb exhibits dose - or time-dependent PK or immunogenicity-related changes in distribution or elimination kinetic properties.

6.7 In a single dose study, the primary parameter should be the $AUC_{(0\text{-inf})}$. Secondary parameters such as C_{max}, t_{max}, volume of distribution, and half-life, should also be estimated.

6.8 In a multiple dose study, the primary parameters should be truncated AUC after the first administration until the second administration ($AUC_{(0\text{-t})}$) and AUC over a dosage interval at a steady state.

6.9 Anti-drug antibodies, i.e. antibodies against the mAb medicinal product, should be measured in parallel to the PK assessment with appropriate sampling time intervals.

6.10 Comparability margins must be defined *a priori* and justified. Considerable inter-subject variability (beyond 80-125 %) of some parameters may have to be accounted for and justified. It should be noted that this may impact on clinical efficacy and safety.

6.11 Usually proof of similar PK profiles should be demonstrated before clinical efficacy trials are initiated. If this is not the case, ~~If this is not feasible and PK comparisons are done in clinical trials,~~ it must be justified on a case to case basis depending on the product profiles observed in the quality and non-clinical data.

6.12 PD parameters may sometimes add to the comparability proof for certain mAbs and certain clinical indications: PK studies can be combined with multiple PD endpoints (if such exist). It is noted that there is often no specific PD endpoints and the comparison will then have to focus of non-clinical PD evaluations such as *in vitro* testing.

6.13 PD markers should be explored as pivotal proof of comparability. Dose-concentration-response or time-response relationships, selected to be within the linear part of the dose-response curve, may provide strong evidence of comparability of the candidate and reference biosimilar products. If the PD markers are provided as pivotal evidence of comparability of efficacy, ~~there should be a clear dose-response relationship and at least one PD marker is an accepted surrogate marker that can be related to patient outcome~~. their selection should be based on evidence of sensitivity to dose-response relationships in previous studies with the reference drug, and at least one PD marker can be related to patient outcome or to the pharmacological effect of the molecule.

7 Clinical ~~efficacy~~ similarity

If dose comparative and sensitive PD studies cannot convincingly demonstrate comparability in a clinically relevant manner, it is necessary to show similar clinical efficacy of the reference product and the biosimilar in an adequately randomised, parallel group comparative clinical trial in accordance with cGCP. Deviations from these established guidelines must be scientifically justified on the basis that the proposal is designed to establish biosimilarity by using PD markers, clinical outcomes or both. The guiding principle is to demonstrate equivalent efficacy and comparable safety of the biosimilar compared to the reference product, *not patient benefit per se*.

7.1 Comparability should be demonstrated in appropriate clinical models and the applicant should justify the choice of model in terms of safety and efficacy.

7.2 The safety of patients should not be compromised and patients should not be exposed to the drug unless clinically indicated and warranted.

In anticancer therapy, clinical and safety margins may be difficult to set and it may be challenging to demonstrate equivalence. The preferred endpoint would be progression or disease free survival or overall survival. Applicants are referred to the ***Guideline on the evaluation of anticancer medicinal products in man*** *(*see ***References****).* Such endpoints may not be feasible or sensitive enough to establish comparability. In all instances the focus should be to demonstrate similar efficacy and safety compared to the reference product and *not patient benefit per se*.

~~7.3 Paediatric patient populations are necessary if the drug product is indicated for use in children. If such data is not provided this must be motivated and scientifically justified.~~

~~7.4 The inclusion of South African patient populations should be considered and may be required to define an equivalence safety and efficacy margin.~~

7.3 Clinical studies in special populations like the paediatric population or the elderly are normally not required since the overall objective of the development programme is to establish comparability, and therefore the selection of primary patient population is driven by the need for homogeneity and sensitivity.

8 Clinical safety

The demonstration of clinical safety is part of the pivotal clinical study or studies demonstrating comparability. The type, severity and incidence of adverse reactions should be compared, focusing on those that have been documented for the reference product. It is advisable to use the same definitions as those that have been used for the reference product.

Immunogenicity assessment is an important aspect and should be evaluated on a comparative basis. Note specifically the clinical outcomes of loss of efficacy and resistance against further treatment. It may therefore not be advisable to include in the clinical trial group patients who have been treated with the reference product. In some cases the development of antibodies are best detected in the healthy volunteer group. It is also important to take into account the potential effects of using a different expression system in evaluating the biosimilar and the reference product. Also consider the dose of the mAb in relation to the expression of immunogenicity. It should be noted that a higher immunogenicity of the biosimilar compared to the reference product may impact on the benefit/ risk ratio and may cast doubt on biosimilarity.

Additional long-term immunogenicity and safety data are ~~may be~~ required as part of the post-marketing authorisation and should be thoroughly discussed in the risk management plan.

9 Pharmacovigilance

The application for registration should include a comprehensive risk management plan on how safety will be monitored after registration of the medicine. This should at least address:

9.1 Occurrence of rare and potentially serious adverse events such as susceptible risk of infection in specific population groups that are described and predicted based on the evidence provided by studies of the reference product.
The pharmacovigilance plan may include participation of existing patient registries or large population based databases and must be part of the risk management plan.

10 References

10.1 *EMEA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues* (EMEA/CHMP/BWP/49348/2005)

10.2 *EMEA: Guideline on development, production, characterisation and specifications for monoclonal antibodies and related substances* (EMEA/CHMP/BWP/157653/2007)

10.3 *WHO: Guidelines on evaluation of similar biotherapeutic products (http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf*

10.4 *CHMP: Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins*" (CHMP/EWP/89249/2004)

10.5 *CHMP: Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)

10.6 *EMEA: Guideline on bio-analytical method validation* (EMEA/CHMP/EWP/192217/2009).

6.10.1 *SA GCP 2010*. *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa*. Department of Health: Pretoria, South Africa (http://www.hsrc.ac.za/Document-3935.phtml)

10.7 *CHMP: Guideline on the evaluation of anticancer medicinal products in man* (CHMP/EWP/205/95/2006)

10.8 *SA GMP: Guidelines for Good Manufacturing Practices in South Africa.* Department of Health: Pretoria, South Africa.