Guidelines on the Evaluation of Biosimilar Products

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This document has been prepared for the purpose of providing general principles and science-based approaches to development and evaluation of biosimilar products on the basis of outcomes from the research activities of the Korea Food & Drug Administration (KFDA), together with comments and suggestions from the interested parties and experts in the relevant industry and academic fields. Based on the KFDA's experience in review of biological products and comments from experts, this document describes the KFDA's current thinking on this topic. It may be amended as new information becomes available.

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1. INTRODUCTION

Since the authorization of a drug product containing recombinant human insulin for treatment of diabetes, various recombinant DNA products have been developed, including a drug for the treatment of arthritis and a drug used for anti-cancer treatment. Biological products have relatively low incidence of adverse events and high efficacy rates owing to targeted treatment. However, their cost has often been excessive, thereby limiting their access to patients. Recently, the expiration of patents and/or data protection for the first major group of the originator biological products has ushered in the era of products that are designed to be "similar" to an authorized originator product in terms of quality, safety, and efficacy, leading to the development of inexpensive biosimilar products.

The term "generic drug product" is used to describe chemical, small molecule drug products that are structurally and chemically equivalent to an originator product whose patent and/or data protection period has expired. However, the approach established for generic drug products is unsuitable for the development, evaluation, and authorization of biosimilar products, since biological products consist of relatively large and complex proteins, the structure and activity of which are highly influenced by the type of cell line and the manufacturing process. Even when the same manufacturer produces the same biological product according to the modified manufacturing process, there is no assurance that the product
has comparability. Therefore, a comparability evaluation is required for the sake of quality, safety, and efficacy. In this context, the EMEA issued regulations and guidelines on biosimilar products and other regulatory authorities are also developing such documentation.

In order to develop the regulations on review and authorization of biosimilar products and provide recommendations to be considered in the evaluation of biosimilar products, comments and suggestions from experts in this field have been invited and various documents issued by overseas governments and/or WHO have been reviewed. From these activities, this document was developed.

2. SCOPE

In principle, this document can apply to all types of biological products. However, in this case, it applies specifically to biological products that contain well-characterized protein as the active ingredient and of which comparability can be demonstrated through characterization, non-clinical studies, and clinical studies.

3. GENERAL CONSIDERATIONS

A biosimilar product is usually developed in the sequential process of carrying out some non-clinical studies and clinical studies to demonstrate the comparability of the biosimilar product to the reference product already
authorized for manufacture, marketing, or import, on condition that the quality of the biosimilar product is comparable to the reference product.

Like other biological products, a biosimilar product is evaluated in terms of quality, safety, and efficacy. When compared to a new drug, it is expected that less information is submitted to get product authorization. However, this practice is acceptable only if the comparable quality of the biosimilar product is demonstrated through extensive quality evaluations. Depending on the nature of the reference product already authorized, the degree and extent of such evaluation activities may vary.

For the biosimilar product, extrapolation of the reference product's indications is the major characteristic compared to other biological products. Even if all clinical studies are not performed for all indications of the reference product, it is possible to apply all clinical indications authorized for the reference product on condition that comparability is assured.

This document describes how to evaluate the comparability of a biosimilar product to a reference product through quality, safety, and efficacy studies. If it is intended to get the authorization of a biological product only based on clinical equivalence, this document does not apply.
4. DEFINITIONS

The definitions given below apply to the terms used in this document. To other terms not defined in this document, the definitions set forth in the Regulation on Review and Authorization of Biological Products (KFDA Notification) apply.

① A "biosimilar product" is a biological product that is comparable to already marketed reference products in terms of quality, safety and efficacy.

② A "reference product" is a drug product already authorized by a regulatory authority on the basis of full regulatory submissions. The reference product is used in demonstrating the comparability of a biosimilar product through quality, non-clinical studies and clinical studies.

③ An "originator product" is a drug product firstly authorized by a regulatory authority on the basis of full regulatory submissions. In general, a drug product with safety data publicly available and long-term marketing experience may be used as a reference product.

④ "Comparability" is a scientific comparison of a biosimilar product with a reference product with the goal to establish that no detectable difference exists in terms of quality, safety, and efficacy.

⑤ "Equivalence" is the state of being equal or virtually identical in major
clinical endpoints of interest. In addition, any observed differences are of no clinical relevance.

6 An "impurity" is any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient, including buffer components. It may be either process- or product-related.

7 "Immunogenicity" is the ability of a substance to trigger an immune response or reaction, such as development of specific antibodies, T-cell response, allergic or anaphylactic reaction.

5. SELECTION OF REFERENCE PRODUCT

The reference product selected for development of a biosimilar product should be a biological product authorized in Korea. However, if a reference product authorized in Korea is not commercially available or if there are other justifiable reasons, the same biological product as the one authorized in Korea (including the manufacturing site and the manufacturing process may be purchased from overseas markets and used as the reference product in the development of the biosimilar product.

The same reference product should be used throughout the quality, safety
and efficacy comparability program during the development of a biosimilar product. The dosage form, dose, and route of administration of the biosimilar biological product should be identical to those of the reference product.

There should be sufficient accumulated data on the safety and efficacy of the reference product. The drug product authorized as the biosimilar product should not be used as the reference product.

6. QUALITY EVALUATION

6.1. Manufacturing process

Since a biosimilar product is produced according to its own specific manufacturing process, a complete description of the manufacturing process for the drug substance and drug product should be provided in detail. The manufacturing process should be reasonable and justifiable taking into account the modern science and technology and the nature of the drug product. In addition, it should be demonstrated that the manufacturing process is able to consistently produce the biosimilar product meeting the quality requirements in compliance with the GMP requirements. Submissions should include the information on quality control/quality assurance, in-process controls, and process validation.
In addition, if a change is introduced to the manufacturing process of the biosimilar product, the comparability studies as described in the "Guidelines on Evaluation of Changes to Manufacturing Processes for Biological Products" or ICH Q5E guideline should be carried out and the comparability of the biosimilar products manufactured before and after such change should be evaluated.

6.2. Comparability studies for quality evaluation

Quality comparison of a biosimilar product and a reference product is a fundamental element in a comparability study. Quality aspects should always be appropriately studied and evaluated with regard to any implications for safety and efficacy. Information on characterization studies, including a comparability study versus a reference product, should be provided. Representative batches produced according to a manufacturing process with proven consistency should be used in comparability studies.

The purpose of these comparability studies is to demonstrate that a biosimilar product is comparable to a reference product in terms of quality, safety, and efficacy. Therefore, the drug substance (active ingredient) and the drug product should be evaluated in comparability studies and the comparability should be finally determined under comprehensive consideration of quality, non-clinical and clinical data. It is not expected that the quality attributes of the biosimilar product and the reference product will be identical. In such instances, supportive information
demonstrating that such differences will not affect the safety and efficacy should be provided.

State-of-the-art analytical techniques and validated analytical procedures which are able to detect any differences between a biosimilar product and a reference product are recommended in a comparability study.

If it is intended to isolate an active ingredient from a reference product because direct comparison at the drug substance level is difficult, supportive information demonstrating that the sample preparation is suitable and the characteristics of the isolated active ingredient are not changed should be provided.

Major process attributes that may affect the product characteristics, adequacy of process controls, and the need for additional non-clinical and clinical data should be considered.

6.2.1. Characterization

Extensive state-of-the-art characterization studies should be performed to demonstrate that the quality of the biosimilar product is comparable to the reference product. Characterization studies should at least include the physicochemical properties, biological properties, immunological properties, purity (process-related and product-related impurities), contaminants, potency, and strength. (Characterization studies may be performed in
accordance with the "Guidelines on Specifications of Biotechnological/Biological Products" or the ICH Q6B guideline.) Characterization studies should be designed to allow direct comparison of the biosimilar product and the reference product at both the drug substance and the drug product levels. However, if characterization studies result in different patterns, the implications of such differences should be evaluated and additional characterization studies may be required.

- **Structural/physicochemical properties**

The physicochemical characterization should include the determination of composition, physicochemical properties, and primary and higher order structures of the active ingredient of the biosimilar product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay may indicate a correct conformational structure. In such instances, the analytical procedures for determination of biological activity should have appropriate precision and accuracy. In addition, if process-related and product-related impurities are generated or if degradation products are identified through stress and accelerated stability studies, such impurities and/or degradation products should also be evaluated.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process. Therefore, the biosimilar product may contain a mixture of post-translationally modified forms. Appropriate efforts should be
made to investigate and identify such forms.

- **Biological properties**

Since proteins used as biological products have a wide range of biological properties, various biological assays should be considered in determining the biological activity. Biological assays can be used in determining the action mechanism of the relevant protein and, in some cases, be linked to clinical activity. Therefore, a set of relevant functional assays designed to evaluate the range of activities of a product with multiple biological activities should be developed and employed.

The biological activity assay is a method to determine the function of a protein and, if there are changes to the quality of a drug product, it can be used to verify if such changes are caused by either a product-related substance with biological activity or an impurity without biological activity. In addition, the biological activity assay can be used in verifying the protein’s higher order structure. Therefore, the biological assay can also serve as a complement to physicochemical analysis. If a biological assay with appropriate accuracy and precision is used, it is possible to demonstrate that a biosimilar product is not significantly different from a reference product in terms of biological functions. However, since the biological activity assay usually has considerable variability, it should be considered that the biological assay may not be able to detect any
differences from the reference product.

The results of the biological assay should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. Such assays should comply with appropriate compendial requirements for biological assays, if applicable.

- **Immunological properties**

Since the presence of any product- or process-related impurities or post-translationally modified forms may trigger immunological responses, it is important to characterize the immunological properties of a biosimilar product. If immunological properties are part of the characterization studies (e.g., for antibodies or antibody-based products), the specificity, affinity, binding activity, Fc function, and others of the biosimilar product should be evaluated in comparison with those of the reference product. In addition, the results from the immunogenicity studies in animal models should be considered.

- **Purity (impurities)**

The purity and impurity profiles of the drug substance and the drug product should be assessed both qualitatively and quantitatively by a combination of analytical procedures. Accelerated conditions, other conditions that may cause degradation, and potential post-translational
modifications should be considered in evaluating the impurity profiles.

The product-related impurities in the biosimilar product should be identified and compared to the reference product using the state-of-the-art technologies. If possible, application of more than one analytical technology to each should be considered.

Since the biosimilar product is produced according to its own unique manufacturing process different from that for the reference product, the process-related impurities in the biosimilar product may be quantitatively and qualitatively different from those in the reference product. Therefore, although the quantitative comparison may not be relevant in the comparability study, the state-of-the-art analytical technologies should be applied to verify the impact of these process-related impurities.

In-process acceptance criteria and action limits for impurities should be appropriately established to assure the quality of the drug substance and the drug product. Any new impurities should be evaluated in terms of quality, safety, and efficacy.

6.3. Specifications

Specifications should be established for routine quality controls. Product-specific tests to be included in the specifications should be selected to assure the quality of the biosimilar product and should comply
with the requirements as specified in the relevant regulations or guidelines.

Each acceptance criterion should be established and justified based on data obtained from representative lots (such as data obtained from lots used in non-clinical and/or clinical studies, data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data, and data obtained from the comparability studies (quality, safety, and efficacy)) and justifications for the methods used and the proposed range should be provided.

6.4. Analytical procedures

In order to demonstrate that the quality of the biosimilar product is comparable to the reference product, extensive state-of-the-art characterization studies should be applied at both the drug substance (active ingredient) and the drug product levels.

Given the complexity of the protein and its inherent heterogeneity, more than one analytical technology may be required for each quality attribute, in order to sufficiently characterize the physicochemical and biological properties.

Although validated analytical procedures are not necessarily required, analytical procedures used in the characterization studies should be scientifically sound and be able to produce reliable results. Analytical
procedures included in the specifications should be appropriately validated in accordance with the "Regulation on Review and Authorization of Biological Products" and the "Guidelines on Specifications of Biotechnological/Biological Products."

6.5. Stability studies

Long-term stability study should be carried out in order to establish the shelf-life (expiry) period and storage conditions of the drug product. Although a comparative stability study (with the reference product) is not necessarily required, accelerated and stress stability studies to establish the impurity profiles at drug substance and drug product levels are often useful in determining the comparability of the biosimilar product and the reference product. The stability studies should be performed on the basis of the representative conditions, including the container-closure system. The stability studies may be designed and performed in accordance with the "Guidelines on Stability Study of Biological Products" and the ICH Q5C guideline.

7. NON-CLINICAL EVALUATION

In order to establish the safety and efficacy of a biosimilar product, non-clinical and clinical evaluations are usually required, in addition to comprehensive quality evaluation.
In principle, non-clinical studies should be conducted with the final formulation intended for clinical use. However, if it is not possible to perform non-clinical studies with such final formulation (toxicity studies requiring administration of high dose), minimal modifications may be made within the justifiable range so as to allow the performance of non-clinical studies. In addition, the dosage form, dose, and route of administration of a biosimilar product should be identical to those of a reference product. Any differences in dosage form, dose, and route of administration should be justified.

Since non-clinical studies of a biosimilar product are conducted as a part of the comparability, they should be designed to demonstrate the comparability of the biosimilar product through comparative studies with a reference product. Such non-clinical studies may be conducted in accordance with existing relevant guidelines (such as ICH S6 document). Design of an appropriate non-clinical study requires a clear understanding of the product characteristics. Results from characterization should be reviewed from the point-of-view of potential impacts on efficacy and safety.

The same reference product should be used throughout non-clinical studies and it should be the one used in quality and efficacy evaluations.

The following *in vivo* and *in vitro* studies may be considered and should be tailored to the specific product concerned on a case-by-case basis. The
approach taken will need to be fully justified.

**In vitro studies**

Assays, such as receptor-binding studies or cell-based assays (e.g., cell-proliferation), should normally be undertaken in order to establish the comparability of the biological/pharmacodynamic activity of the biosimilar product and the reference product. Such data are usually already available from the biological assays of the quality evaluation. These studies may be referenced in the non-clinical evaluation.

**In vivo studies**

Animal studies should be performed in species known to be relevant, designed to maximize the information obtained (e.g., a species in which the reference product has shown to possess pharmacodynamic and/or toxicological activity), and employ state-of-the-art technology. In general, consideration should be given to the following conclusions:

- Biological/pharmacodynamic activity relevant to the clinical application:
  These data should usually be available from biological assays described in the quality evaluation and these studies can be made in the non-clinical part of the dossier, if feasible.

- Non-clinical toxicity as determined in at least one repeat dose toxicity
study in a relevant species and including toxicokinetic measurements: If possible, these measurements should include determination and characterization of antibody responses. The duration of the studies should be sufficiently long to allow detection of potential differences in toxicity and antibody responses between the biosimilar product and the reference product. Although the predictive value of animal models for immunogenicity in humans is considered low, data from immunogenicity studies in animal models are useful in interpretation of toxicokinetic data and assessment of overall comparability studies.

In addition, the comparative repeat dose toxicity study is useful in predicting any "unexpected" toxicity during clinical use of the biosimilar product. If performed with the final formulation intended for clinical use, the repeat dose toxicity study will, in principle, allow for detection of potential toxicity associated with the active ingredient and product- and process-related impurities.

- Local tolerance study:
  Depending on the route of administration of a biosimilar product, the local tolerance study may be performed. If appropriate, the evaluation can be performed by a part of repeat dose toxicity study.

- Other toxicological studies:
  If the comparability of the biosimilar product and the reference product is verified through quality evaluation, other toxicological studies, such as
safety pharmacology, reproductive toxicology, genotoxicity, and carcinogenicity studies, are not generally required, unless triggered by results of the repeat dose toxicity study and/or by other known toxicological properties of the reference product (e.g., known adverse effects of the reference product on reproductive function).

8. CLINICAL EVALUATION

Pivotal clinical data should be generated using the product derived from the final manufacturing process. If the manufacturing process of the drug products used in clinical studies is different from the final manufacturing process for which marketing authorization is sought, such differences should be justified and additional data may be required.

The clinical comparability studies include pharmacokinetic, pharmacodynamic, and efficacy studies. If the comparability can be demonstrated by confirmatory pharmacokinetic/pharmacodynamic data, an efficacy study may be omitted.

8.1. Pharmacokinetic (PK) studies

The PK profile is an essential part of the basic description of a drug product and should always be investigated. PK studies should generally be performed for all proposed routes of administration and using doses within the therapeutic dose range recommended for the reference product.
PK studies should be comparative in nature to demonstrate the comparability of the biosimilar product and should be designed to enable detection of potential differences between the biosimilar product and the selected reference product. This is usually best achieved by performing single-dose PK studies in a sensitive and homogenous study population and by using a dose where the sensitivity to detect differences is largest. For example, for a drug product with saturable absorption (saturation kinetics), the lowest therapeutic dose would be most appropriate, provided that the employed assay can measure the resultant drug plasma levels with sufficient accuracy and precision. Comparative PK studies could be performed in healthy volunteers as a sufficiently sensitive and homogenous population, if considered ethical.

The choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population should be justified. The cross-over design may not be appropriate for biological products with a long half-life or for proteins for which formation of anti-product antibodies is likely. Therefore, if the cross-over design is adopted, it is necessary to demonstrate that the half-life, antibody formation, and other characteristics do not affect the PK profiles. If the parallel design is selected, careful attention should be paid to avoid potential imbalances between groups.

Since differences in elimination rate of the biosimilar product and the
reference product may exist, the PK comparison should include absorption/bioavailability as well as elimination characteristics, i.e., clearance and/or elimination half-life.

Acceptance criteria for demonstration of similar PK between the biosimilar product and the reference product should be pre-defined and appropriately justified. The criteria used in standard clinical PK comparability studies (bioequivalence studies) developed for chemically-derived, orally administered products may not be applicable for biological products.

If there is evidence of comparability from the quality and non-clinical studies, other PK studies, such as interaction studies (with drugs likely to be used concomitantly) or studies in special populations (e.g., children, the elderly and patients with renal or hepatic insufficiency) are not usually required for a biosimilar product.

Historically, the PK evaluation of peptide or protein products has suffered from limitations in the assay methodology, thus limiting the usefulness of such studies. Special emphasis should therefore be given to the analytical method selected and its capability to detect and follow the time course of the protein (the parent molecule and/or metabolites). The method should be optimized to have satisfactory specificity, sensitivity and a range of quantification with adequate accuracy and precision.

If the active ingredient of a biosimilar product is an endogenous protein
and the concentration of the endogenous protein is measurable, the concentration-time profile of the administered exogenous protein may be substantially affected. In such cases, the approach to minimize the influence of the endogenous protein on the results should be described and justified.

8.2. Pharmacodynamic (PD) studies

In general, the pharmacodynamic (PD) studies may be performed in combination with PK studies and the PD parameters should be selected on the basis of their relevance to demonstrate clinical efficacy. Since biological products may have different PK and dose-response relationships, combined PK/PD studies may provide useful information in evaluating the comparability of the biosimilar product and the reference product. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different doses.

In the comparative PD studies, PD effects should be investigated in a suitable patient population using one dose within the steep part of the dose-response curve in order to best detect potential differences between the biosimilar product and the reference product. If it is possible to use PD markers well established in healthy volunteers, the comparative evaluation of PD effects may be conducted using healthy volunteers.

Usually, the clinical comparability of the biosimilar product and the
reference product should be demonstrated in the efficacy studies. However, if similar PD profiles are obtained, the equivalence in efficacy trials can be expected.

8.3. Efficacy studies

Dose finding studies are not required for biosimilar products, since the dosage and administration of the reference product are usually adopted.

If the dosage and administration of a reference product are adopted for a biosimilar product and if it is intended to extrapolate efficacy data to other approved indications of the reference product (including extrapolation to other dosage, equivalence design is more desirable than non-inferiority design. Equivalence margin should be pre-defined and appropriately justified. In other words, the margin should be selected within the range that would not show any clinical differences from the reference product.

Similar efficacy of the biosimilar product and the reference product should be demonstrated in an adequately powered, randomized, and parallel group clinical trial (‘equivalence trials’). Such clinical studies should preferably be double-blinded or at a minimum observer-blinded. In the absence of any blinding, careful justification is required to prove that trial results are free from significant bias.

Potential differences between the biosimilar product and the reference
product should be investigated in a sensitive and preferably well-established model. For example, in the case of hormone, patients with hormone deficiency may be the most appropriate study population.

8.4. Confirmatory PK/PD studies

Usually, clinical trials are required to demonstrate similar efficacy between the biosimilar product and the reference product. However, comparative PK/PD studies may be appropriate for the following cases:

- If the PK and PD properties of the reference product are well-characterized.
- If at least one PD marker is an accepted surrogate-marker for efficacy.
- If the relationship between dose/exposure, the relevant PD marker(s), and response/efficacy of the reference product is well-established.

The study population and dosage should represent a test system known to be sensitive to detect potential differences between the biosimilar product and the reference product. Otherwise, it will be necessary to investigate a relevant dose range to demonstrate that the test system is discriminatory. In addition, the acceptance ranges for demonstration of comparability in confirmatory PK and PD parameters should be pre-defined and appropriately justified.
8.5. Safety

Pre-authorization safety data should be obtained in a sufficient number of patients to characterize the safety profile of the biosimilar product.

In general, safety data obtained from clinical trials may be about frequent and short-term adverse reactions. Comparison with the reference product should include type, frequency and severity of adverse reactions. Such safety data obtained from clinical trials are usually sufficient for product authorization, but further close monitoring of clinical safety of the biosimilar product is usually necessary in the post-marketing phase.

8.6. Immunogenicity

Even if efficacy and safety of a biosimilar product and a reference product have been shown to be similar, immunogenicity may still be different. The immune response against a biological product is influenced by many factors such as the nature of the active ingredient, impurities, excipients, stability of the product, route of administration, dosage, and patient- and disease-related factors. The consequences of unwanted immunogenicity may vary considerably, ranging from clinically irrelevant to serious and life-threatening. For example, the formation of neutralizing antibodies alters the pharmacodynamic effects, binding antibodies often affect pharmacokinetics, and the anti-product antibody formation might significantly affect the safety.
Accordingly, the frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared for a biosimilar product and a reference product before authorization.

Immunogenicity of a biosimilar product should always be investigated in humans since animal data are usually not predictive of the immune response in humans. All patients in the clinical studies should be evaluated for the immunogenicity.

The antibody-testing strategy, including the selection, assessment, and characterization of assays, identification of appropriate sampling time points, sample volumes and sample preparation/storage as well as selection of statistical methods for data analysis should be described in detail. Antibody assays need to be validated for their intended purpose. A screening assay with sufficient sensitivity should be used for antibody detection and a neutralization assay should be available for further characterization of antibodies, if present. Possible interference of the circulating antigen with the antibody assay(s) should be taken into account.

If the amount of antibodies induced by the biosimilar product is increased when compared to the reference product, the potential clinical implications regarding safety, efficacy and pharmacokinetics should be evaluated. Special attention should be paid to the possibility that the immune
response seriously affects the endogenous protein, its unique biological function, and the resultant homeostasis.

The required observation period for immunogenicity testing should be specified in the manner of allowing observation of clinically significant antibody formation. The period usually depends on the intended duration of therapy and the expected time of antibody development. In the case of chronic administration, investigation should be conducted for the sufficient period to evaluate antibody incidence, their persistence, development of antibody titers over time, potential changes in the character of the antibody response and the possible clinical implications.

When application for product authorization is submitted, the immunogenicity data obtained till the completion of efficacy studies should be provided and, if necessary, follow-up data should be additionally submitted. Since pre-authorization immunogenicity data are often limited, further characterization of the immunogenicity profile may be necessary post-marketing, particularly, if rare antibody-related serious adverse events may occur that are not likely to be detected in the pre-marketing phase.

8.7. Extrapolation to other clinical indications

If similar efficacy and safety of the biosimilar product and the reference product have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the reference product for
which post-marketing survey was completed may be possible if all of the following conditions are fulfilled:

• A sensitive clinical test model has been used that is able to detect potential differences between the biosimilar product and the reference product;
• The clinically relevant mechanism of action and/or involved receptor(s) are the same;
• Safety and immunogenicity have been sufficiently characterized.

9. REFERENCES


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