- Degree to which differences in product characteristics (e.g., product structure and physical properties) can be detected,
- Degree of product heterogeneity,
- The effect of potential changes in the impurities on product safety,
- The robustness of the product (i.e., the ability of product to remain unaffected by process changes), and
- Rigorousness of the manufacturing process controls (i.e., the ability of the manufacturing process controls to ensure that the product remains unaffected by changes).

We recommend that you consider a comparability protocol only if you expect: (a) the product resulting from the changes to meet the approved drug substance and/or drug product specifications and predetermined acceptance criteria for non-routine characterization studies; (b) appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for non-routine tests such as characterization studies) to assess the effect of the change on the approved product; and (c) the approved manufacturing process and equipment has been fully qualified and validated, when appropriate.

Some specific examples submitted to us of changes to the manufacturing process where a comparability protocol has been used include, but are not limited to, the following:

- Increase or decrease in batch size that affects equipment size,
- Modification of production operating parameters in fermentation (e.g., time, temperature, pH, dO_2 (dissolved oxygen)),
- Adding, deleting, or substituting raw materials (e.g., buffer or media components),
- Mode changes (usually associated with equipment changes such as tangential flow filtration to centrifugation),
- Establishing a new working cell bank using a modified procedure,
- Reprocessing the drug substance or drug product, as appropriate,
- Addition, deletion, or rearrangement of production steps; and
- Facility-related changes for products with facility/establishment information provided in a BLA, or postapproval supplement to a BLA (see examples provided in Section V. E.).

C. When Might a Comparability Protocol Be Inappropriate?

A comparability protocol would be inappropriate for some CMC changes. In some cases, it may be impossible for the changes and/or plan for evaluating the effect of the CMC changes on the product to be fully described in advance. For example, a change may also be too complex to evaluate its effect on the product without efficacy, safety (clinical or nonclinical), or pharmacodynamic or pharmacokinetic (PK/PD) information.

In general, we do not recommend comparability protocols for:

- Nonspecific plans for CMC changes,
- A CMC change for which the adverse effect on the product cannot be definitively evaluated by prespecified tests, studies, analytical procedures, and acceptance criteria,
- Any CMC change that warrants the submission of an investigational new drug (IND),[13] investigational new animal drug (INAD), or new original application, and
- A CMC change that requires efficacy, safety (clinical or nonclinical), or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities, assess impurities or assess immunogenicity/antigenicity).

It may be possible to design a comparability protocol for certain CMC changes, but we may be limited in our ability to designate a reporting category other than PAS for changes implemented under such a protocol. Moreover, in some situations, these changes could require the submission of an IND, INAD, or new application. Examples of such changes can include:

- A change in the drug substance or drug product specifications (for exceptions, See Sections V.A.4 and V.C),
- A change in the qualitative or quantitative formulation of the drug product,[14]
- A change in the type of delivery system.
- A change in or move to a manufacturing site, facility, or area when a prior approval supplement is recommended because an inspection (e.g., current good manufacturing

[13] INDs may be warranted in certain circumstances, such as for a change from plant, animal, or multicellular (e.g., algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal), a change in the species of a microorganism or cell line used as source, a change in the microorganism or cell line used as source from non-recombinant to recombinant-DNA-modified, a change from a non-transgenic source to a transgenic plant or animal, or a change from one plant or animal transgenic source material to another.

[14] A comparability protocol might be useful in certain cases for quantitative changes in excipients, and FDA might designate a reduced reporting category for certain types of products and changes if you have sufficient information to assess the potential effect of the change.

practice (cGMP) inspection) is warranted (e.g., see examples in guidances listed in Section II.D.), and

- Facility-related changes for products with facility/establishment information provided in a BLA or postapproval supplement to a BLA. See examples provided in Section V.E.

IV. PROCEDURES FOR COMPARABILITY PROTOCOLS

A. How Should a Comparability Protocol Be Submitted?

You can submit a comparability protocol in a prior approval supplement or as part of the original application. However, we recommend that you evaluate the appropriateness of including the comparability protocol in the original application when your experience manufacturing the product is limited and it may be difficult to identify the elements of an appropriate comparability protocol (see considerations in Section III.B.). We recommend that you indicate that you are submitting a comparability protocol.

You may submit the proposed comparability protocol in:

- A prior approval supplement that consists only of the proposed comparability protocol. You may want us to review and approve the protocol and determine the reporting category for changes, evaluated under the protocol, prior to generating data specified in the protocol.
- A prior approval supplement that includes the proposed comparability protocol, study results, and any other pertinent information as specified in the proposed comparability protocol. Note that the comparability data submitted would be evaluated as part of the prior approval supplement. The product already manufactured with the change can be distributed only after approval of the supplement.
- A part of an original market application. You may want the comparability protocol reviewed and approved and the reporting category determined, prior to generating data specified in the protocol.

In all cases, the comparability protocol must be approved prior to distributing the product made using the CMC changes specified in the protocol. As specified in your protocol, you must also complete the studies that assess the effect of the changes on the identity, strength, quality, purity, and potency of the product and report the results to us in accordance with the reporting category we designated as part of our approval of the protocol, prior to distributing the product made with the change (Section 506A(b) of the act, and 21 CFR 601.12).

B. How are Changes and Study Results Submitted After a Comparability Protocol is Approved?

After a protocol is approved, we recommend that you document and submit each implemented change within the scope of the protocol using the reporting category that we designated. Include (1) the results of all tests and studies specified in your comparability protocol; (2) discussions of significant deviations that occurred during the tests or studies and that may have affected the tests or studies; (3) a summary of investigations performed, with analysis of the circumstances, product impact, corrective actions, and conclusions reached; and (4) any other pertinent information. We recommend that you indicate in the submission that it includes data from a change covered under a comparability protocol and provide a reference to the submission in which the comparability protocol was approved.

C. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?

In certain instances, the changes, the tests, and/or the studies specified in an approved comparability protocol can lead to an unpredicted or unwanted outcome (e.g., test results do not meet predefined acceptance criteria). If this occurs, you can elect not to implement the change. If you decide to pursue the change, we recommend that you submit a prior approval supplement that provides the supporting data to justify why the change will not adversely affect the identity, strength, quality, purity, and potency of the specific drug product as they may relate to the safety and effectiveness of the product.

D. When Does a Comparability Protocol Become Obsolete?

New regulatory requirements, identification of a safety issue (e.g., screening for new infectious agents in materials from a biological source), identification of a new scientific issue, or technological advancement after the comparability protocol has been approved can render a protocol obsolete. We recommend that you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure that they remain current and consistent with the approved application and current regulatory and scientific standards. We recommend that you determine whether the tests, studies, analytical procedures, and acceptance criteria described in your comparability protocol are still appropriate prior to implementing and submitting a change under the protocol. We may determine that a reporting category made in the approval of a comparability protocol that becomes obsolete is no longer applicable. We may also request additional information to support a change that is evaluated using an obsolete protocol. If you find the comparability protocol is no longer correct or adequate, you should modify or withdraw the current protocol.

E. How is an Approved Comparability Protocol Modified?

You can submit a revised protocol at any time. Like an original protocol, you can submit a revised protocol as a PAS to your application following the recommended submission procedures summarized in Section IV.A. We recommend that you indicate in the submission that it includes a revision to an approved comparability protocol and identify all modifications.

A comparability protocol should also be modified to reflect relevant changes in the application. For example, you may ask FDA to approve a change in an analytical procedure that is used for release testing. The new analytical procedure should also be incorporated into approved comparability protocols, if appropriate. As part of the request to make the change in release testing, we recommend that you clearly indicate in your submission all comparability protocols that will also be affected. The specified comparability protocols would be updated as part of the submission for the change in release testing, using the reporting category appropriate for that change. There would be no need to make a separate submission requesting a modification of each comparability protocol. However, you should wait to implement the modified comparability protocol until you are authorized to implement the change in release testing.

V. CONTENT OF A COMPARABILITY PROTOCOL[15]

We recommend that that you develop and use a comparability protocol within the context of existing change control procedures. Such procedures ensure that specified changes do not adversely affect the identity, strength, quality, purity, or potency of the product.

In the comparability protocol, you can describe a single CMC change or multiple changes. We recommend that you specify each change and define the acceptance criteria for evaluating the effect of the changes. If multiple changes are included in a protocol, we recommend that the multiple changes be interrelated (i.e., one change cannot be made without the others; changes focus on a common goal such as production optimization). For example, a change in a fermentation medium component used to produce a protein results in more rapid cell growth that in turn, causes a higher production rate of the protein. Changes related to this change in culture medium could include modification in the length of cell fermentation, increase in harvesting time, and/or changes to purification columns. We recommend that you submit separate comparability protocols for unrelated changes.

[15] For brevity, the text focuses on comparability protocols submitted in postapproval supplements, although the option is available to include a comparability protocol in an original submission.

A. What are the Basic Elements of a Comparability Protocol?

1. Description of the Planned Changes

A comparability protocol should provide a detailed description of the proposed changes clearly identifying all differences from the conditions approved in the application. A table, diagram, and/or flow chart can be included to help illustrate the differences.

2. Specific Tests and Studies to Be Performed

We recommend that you include a list of the specific tests (e.g., release, in-process) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation, validation, process development) that you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g., container closure system) directly affected by the change. We recommend that you include the rationale for selecting the particular battery of tests and studies. This rationale could include a discussion of the type and extent of the change, potential effect of the change, experience with the manufacturing process, and product robustness. For example, the inclusion of additional tests to check for new impurities, glycosylated species or other posttranslation modifications that may be formed as a result of the change, or use of nonroutine studies (e.g., characterization) may be warranted. Such additional testing is especially important in cases where in-process or release specifications are not sufficiently discriminatory to evaluate the change, (e.g., tests for secondary or tertiary structure). We recommend that you include a plan, within the protocol, to compare results from routine batch release testing and, as appropriate, nonroutine testing (e.g., characterization studies) on pre- and postchange products or other material, if appropriate. We recommend that you specify the number and type (e.g., pilot, production) of pre- and postchange batches and/or samples that will be compared. The number and type of batches and/or samples to be compared can vary depending on the extent of the proposed change, type of product or process, and available manufacturing information. You can use retained samples of prechange material for comparison, provided there is no significant change in material during storage (e.g., level of degradants increasing over time). If you plan to use retained samples, we recommend that you specify their maximum age and provide a justification with supporting data for using retained samples. In general, the results from postchange material should fall within the normal batch-to-batch variation observed for prechange material.

In a comparability protocol we recommend that you include a plan for the stability studies that will be performed to demonstrate the comparability of the pre- and postchange product. The comparability protocol should provide: (1) information that is typically provided in a stability protocol, such as the number and type of batches that will be studied, test conditions, and test time points, or (2) a reference to the currently approved stability protocol. You should specify the amount of stability data that will be collected before the product made with the change is distributed. The plan for evaluating stability could vary depending on the extent of the proposed change, type of product, and available manufacturing

information. In some cases, no stability studies may be warranted or a commitment to report results, when available (e.g., annual report), from stability studies postapproval can be sufficient. If you don't plan to conduct stability studies, we recommend that you state this clearly and provide justification for not doing so.

We recommend that you describe the differences, if any, in the tests and studies from those previously reported in the approved application or subsequent updates (i.e., supplements, annual reports). We recommend that you include a citation of the location in your application of any referenced tests or studies.

3. Analytical Procedures to Be Used

In a protocol we recommend that you specify the analytical procedures that you intend to use to assess the effect of the CMC changes on the product or intermediate material. We recommend that you use analytical procedures capable of detecting and quantifying impurities (e.g., process-related impurities such as host cell proteins, product-related impurities, etc.) or other effects on the product that can result from the change.

Because the currently approved analytical procedures are optimized for the approved product and process, you may want to use modified or new analytical procedures (for example, to monitor the removal of a new process impurity generated by a new manufacturing process). In this situation, we recommend that you submit results for pre- and postchange products using both the old and new analytical procedures. Studies that you perform to assess the feasibility of the proposed change can often be helpful in determining whether the current approved analytical procedures will be appropriate for assessing the effect of the change on the product (see Section V.A.5). As appropriate, you should validate new or modified analytical procedures (with establishment of corresponding acceptance criteria) or revalidate existing analytical procedures. Alternatively, the plan for validation of a new analytical procedure or re-validation of an existing procedure can be included within the protocol and the validation report provided to the Agency in accordance with the designated reporting category (see Section V.C.).

In some instances, analytical procedures are used in the characterization and/or assessment of the functionality of a product, but not for batch release or for process control (e.g., NMR spectroscopy, carbohydrate structural analysis, attachment site determination). If you specify these analytical procedures in a comparability protocol, we recommend that you provide any replacement or modification to those procedures submitted in the approved application and, as appropriate, report to us results from qualification studies when a postapproval CMC change is implemented using the approved comparability protocol.

In cases where changes in analytical procedures are intended to be implemented independent of other CMC changes, we recommend that you submit a comparability protocol specific for analytical procedure changes (see Section V.C.).

4. Acceptance Criteria

We recommend that you include the acceptance criteria (numerical limits, ranges or other criteria) or other acceptable results for each test and study in the protocol that will be used to assess the effect of the CMC change on the product or other material and assess comparability between pre- and postchange material. In general, the drug substance and drug product specifications would be identical to or tighter than those in the approved application, unless otherwise justified. We recommend that you identify any statistical analyses that will be performed and the associated evaluation criteria.

After implementing a change under a comparability protocol, you may find that the CMC change calls for a revision of the drug product or drug substance specification. Change to that specification under these circumstances would not fall under the determination of reporting category made for the comparability protocol submission. Accordingly, in making your CMC change submission, we recommend that you consider the recommended reporting category[16] for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), we recommend that you use the reporting category associated with the specification change, that is, the higher reporting category. If the recommended reporting category for the specification change is the same or lower than the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided when you report a postapproval CMC change implemented using the approved comparability protocol.

5. Data to Be Reported Under or Included With the Comparability Protocol

We recommend that you identify the type (e.g., release, long-term, accelerated and/or stress stability data, as appropriate) and amount of data (e.g., 3-month accelerated, 6-month real-time stability data) that you will submit at the time you report to us a postapproval CMC change implemented using the approved comparability protocol and, when appropriate, generated prior to your distributing the product made with the change (e.g., when proposed reporting category is a CBE-30, CBE-0, or AR).

If available, you can include any data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Data obtained from a small-scale process or other studies incorporating the proposed change can provide preliminary evidence that the change is feasible,

[16] The recommended reporting categories for specification changes may be found in the guidance on *Changes to an Approved Application For Specified Biotechnology and Specified Synthetic Products and Changes To An Approved Application For Biologics.*

as well as preliminary information on the effect of the change on the product. Development or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product and/or process.

6. Proposed Reporting Category

The use of an approved comparability protocol may support a reduction in the reporting category for the particular CMC change when implemented (see Section III.A). We recommend that you include a proposal for the reporting category that you would use for changes implemented using the approved comparability protocol. We will evaluate your proposed reporting category as part of our review of the comparability protocol and communicate any concerns about your proposal. A designation of the reporting category for the specified CMC changes will be included as part of the approval process for the comparability protocol.

7. Comparability Not Demonstrated Using the Approved Comparability Protocol

It is anticipated that some changes in the manufacturing process will result in a postchange product that cannot be demonstrated to be comparable to the prechange product without more extensive physicochemical, biological, pharmacological, PK/PD, efficacy, or safety testing or in a product that does not meet the prespecified acceptance criteria in the protocol. We recommend that you identify in the protocol the steps you will take in such circumstances (see Section III.C.).

8. Commitment

We recommend that you include a commitment in your comparability protocol to update or withdraw your protocol when it becomes obsolete (see Section IV.D).

B. Does FDA Have Specific Concerns About Changes in the Manufacturing Process That Should Be Addressed in a Comparability Protocol?

In addition to the general considerations provided in Section V.A, we recommend that you consider the following issues related to changes in the manufacturing process, where applicable:

1. Physicochemical and Biological Characterization

A comparability protocol would include a plan to compare the physicochemical and biological characterization of the product produced using the old and new processes when these characteristics are potentially affected by the change and are relevant to the safety and/or efficacy of the product. For recombinant DNA-derived protein products and other products when appropriate, such characterization can include structural analysis (e.g., primary, secondary, tertiary, quaternary), glycoform analysis, and bioassay, as appropriate.

541
542 2. Comparison of Impurity Profiles
543
544 A comparability protocol should include a plan to determine the impurity profile of the product
545 produced using the new process. The studies should assess product-related impurities and process-
546 related impurities including, if applicable, cell substrate-derived, cell culture-derived and downstream-
547 derived impurities. We recommend that you demonstrate the absence of any new impurities or
548 contaminants, or that they are removed or inactivated by downstream processing (e.g., clearance
549 study). You should justify any changes in the impurity profile.
550
551 If during implementation of a change under an approved comparability protocol, the data indicate that
552 nonclinical or clinical qualification studies to evaluate safety for impurities are warranted, the change
553 would not be appropriate for implementation under the approved comparability protocol (see Sections
554 III.C and V.A.7).
555
556 3. Effect on Downstream Processes
557
558 We recommend that you examine the effect of the change on downstream processes. Downstream
559 processes such as purification steps can be affected by higher product yields or shifts in impurity profiles
560 when upstream processes are modified. For example, adventitious agent removal or inactivation may
561 have to be reassessed for processes involving materials or reagents derived from a biological source.
562 We recommend that you discuss in your comparability protocol how to ensure that the entire
563 manufacturing process is adequately controlled.
564
565 4. Effect on Process Controls and Controls of Intermediates and/or In-process Materials
566
567 We recommend that you identify and justify implementation of new controls or variations from approved
568 controls. We recommend that you include in the protocol a statement that controls, including those that
569 have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new
570 production process, if appropriate.
571
572 **C. Does FDA Have Specific Concerns About Changes in Analytical Procedures**
573 **That Should Be Addressed in a Comparability Protocol?**
574
575 A comparability protocol for changing an analytical procedure should provide the plan for validation of
576 the changed analytical procedure and indicate whether the protocol will be used to modify the existing
577 analytical procedure (i.e. retaining the same principle), or to change from one analytical procedure to
578 another. We recommend that you design the comparability protocol to demonstrate that the proposed
579 changes in the analytical procedures improve or do not significantly change analytical procedure

characteristics that are relevant to the type of analytical procedure, its validation, and intended use (e.g., accuracy, precision, specificity, detection limit, quantitation limit, linearity, range).[17]

Methods validation includes an assessment of the suitability of the analytical procedure. You should have in your validation plan prespecified acceptance criteria for relevant validation parameters such as precision, range, accuracy, specificity, detection limit, and quantitation limit. The proposed acceptance criteria for these parameters should ensure that the analytical procedure is appropriate for its intended use. In the validation plan you would assess whether a revised procedure is more susceptible than the original procedure to matrix effects by process buffers/media, product-related contaminants, or other components present in the dosage form. You should identify in the plan any statistical analyses that you will perform and whether you intend to perform product testing to compare the two procedures. The need and plan for providing product testing to compare the two procedures could vary depending on the extent of the proposed change, type of product, and type of test (e.g., chemical, biological). When you use the new revised analytical procedure for release or process control, you should not delete a test or relax acceptance criteria that we approved in your application, unless and until FDA informs you that the approved acceptance criteria are no longer required.

D. Does FDA Have Specific Concerns About Changes in Manufacturing Equipment That Should Be Addressed in a Comparability Protocol?

Comparability protocols may be useful if applicants plan to use different equipment or plan equipment changes that would effectively result in different equipment. These changes are often made in conjunction with changes to the manufacturing process. Different equipment can include new models, changes in capacity, construction materials (e.g., glass-lined tanks to stainless steel), equipment design, and/or equipment operating principles. Comparability protocols may also be useful when additional duplicative process trains (such as fermentation trains) or equipment will be added to an approved manufacturing facility. We recommend that you evaluate these types of change with respect to its effect on the production process prior to deciding whether a comparability protocol would be appropriate. We encourage you to initiate early dialogue with us to facilitate the change, as needed.

E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?

The utility of a comparability protocol is often limited due to the scope of the change and the need, in some cases, for an inspection. For example, a move to a new facility can involve many changes (e.g., new equipment, modified manufacturing process) that are difficult to prospectively identify as part of a comparability protocol because the new facility is unknown or not constructed at the time the

[17] Guidance on validation of some analytical procedures can be found in the ICH guidances on *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology* or VICH guidances on *GL1 Validation of Analytical Procedures: Definition and Terminology* and *GL2 Validation of Analytical Procedures: Methodology*.

comparability protocol is being considered. We recommend that you consider carefully the appropriateness of a comparability protocol for a facility change, especially one that involves many other changes. For biologics, which also have application requirements described in an Establishment Description section, there may be additional situations when a comparability protocol can be useful. We encourage early dialogue with us.

There are CMC changes where a preapproval inspection may be conducted prior to distribution of product made with the change to confirm an acceptable cGMP compliance status.[18] You may consult the guidance documents listed in section II.E, or consult FDA, to determine whether FDA would require such a prepproval inspection. If a preapproval inspection would be needed, your comparability protocol would identify the preapproval inspection requirement and acknowledge that product made at a different drug substance or different drug product manufacturing site will not be distributed until FDA has verified the satisfactory cGMP compliance status for the type of operation at the new site. Furthermore, in the case of aseptically processed product, your protocol would also provide that a product manufactured in a different facility or area (e.g., room or building on a campus) will be distributed only when that specific facility or area has a satisfactory cGMP compliance status. For a move to another type of site (e.g., drug substance intermediate manufacturing site, packaging, testing laboratory), the protocol would provide that a product manufactured at the site would not be distributed if there were an unsatisfactory cGMP compliance status for the site.

For BLAs, some major changes at an existing facility (i.e., those that have a substantial potential to adversely affect the product) may require, under 21 CFR 601.2(d), a satisfactory cGMP compliance status prior to distribution of the product made with the change. For these major changes the comparability protocol would provide that the product would not be distributed if an unsatisfactory cGMP compliance status exists.

A comparability protocol has been beneficial when introducing additional products into an approved dedicated area in a facility for biologics and protein drug products. In addition, for products with facility/establishment information provided in a BLA or postapproval supplement to a BLA, (i.e., Establishment Description section), FDA may be limited in its ability to designate a reduced reporting category for changes that include:

- Major changes in equipment, or utilities (e.g., new heating ventillation and air conditioning system; new filling line for aseptically processed sterile products; in some limited instances duplicative, discrete changes may be appropriate for a reduced reporting category (e.g., extensive modification of an existing Water For Injection system); or

[18] A satisfactory cGMP compliance status includes a satisfactory cGMP inspection - an FDA inspection during which (1) no objectionable conditions or practices were found (No Action Indicated (NAI)) or (2) objectionable conditions were found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI), and satisfactory disposition of other relevant actions (e.g., investigations, warning letter, product recalls).

- The introduction of additional product(s) into an approved product-dedicated manufacturing area of a facility where containment is a concern (e.g., live virus manufacturing operations such as replication competent gene therapy vector propagation, or live attenuated viral vaccine finishing operations).

F. Can a Comparability Protocol Be Used for Container Closure System Changes?

Yes. In the past, applicants have used protocols for container closure system changes, and they can continue to use them. A comparability protocol can be particularly useful for repetitive container closure system changes.

G. Can Implementation of or Changes in Process Analytical Technology (PAT) Be Addressed in a Comparability Protocol?

We anticipate that implementation of, or changes in, PAT could be addressed in a comparability protocol. We encourage early dialogue with us. We intend to publish a PAT guidance in the future.

H. Can a Master File Be Cross-Referenced in an Applicant's Comparability Protocol?

You can cross-reference a master file in a comparability protocol that provides for CMC changes (e.g., container resin). We recommend that you include, in the protocol, a commitment to provide a letter authorizing us to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to us. We recommend that you indicate in the comparability protocol the type of information (e.g., manufacturing and formulation information for a plastic resin) that will be referenced in the master file and the information that you will provide such as the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to approved specification, compatibility studies, stability studies).

I. Can a Comparability Protocol Be Included in a Master File?

A comparability protocol can be included in a master file. The protocol can be cross-referenced for CMC changes. In your PAS submission for your product, you must include a letter authorizing us to review the master file (21 CFR 314.420(b)). Comparability protocols are product specific. Therefore, in your PAS submission we recommend that you provide a comparability protocol that augments the information provided in the master file by specifying, for example, any additional studies that you will perform to demonstrate the suitability of the postchange material (e.g., conformance to approved specification, compatibility studies, stability studies). Ordinarily, we neither independently review master files nor approve nor disapprove submissions to a master file.

添付資料5

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 20 September 2001
CPMP/BWP/3207/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS DRUG SUBSTANCE

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COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE

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1. INTRODUCTION

1.1 Purpose

It is well acknowledged that medicinal products of biotechnological origin are often subject to change in their manufacturing process (drug substance and/or drug product). Improvement of product quality, increase in production yield and global productivity or improving process economics are the main reasons for introduction of such changes. These changes can be introduced either during the development phase or after the Marketing Authorisation has been granted. Whatever the production step at which the change occurred, there is a necessity to compare the product derived from the modified process to the one derived from the currently used process, essentially to ascertain that introduction of the change did not alter the physico-chemical and biological characteristics of the product. These characteristics (mainly reflected by the current in-process controls and release specifications) are of utmost importance as they are the basis on which quality, safety and efficacy of the product are claimed. A change in these characteristics may lead to a different safety or efficacy profile of the product. As a consequence, a comparability exercise should be considered for a given product following change made in its manufacturing process.

This Note for Guidance does not cover changes introduced at a very early stage of development (namely before pre-clinical studies and initial clinical trials to evaluate preliminary safety are conducted).

In addition, there is a need to consider the necessity for conducting comparability studies for situations where a manufacturer is seeking approval of a Marketing Authorization for a biotechnology-derived product claimed to be similar to one already authorised.

Whatever the situation, the reasoning (step by step approach) as regards the comparability exercise should be identical. In this approach, the following parameters should be considered as key points: i) characterisation studies, ii) validated manufacturing process, iii) release data, iv) stability data, and, in wider perspective v) pre-clinical and clinical studies.

This Guideline has been prepared with reference to the scientific principles already developed, for example in the following documents:

1.2 Regulatory framework

- CPMP Guideline on Production and Quality Control of Medicinal Products derived by Recombinant DNA Technology,
- CPMP Guideline on Production and Quality Control of Monoclonal Antibodies
- CPMP/ICH/365/96 Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B),
- CPMP/ICH/139/95 Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products (Q5B),
- CPMP/ICH/138/95/ Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C),
- CPMP/ICH/294/95 Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products (Q5D),
- CPMP/ICH/295/95 Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products derived from Cell Lines of Human or

Animal Origin (Q5A).

These Guidelines address the key elements on which specifications for quality control of biotechnology-derived proteins should be set. Further guidelines on general quality requirements should also be taken into account.

1.3 Scope

This Guideline addresses the issue of demonstration of comparability for medicinal products containing proteins derived from r-DNA and hybridoma techniques. As a consequence the principles adopted and explained in this document should apply to proteins and peptides, their derivatives and products of which they are components (e.g. conjugates). These proteins are produced from recombinant cell-culture expression system and can be highly purified and characterised using an appropriate set of analytical procedures. The principles and arguments outlined in this document may be used as a framework when envisaging similar situations for other biological products not covered by this Note for Guidance.

It is important to note that the concept of "comparability" as referred to in this Note for Guidance is a separate concept from that of "essential similarity" as referred to in Article 4.8.a of Council Directive 65/65/EEC (as amended). "Essential similarity" is assessed in accordance with its own, separate criteria and does not fall within the scope of this Note for Guidance.

1.4 Comparability exercise

Comparability is the exercise that will demonstrate that two products have similar profile in terms of Quality, Safety, Efficacy. The comparability exercise should be viewed as a sequential process. The claim of comparability in terms of Quality, Safety and Efficacy can be deduced from quality studies (partial or comprehensive) and may need to be supported by bridging preclinical/clinical studies.

The comparability exercise and the claim of comparability is applicable to the two situations,

i) change introduced by one manufacturer (or related manufacturers) into its own process, ii) for a product claimed to be similar to another one already marketed

2. COMPARABILITY EXERCISE FOR CHANGE INTRODUCED IN THE MANUFACTURING PROCESS OF A GIVEN PRODUCT

As mentioned in the introduction, it is frequent for a manufacturer, in the life cycle of a product, to introduce changes in the production process. These changes can be introduced either during the development phase (see also 2.2.1) or after the marketing authorisation has been granted. In all cases, whatever the stage of development where the change is introduced, it is the responsibility of the manufacturer to assess to what extent the change introduced i) modify the quality profile of the resulting product and ii) may potentially impact on safety and efficacy.

In this chapter, the various key elements to be considered in designing the comparability exercise and extensiveness of the required studies are presented.

2.1 Points to consider in performing comparability studies

The comparability exercise should be considered as a whole set of interrelated considerations encompassing the three evaluation criteria of quality, safety, and efficacy.

Indeed, any change or modification made to a production process may impact on the quality, safety and efficacy of the drug product. Many different types of changes can be introduced in the manufacturing process. Annex I lists the most common changes introduced in the manufacturing process. Regulations have classified pharmaceutical variations as minor and major. However this classification may not be appropriate as the basis for designing

comparability strategies sinceeven changes considered as minor may result in relevant modifications of the quality profile of the product. Consequently, it is advisable not to classify *a priori* any changes as minor or major based on the type of change itself, but to consider the potential consequences (which will be major or minor) of the change introduced on product quality, safety and efficacy.

Depending on the consequences in terms of quality, safety and efficacy of the introduced change, various situations with different levels of complexity can be foreseen and thus the comparability exercise:

- will be limited to the strict process validation of the change introduced,
- will be extended to various quality criteria such as in-process controls, stability data, thorough analytical and biological characterisation of the product,
- cannot be fully carried out based solely on quality criteria and needs to be further documented as regards *in vivo* safety/efficacy profile.

Consequently, extensiveness of the comparative studies will depend on:

- the stage of development when the change is introduced
- the quality criteria consideration regarding the potential impact of the change introduced on the purity as well as physico-chemical and biological properties of the product
- the suitability and availability of analytical methods to detect potential modification(s) as regards product characteristics,
- the relationship between quality criteria set with safety and efficacy results, based on the overall pre-clinical and clinical experience (safety and efficacy criteria consideration).

2.1.1 Stage of Development when the change is introduced

The comparability exercise should be carried out when change is introduced either during development, i.e. after critical studies (demonstration of product consistency, stability studies, pre-clinical studies, pivotal phase II/III clinical studies) have been initiated or after the marketing authorisation has been granted. Needless to say that where change is introduced at a very early stage of development (namely before pre-clinical studies and initial clinical trials to evaluate preliminary safety are conducted) the basic issue of comparability is not raised.

2.1.2 Quality criteria consideration

The complexity of the concerned molecular entity should be considered as a major criterion in discussing comparability. Indeed, depending on the physico-chemical properties of the molecule (e.g. from primary to quaternary structure, length of the sequence, post-translational modifications such as extent and nature of glycosylation, N/C terminal modifications), it can sometimes be difficult to define precisely the product and there is a need to use an extensive series of analytical techniques exploiting the various physicochemical properties (size, charge, hydrophobicity, etc.) and biological activity of the molecule.

In many cases, due to the inherent variability of the biological process, the end-product consists of a complex mixture of molecules (product-related substances). This heterogeneity, which is taken into account when assessing the in-vivo behaviour of the product, should be characterised to assure batch-to-batch consistency. Heterogeneity contributes to the difficulty of the comparability study due to the complexity of these products. The *Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* stipulates that specifications for drug substances and drug products should be considered as the result of a total quality control strategy which includes cloning strategy, expression and genetic stability, thorough product characterisation, validation and consistency

of the manufacturing process (in-process controls, quality monitoring of raw materials and reagents), stability data, as well as quality of the batches used in pre-clinical and clinical studies. It is noteworthy that, in some cases, it may not be sufficient to demonstrate only compliance with the approved specifications and additional studies on protein structure, impurity profile and/or biological activity may be needed.

Consequently, as an initial approach when introducing a change in a given process, the following parameters, on which specifications have been based, should be considered as key points: i) characterisation studies, ii) validated manufacturing process, iii) release data, iv) stability data, and, in wider perspectives v) pre-clinical and clinical experiences. They should be evaluated in a step by step approach when discussing comparability.

2.1.3 Suitability of available analytical methods

Given the complexity of the molecule and its inherent heterogeneity, it is sometimes difficult to guarantee that the set of analytical techniques (even state-of-the-art and acknowledging the huge progress made in the field) selected by the manufacturer will be relevant or able to detect any slight or discrete modifications of the characteristics of the biotechnology-derived product. It is however the demonstration of absence of such discrete modifications which could authorise a manufacturer to declare its product indistinguishable in all aspects pertinent to the evaluation of quality.

Whenever a change is introduced in the production process, manufacturers should provide assurance that a comprehensive quality control program has been developed and an appropriate set of analytical methods have been selected in order to assess the comparability of the product before and after the change have been introduced. The degree of validation of the analytical methods used should be appropriate to the stage of development. Whatever the impact of the change(s), the analytical methods should allow suitable assessment of the manufacturing process as well as specifications regarding both the drug substance and the drug product. The main task will be to establish to what extent the analytical methods used are able to detect any slight modification possibly introduced by the change

2.1.4 Safety and efficacy criteria consideration

It should be noted that specifications for drug substance and drug product are based on data derived from batches which have been used in pre-clinical and clinical studies. This means that specifications applied have been validated both by and for the *in vivo* use of the product.

When a change in the manufacturing process results in modifying the specifications (drug substance/drug product) and/or in process controls, it should be considered whether the comparability exercise can be restricted to quality aspects or, if quality aspects are not sufficient, it should also include safety and/or efficacy criteria. In situation where differences either are identified or are suspected, appropriate pre-clinical and clinical studies could be considered as the only definite way to demonstrate comparability, at least for some specific features such as immunogenicity.

In this respect, the nature and the extent of the pre-clinical and/or clinical studies to be performed when assessing the potential consequences of the change introduced should be justified and designed taking into account the degree of knowledge of the molecule, its mode of action and the experience already gained as regards *in vivo* behaviour.

2.2. Strategies of comparison depending on the change introduced in the manufacturing process

The manufacturer, when introducing a change in a manufacturing process (drug substance or drug product) is confronted with two different approaches as regards the strategy to be

applied:

a) the initial hypothesis considers that the change introduced will not have any impact on the quality criteria of the product. In this case, assurance has to be provided that the in-process control and/or the release data found (drug substance or drug product specifications), as compared to those obtained using the previous process, have not been modified. The comparability exercise can be acceptable provided that the methods used are sensitive enough to detect slight differences in the structure of the molecular entity. When routine tests are considered as inappropriate to pick up subtle differences, additional studies, using more powerful analytical methods such as those previously performed in characterisation studies (during the initial development), should also be envisaged. In case the expected quality acceptance criteria are not met, a complete validation program should be carried out (see point 2 here below).

b) the initial hypothesis considers that the change introduced will impact on the quality of the product. In this case, consequences of the change(s) on the characteristics of the product should be investigated using a full set of validation data with particular emphasis on characterisation, batch-to-batch consistency and stability. In addition, the potential impact of the change as regards safety and efficacy has to be taken into consideration.

Depending on the process level where the change is introduced, several controls (monitoring, follow-up) would have to be performed sequentially all along the process leading to the final intended drug product.

2.2.1 Change with no impact on quality criteria (in-process controls as well as drug substance and/or drug product specifications)

In this case, the comparability exercise can be restricted to the change introduced. Manufacturer should focus on the modification introduced and illustrate that the change has no impact on the whole set of quality acceptance criteria by the results obtained for a suitable number of consecutive batches (in-process controls and release specifications). However, depending on the change introduced, the need for stability data cannot be systematically excluded. Such change does not call into doubt the quality of the drug substance/drug product and thus does not put into question what has already been established dealing with safety/efficacy.

This case could be encountered in situations such as: change in reagent supplier, change in excipient supplier, etc. In such cases, if the quality results for one batch are found different, assurance that these results are directly linked to the specific change introduced (and not linked to any other adverse events) should be provided and the others situations, as described hereafter, should apply.

2.2.2 Change with impact on in-process controls without impact on drug substance and/or drug product specifications

Consequent to the change (introduced, although there are no modification with respect to release specifications (drug substance and/or drug product), some in-process controls needs to be refined in a way to guarantee reproducibility of the modified process. Data (revised in-process controls but unmodified release specifications) on a suitable number of consecutive batches have to be provided to i) illustrate the consistency of the manufacturing process and ii) ascertain that release specifications remain unchanged. In addition, stability studies should be initiated and data provided on several batches (drug substance and/or drug product). In this situation, as for the one mentioned in section (3.1), change introduced does not put into question what has already been established dealing with safety/efficacy.

The comparability exercise can be acceptable provided that the methods used are sensitive