

# ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

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# ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

*Notice to the Reader: Where reference is made to nonclinical and clinical studies, additional information and modification of these specific items will be provided by ICH Safety and Efficacy Experts.*

## 1.0 Introduction

### 1.1 Objectives of the Guideline

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. This guideline is intended to assist in the design and conduct of studies used to collect the technical information to establish the comparability of pre-change and post-change products and, thereby, confirm that the manufacturing process changes did not have an adverse impact on the quality, safety and efficacy of the drug product.

### 1.2 Background

Manufacturers<sup>1</sup> of biotechnological/biological products frequently make changes to manufacturing processes<sup>2</sup> of products<sup>3</sup> both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate.

While ICH documents have not specifically addressed considerations for demonstrating comparability between pre-change and post-change products, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes (see References). This document builds upon the previous ICH guidelines and provides additional direction regarding approaches to:

- Compare post-change product to pre-change product following manufacturing process changes and
- Assess the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy.

<sup>1</sup> For convenience, when the term “manufacturer” is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).

<sup>2</sup> For convenience, when the term “manufacturing process(es)” is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.

<sup>3</sup> For convenience, when the term “product” is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.

### 37 1.3 Scope

38 The principles adopted and explained in this document apply to:

- 39 • Proteins and polypeptides, their derivatives, and products of which they are  
40 components (e.g., conjugates). These proteins and polypeptides are produced  
41 from recombinant or non-recombinant cell-culture expression systems and can  
42 be highly purified and characterised using an appropriate set of analytical  
43 procedures;
- 44 • Products where changes are made by a single manufacturer, including those  
45 made by a contract manufacturer, who can directly compare results from the  
46 analysis of pre-change and post-change products; and
- 47 • Products where process changes are made in development or for which a  
48 marketing authorisation has been granted.

49 The principles outlined in this document might also apply to other product types such as  
50 proteins and polypeptides isolated from tissues and body fluids. Manufacturers are  
51 advised to consult with the appropriate regional Regulatory Authority to determine  
52 applicability.

### 53 1.4 General Principles

54 The goal of the comparability exercise is to ensure the quality, safety and efficacy of the  
55 drug product produced by a changed manufacturing process through collection and  
56 evaluation of the relevant data to determine whether there is any adverse impact on the  
57 drug product due to the manufacturing process changes.

58 The demonstration of comparability does not necessarily mean that the quality attributes  
59 of the pre-change and post-change products are identical; but that they are highly similar  
60 and that the existing knowledge is sufficiently predictive to ensure that any differences in  
61 quality attributes have no adverse impact upon safety or efficacy of the drug product.

62 A determination of comparability can be based on a combination of analytical testing,  
63 biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer  
64 can provide assurance of comparability through analytical studies alone, nonclinical or  
65 clinical studies with the post-change product might not be warranted. However, where  
66 the relationship between specific quality attributes and safety and efficacy has not been  
67 established, and differences between quality attributes of the pre- and post-change  
68 products are observed, it might be appropriate to include a combination of quality,  
69 nonclinical, and/or clinical studies in the comparability exercise.

70 To identify the impact of a manufacturing process change, a careful evaluation of all  
71 potential consequences on the product, not just the obvious, should be performed. Based  
72 on this evaluation, acceptance criteria to define highly similar post-change product can be  
73 established. Quality data on the pre- and post-change products are generated, and a  
74 comparison is performed that integrates and evaluates all data available, e.g.,  
75 characterisation, routine batch analyses, stability, in-process control, and process  
76 validation/evaluation data. The comparison of the results to the predefined acceptance  
77 criteria allows an objective assessment of whether or not the pre- and post-change  
78 products are comparable.

79 Following the evaluation of the quality attributes the manufacturer could be faced with  
80 one of several outcomes including:

- 81 • Based on appropriate comparison of relevant quality attributes, pre- and post-  
82 change products are highly similar and considered comparable, i.e. no adverse  
83 impact on safety or efficacy profiles is foreseen.

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- Although the products appear highly similar, there is doubt concerning the capability of the analytical procedures to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider performing additional nonclinical and/or clinical studies.
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- Some differences have been observed in the quality attributes of the pre-change and post-change products, but it can be justified that no adverse consequence on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and post-change products can be considered comparable.
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- Although the pre- and post-change products are similar, some differences have been identified in the comparison of quality attributes and possible adverse consequences on safety and efficacy profiles cannot be excluded. In such situations, the generation and analysis of additional data on quality attributes is unlikely to be sufficient to determine if pre- and post-change products are comparable. The manufacturer should consider performing nonclinical and/or clinical studies to reach a definitive conclusion, taking into account characteristics of the drug product such as therapeutic window, clinical usage (acute vs. chronic administration), dosing characteristics, and potential for immunogenic responses.
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- Differences are so significant that it is determined that quality attributes for products are not comparable (i.e., they are not highly similar). This outcome is not within the scope of this document and is not discussed further.

## 105 **2.0 Guidelines**

### 106 **2.1 Considerations for the Comparability Exercise**

107 The goal of the comparability exercise is to ascertain that pre- and post-change drug  
108 product is comparable in terms of quality, safety, and efficacy. Therefore, it might be  
109 appropriate to collect data on the drug product to support the determination of  
110 comparability even though all process changes occurred in the manufacture of the drug  
111 substance. Comparability can be deduced from quality studies (partial or  
112 comprehensive), but might sometimes need to be supported by comparability bridging  
113 studies. The extent of the studies that demonstrate comparability will depend on:

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- The production step where the changes are introduced;
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- The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, related substances);
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- The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and
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- The relationship between quality attributes and safety and efficacy, based on the overall nonclinical and clinical experience.
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123 When considering the comparability of products, the manufacturer should evaluate, for  
124 example:

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- Relevant physicochemical and biological characterisation data regarding quality attributes;
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- Results from analysis of relevant samples from the appropriate stages of the manufacturing process (e.g., intermediate, drug substance, and drug product);
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- The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the protein and, hence, potential product-related substances and product-related impurities;
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- Batches used for demonstration of manufacturing consistency;
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- Historical batch data that provide insight into potential “drift” of quality attributes with respect to safety and efficacy, following either a single or a series of manufacturing process changes. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.
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- In addition to evaluating the data, manufacturers should also consider:
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- Critical control points in the manufacturing process that affect product characteristics, e.g., the ability of downstream steps to accommodate material from a changed cell culture process, as well as the impact of the process change on the quality of downstream product;
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- Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the post-change process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
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- Nonclinical or clinical characteristics of the drug product: Clinical characteristics, such as therapeutic index, clinical use (e.g., acute vs. chronic administration), dosing, route of administration, and potential for immunogenic response, of the drug product can be important in planning the comparability exercise; and
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- Each indication for a multi-indication product: The structure-activity relationships, mechanism of action, safety profile, and toxicities of the same product can vary with each clinical indication and, if so, should be addressed for each clinical indication.
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## 156 2.2 Quality Considerations

### 157 2.2.1 Analytical Techniques

158 The battery of tests for the comparability exercise should be carefully selected and  
159 optimised to the product to maximise the potential of detecting differences in the  
160 quality attributes that might result from the proposed manufacturing process change.  
161 To address the full range of physicochemical properties or biological activities, it  
162 might be appropriate to apply more than one analytical procedure to evaluate the  
163 same quality attribute (e.g., molecular weight, impurities, secondary/tertiary  
164 structures). In such cases, each method should employ different physicochemical or  
165 biological principles to collect data for the same parameter to maximise the possibility  
166 that differences in the product caused by a change in the manufacturing process  
167 might be detected.

168 It can be difficult to ensure that the chosen set of analytical procedures for the pre-  
169 change product will be able to detect modifications of the product due to the  
170 limitations of the assays (e.g., precision, specificity, and detection limit) and the  
171 complexity of some products due to molecular heterogeneity. Consequently, the  
172 manufacturer should determine:

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- Whether or not existing tests remain valid for their intended use or should be modified. For example, when the manufacturing process change gives rise to a different impurity profile in the host cell proteins, manufacturers should confirm
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176 that the test used to quantitate these impurities is still suitable for its intended  
177 purpose. It might be appropriate to modify the existing test to detect the new  
178 impurities;

179 • The need to add new tests as a direct result of changes in quality attributes that  
180 the existing methods are not capable of measuring. That is, when specific  
181 changes occur in quality attributes as a result of process change (e.g., following  
182 addition of a new raw material or modification of a chromatographic purification  
183 step), it might be appropriate to develop new analytical procedures, i.e., to  
184 employ additional analytical techniques above and beyond those used previously  
185 for characterisation or to establish routine specifications.

186 The measurement of quality attributes does not necessarily entail the use of validated  
187 assays but the assays should be scientifically sound and provide results that are  
188 reliable. Those methods used for batch release should be validated in accordance  
189 with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

## 190 2.2.2 Characterisation

191 Characterisation of a biotechnological/biological product by appropriate techniques,  
192 as described in ICH Q6B, includes the determination of physicochemical properties,  
193 biological activity, immunochemical properties (if any), purity, impurities,  
194 contaminants, and quantity.

195 When a manufacturing process change has been made that has the potential to have  
196 an impact on quality attributes, a complete or limited (but rationalised) repetition of  
197 the characterisation activity conducted for the market application is generally  
198 warranted to directly compare the pre-change and post-change products. However,  
199 additional characterisation might be indicated in some cases. When process  
200 changes result in a product characterisation profile that differs from that observed in  
201 the material used during nonclinical and clinical studies or other appropriate  
202 representative materials, the significance of these alterations should be evaluated.

203 Each of the following criteria should be considered as a key point in the conduct of  
204 the comparability exercise.

### 205 Physicochemical Properties

206 The manufacturer should address the concept of the desired product (and its  
207 variants) as defined in ICH Q6B when designing and conducting a comparability  
208 exercise. The complexity of the molecular entity with respect to the degree of  
209 molecular heterogeneity should also be addressed. Following a manufacturing  
210 process change, manufacturers should attempt to determine that higher order  
211 structure (secondary, tertiary, and quaternary structure) is maintained in the  
212 product. If the appropriate higher order structural information cannot be  
213 obtained, a relevant biological activity assay (see biological activity below) could  
214 indicate a correct conformational structure.

### 215 Biological Activity

216 Biological assay results serve multiple purposes in the confirmation of product  
217 quality attributes that are useful for characterisation and batch analysis, and, in  
218 some cases, serve as a link to clinical activity. The manufacturer should  
219 recognise the limitations of biological assays, such as high variability, that might  
220 prevent detection of differences that occur as a result of a manufacturing process  
221 change.

222 In cases where the biological assay also serves as a complement to  
223 physicochemical analysis, e.g., as a surrogate assay for higher order structure,  
224 the use of a relevant biological assay with appropriate precision and accuracy  
225 might provide a suitable approach to confirm that change in specific higher order  
226 structure has not occurred following manufacturing process changes. Where  
227 physicochemical or biological assays are not considered adequate to confirm that  
228 the higher order structure is maintained, it might be appropriate to conduct a  
229 nonclinical or clinical study.

230 When changes are made to a product with multiple biological activities,  
231 manufacturers should consider performing a set of relevant functional assays  
232 designed to evaluate the range of activities. For example, certain proteins  
233 possess multiple functional domains that express enzymatic and receptor  
234 mediated activities. In such situations, manufacturers should consider evaluating  
235 all relevant functional activities.

236 Where one or more of the multiple activities are not completely correlated with  
237 clinical safety or efficacy or if the mechanism of action is not understood, the  
238 manufacturer should confirm that nonclinical or clinical activity is not  
239 compromised in the post-change product.

#### 240 **Immunochemical Properties:**

241 When immunochemical properties are part of the characterisation (e.g., for  
242 antibodies or antibody-based products), the manufacturer should confirm that  
243 post-change product is comparable in terms of the specific properties.

#### 244 **Purity, Impurities, and Contaminants:**

245 The combination of analytical procedures selected should provide data to  
246 evaluate the change in purity profile in terms of the desired product.

247 If differences are observed in the purity and impurity profiles of the post-change  
248 product relative to the pre-change product, the differences should be evaluated  
249 to determine their impact on safety and efficacy. Where the change results in the  
250 appearance of new impurities, it might be appropriate to characterise the new  
251 impurities, and in some cases, to conduct appropriate nonclinical or clinical  
252 studies to confirm that there is no adverse impact on safety or efficacy of the  
253 drug product.

254 Contaminants should be strictly avoided and/or suitably controlled with  
255 appropriate in-process acceptance criteria or action limits for drug substance or  
256 drug product.

### 257 **2.2.3 Specifications**

258 The tests and analytical procedures chosen to define drug substance or drug product  
259 specifications alone are generally not considered adequate to assess the impact of  
260 manufacturing process changes since they are chosen to confirm the routine quality of  
261 the product rather than to fully characterise it. The manufacturer should confirm that  
262 the specifications after the process change are appropriate to ensure product quality. Results  
263 within the established acceptance criteria, but outside historical manufacturing control  
264 trends, might suggest product differences that warrant additional study or analysis.  
265 Modification, elimination, or addition of a test (i.e., in the specification) might be indicated  
266 where data suggest that the previous test is no longer relevant for routine batch analysis  
267 of the post-change product. For example, the elimination of bovine serum from the cell  
268 culture process would remove the need for related analyses. However, a widening of the  
269 acceptance criteria is generally not considered appropriate and should be justified. In

270 some cases, additional tests and acceptance criteria on the relative abundance of  
271 specific new impurities might be appropriate if the impurity profile is different following the  
272 manufacturing process changes. When evaluating both the test methods and  
273 acceptance criteria for the post-change product, it is important to consider the general  
274 principles for setting specifications as defined in Q6B, i.e., the impact of the changes on  
275 the validated manufacturing process, characterisation studies, batch analysis data,  
276 stability data, and nonclinical and clinical experience.

#### 277 **2.2.4 Stability**

278 For many manufacturing process changes even slight modifications of the production  
279 procedures, including those made early in the manufacturing process for the drug  
280 substance, might cause changes in the stability of the post-change product. Any change  
281 with the potential to alter protein structure or purity and impurity profiles should be  
282 evaluated for its impact on stability, since proteins are frequently sensitive to changes,  
283 such as those to buffer composition, processing and holding conditions, and use of  
284 organic solvents. Furthermore, stability studies might be able to detect subtle differences  
285 that are not readily detectable by the characterisation studies. For example, the  
286 presence of trace amounts of a protease might only be detected by product degradation  
287 that occurs over an extended time period; and, in some cases, divalent ions leached from  
288 container closure might change the stability profile because of the activation of trace  
289 proteases not detected in stability studies of the pre-change product. Generally,  
290 therefore, real-time concurrent stability studies on the product potentially affected by the  
291 change should be conducted, as appropriate.

292 Accelerated and stress stability studies are often useful tools to establish degradation  
293 profiles and provide a further direct comparison of pre-change and post-change products.  
294 The results thus obtained might show product differences that warrant additional  
295 evaluation and also identify conditions indicating that additional controls should be  
296 employed in the manufacturing process and during storage to eliminate these  
297 unexpected differences. Appropriate studies should be considered to confirm that  
298 suitable storage conditions and controls are selected.

299 ICH Q5C and Q1A(R) should be consulted to determine the conditions for stability  
300 studies that provide relevant data to be compared before and after a change.

### 301 **2.3 Manufacturing Process Considerations**

302 A well-defined manufacturing process with its associated process controls is necessary to  
303 assure that acceptable product is produced on a consistent basis. Approaches to  
304 determining the impact of any process change will vary with respect to the specific  
305 process, the product, the extent of the manufacturer's knowledge of and experience with  
306 the process, and development data generated. The manufacturer should confirm that the  
307 process controls in the modified process provide similar or more effective control of the  
308 product quality, compared to those of the original process.

309 A careful consideration of potential effects of the planned change on steps downstream  
310 and quality parameters related to these steps is extremely important (e.g., for acceptance  
311 criteria, in-process specification, in-process tests, operating limits, and  
312 validation/evaluation, if appropriate). This analysis will help identify which tests should be  
313 performed during the comparability exercise, which in-process or batch release  
314 acceptance criteria or analytical procedures should be re-evaluated and which steps will  
315 not need to be considered. For example, analysis of process intermediates might  
316 suggest potential differences that should be evaluated to determine the suitability of  
317 existing tests to detect these differences in the product. The rationale for excluding parts  
318 of the process from this consideration should be justified.



319 While the process will change and the associated controls might be redefined, the  
320 manufacturer should confirm that pre-change and post-change products are comparable.  
321 To support the comparison it is often useful to demonstrate, for example, that specific  
322 intermediates are comparable or that the modified process has the capability to provide  
323 appropriate levels of removal for process- and product-related impurities, including those  
324 newly introduced by the process change. To support process changes for approved  
325 products, data from commercial-scale batches are generally indicated.

326 The process assessment should consider such factors as the criticality of the process  
327 step and proposed change, the location of the change and potential for effects on other  
328 process steps, and the type and extent of change. Information that can aid this  
329 assessment is generally available from several sources. The sources can include  
330 knowledge from process development studies, small scale evaluation/validation studies,  
331 experience with earlier process changes, experience with equipment in similar  
332 operations, changes in similar manufacturing processes with similar products, and  
333 literature. Although information from external sources is useful to some extent, it is within  
334 the context of the specific manufacturing process and specific product that the change  
335 should be assessed.

336 When changes are made to a process, the manufacturer should demonstrate that the  
337 associated process controls, including any new ones, provide assurance that the  
338 modified process will also be capable of providing comparable product. The modified  
339 process steps should be re-evaluated and/or re-validated, as appropriate. The in-  
340 process controls, including critical control points and in-process testing, should ensure  
341 that the post-change process is well controlled and maintains the quality of the product.  
342 Typically, re-evaluation/re-validation activities for a simple change might be limited to the  
343 affected process step, if there is no evidence to indicate that there is impact on the  
344 performance of subsequent (downstream) process steps, or on the quality of the  
345 intermediates resulting from the subsequent steps. When the change considered affects  
346 more than a single step, more extensive analysis of the change and resultant validation  
347 might be appropriate.

348 Demonstration of state of control with the modified/changed manufacturing process might  
349 include, but is not limited to, such items as:

- 350 • Establishment of modified specifications for raw, source and starting materials,  
351 and reagents;
- 352 • Appropriate bioburden and/or viral safety testing of the post-change cell banks  
353 and end-of-production cells;
- 354 • Adventitious agent clearance;
- 355 • Removal of product- or process-related impurities, such as residual host cell  
356 DNA and proteins; and
- 357 • Maintenance of the purity level.

358 For approved products, an appropriate number of post-change batches should be  
359 analysed to demonstrate consistent performance of the process.

360 To support the analysis of the changes and the control strategy, the manufacturer should  
361 prepare a description of the change that summarises the manufacturing process of the  
362 pre-change process and the post-change process and that clearly highlights  
363 modifications of the process and changes in controls in a side-by-side format.

## 364 **2.4 Demonstration of Comparability during Development**

365 During product development, it is expected that multiple changes in the manufacturing  
366 process will occur that could impact drug product quality, safety, and efficacy.

367 Comparability exercises are generally performed to bridge nonclinical and clinical data  
368 generated with pre-change to post-change product in order to facilitate further  
369 development and, ultimately, to support the marketing authorisation. Comparability  
370 studies conducted for products in development are influenced by factors such as the  
371 stage of product development, the availability of validated analytical procedures, and the  
372 extent of product and process knowledge, which are limited at times due to the available  
373 experience that the manufacturer has with the process.

374 Where changes are introduced in development before nonclinical studies, the issue of  
375 assessing comparability is not generally raised because the manufacturer subsequently  
376 conducts nonclinical and clinical studies using the post-change product as part of the  
377 development process. During early phases of nonclinical and clinical studies,  
378 comparability testing is generally not as extensive as for an approved product. As  
379 knowledge and information accumulates, and the analytical tools develop, the  
380 comparability exercise should utilise available information and will generally become  
381 more comprehensive. Where process changes are introduced in late stages of  
382 development and no additional clinical studies are planned to support the marketing  
383 authorisation, the comparability exercise should be as comprehensive and thorough as  
384 one conducted for an approved product. Some outcomes of the comparability studies on  
385 quality attributes can lead to additional nonclinical or clinical studies.

386 In order for a comparability exercise to occur during development, appropriate  
387 assessment tools should be used. It should be recognised that during development,  
388 analytical procedures might not be validated, but should always be scientifically sound  
389 and provide results that are reliable and reproducible. Due to the limitations of the  
390 analytical tools in early development, physicochemical and biological tests alone might be  
391 considered inadequate to determine comparability, and therefore, repeating elements of  
392 the nonclinical or clinical studies already performed would be considered appropriate.

### 393 **3.0 Nonclinical and Clinical Considerations**

394 *Notice to the Reader: Where reference is made to nonclinical and clinical studies,*  
395 *additional information and modification of these specific items will be provided by ICH*  
396 *Safety and Efficacy Experts.*

397 Determinations of product comparability can be based solely on quality considerations  
398 (see section 2.2) if the manufacturer can provide assurance of comparability through  
399 analytical studies as outlined in this document. Additional evidence from nonclinical or  
400 clinical studies is appropriate when quality data are insufficient to establish comparability.  
401 The extent and nature of nonclinical and clinical studies should be determined on a case-  
402 by-case basis in consideration of various factors, which include:

- 403 • Quality findings, e.g.,
  - 404 • The type, nature, and extent of differences between the post-change product
  - 405 and the pre-change product with respect to quality attributes including
  - 406 product-related substances and the impurity profile;
  - 407 • The results of the evaluation/validation studies on the new process including
  - 408 the results of relevant in-process tests; and
  - 409 • The capabilities and limitations of tests used for any comparability studies.
- 410 • The nature of the product, e.g., product complexity, therapeutic class;
- 411 • Dosing regimen;
- 412 • Route of administration;
- 413 • The therapeutic window based upon dose ranging studies;

- 414 • Chronic vs. acute use;
- 415 • Extent of knowledge regarding structure-activity relationships;
- 416 • Previous experience with immunogenic events or responses in patients;
- 417 • Mechanism of action;
- 418 • Patient population;
- 419 • Availability of existing nonclinical and clinical data; and
- 420 • Knowledge of how a difference in quality attributes might impact on safety and
- 421 efficacy.

## 422 **4.0 Glossary**

### 423 **Comparability Bridging Study:**

424 A study performed to provide nonclinical or clinical data that allows extrapolation of the  
425 existing data from the drug product produced by the current process to the drug product  
426 from the changed process.

### 427 **Comparable:**

428 A conclusion that products are highly similar before and after manufacturing process  
429 changes and that no adverse impact on the quality, safety, or efficacy of the drug product  
430 occurred. This conclusion can be based on an analysis of product quality attributes. In  
431 some cases, nonclinical or clinical data might be indicated.

### 432 **Comparability Exercise:**

433 The activities, including study design, conduct of studies, and evaluation of data, that are  
434 designed to investigate whether the products are comparable.

### 435 **Quality Attribute:**

436 A molecular or product characteristic that is selected for its ability to help indicate the  
437 quality of the product. Collectively, the quality attributes define the adventitious agent  
438 safety, purity, potency, identity, and stability of the product. Specifications measure a  
439 selected subset of the quality attributes.

## 440 **5.0 References**

- 441 Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or  
442 Animal Origin (Q5A)
- 443 Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived  
444 Protein Products (Q5B),
- 445 Stability Testing of Biotechnological/Biological Products (Q5C)
- 446 Derivation and Characterisation of Cell Substrates Used for Production of  
447 Biotechnological/Biological Products (Q5D)
- 448 Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological  
449 Products (Q6B)
- 450 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Q7A)
- 451 Text on Validation of Analytical Procedures (Q2A)
- 452 Validation of Analytical Procedures: Methodology (Q2B)
- 453 The Common Technical Document (M4Q)
- 454 Stability Testing of New Drug Substances and Products Q1A(R)