



February 7, 2005

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0355: Scientific Considerations Related to Developing Follow-on Protein Products

Dear Sir or Madam:

Hoffmann-La Roche, Inc (Roche) appreciates the opportunity to provide comments on the scientific considerations related to the development of follow-on protein products, addressing points raised in 69 FR 50387 (Aug. 16, 2004) and discussed at the September 14, 2004 Public Workshop on Scientific Considerations Related to Developing Follow-On Protein Products. Roche concurs with many of the comments made to this docket since the September meeting and we are providing our specific input below on the key points raised to date. We agree with previous comments that the term "follow-on biologic" (FOB) should be used, rather than "follow-on protein products", as the discussion does not involve synthetically produced protein products. The term FOB will be used throughout this document.

Key Points

- All biotechnology-derived proteins have unique biological properties that distinguish them from other proteins. These properties are intimately and inherently related to the processes used to manufacture the protein. This has been consistently applied by regulators when considering changes to manufacturing processes of innovator products.
- Changes to processes for existing approved products are usually incremental and allow an impact analysis of the change by comparability assessment with reference to the process history.
- An FOB is inherently different from an innovator protein as it is derived from a new independently developed process (with a new cell line, manufacturing steps, IPCs, etc.). Assessment of the similarity to an innovator protein product would require, at a minimum, access to the development, manufacturing and post-approval history of the innovator. Access to this intellectual property can only be obtained with the consent of the innovator.
- Without access to the detailed historical data of the innovator's process, an FOB will need to be clinically evaluated for safety and efficacy (including immunogenicity). In most, if not all, cases the clinical evaluation will be equivalent to that required of the innovator and an FOB will require its own post-approval risk management program.
- An FOB will need to be distinctly branded for optimal, and accurate post-marketing surveillance.

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General Comments

- **Manufacturing Considerations:** Analytical comparability studies alone cannot establish similarity between the FOB and innovator product. It is critical to make clear distinctions between comparability and similarity assessments, to understand the impact of the manufacturing process on the attributes, including efficacy and safety, of such products and to recognize the limitations on the analysis of the final product alone. The database gathered during development (and further supported with post approval data) gives the innovator the experience and confidence to support future manufacturing changes and to fully evaluate their impact on the final product. Without reference to this database, with appropriate trending, assessment of the impact of any new process is limited.
- **Characterization:** 'Comprehensive' analytical characterization of a biological is not possible and cannot be used as a surrogate to accurately predict safety and efficacy of FOBs. Biological products are complex and there is a potential that even small changes to the manufacturing process can have a large impact on the properties of the biological protein. Because of the limitations of current technology, the likelihood is high that variability will be missed, even when analyzed with state-of-the art analytical methods. Variability can be critical for the safety and efficacy of the products. Based on current knowledge, analytical characterization should only be used as a means to assess the consistency of a defined process, and not to establish the safety and efficacy of a product on its own.
- **Immunogenicity:** The potential for immunogenicity and its clinical impact needs to be assessed for all proteins. Scientific experience to date show that it is not possible to predict the precise nature or relative rate of occurrence of an immunogenic response based solely on preclinical tests and modelling. Also, an increase in a known response due to subtle changes in the composition of the FOB cannot be based entirely on preclinical testing. Because of the limitations of the current technology, there is an absolute need for a complete assessment of immunogenicity with clinical studies. Comparative immunogenicity studies in transgenic animals or in other similar non-clinical settings are not sufficient to determine immunogenic potential as they are not validated models for immune response in humans. Immunogenicity assessment should also be incorporated into post marketing surveillance for all biologics, including both innovator products and FOBs.
- **Preclinical and Clinical Studies:** We do not support the concept that assessments of potency, efficacy and safety of an FOB in preclinical tests can be considered valid surrogates for clinical efficacy and safety. Manufacturers of FOBs must necessarily implement new and different manufacturing processes to develop their product. As such, the potential exists that many critical parameters, including differences in cell line, culture conditions and the purification scheme, etc. will be changed and significantly effect the biological properties of the FOB. Preclinical comparisons may only be suitable to assess comparability for process changes within one process for one product during development or after establishment of the defined manufacturing process. In the absence of historical information, the FOB manufacturer should be required to support the efficacy and safety of the new product with clinical data. Only dose-ranging studies may

safely be omitted or minimized in the program, if justified based on the pharmacokinetic and pharmacodynamic properties of the molecule in question.

- **Potency and Surrogates for Efficacy and Safety:** Bioactivity and potency assays cannot replace clinical studies. Only where a surrogate clinical endpoint is validated for the indication in question would that endpoint also be acceptable for the FOB.
- **Terminology:** In the interest of promoting communication among sponsors and health authorities in this complex environment, Roche recommends harmonization of terminology between the US and Europe as much as possible to minimize misunderstandings as to both terms and concepts. We consider it critical that nomenclature for an FOB be kept separate and distinct from the innovator product to support the unique risk management program for the FOB.

SPECIFIC COMMENTS

Manufacturing Considerations

At Roche, we believe it is the innovator's intimate knowledge of the process and control of the product that allow us to best manage and monitor the impact of changes on a biologic product.

As comparability and similarity are key concepts for this discussion, we are providing clarification of their definitions here.

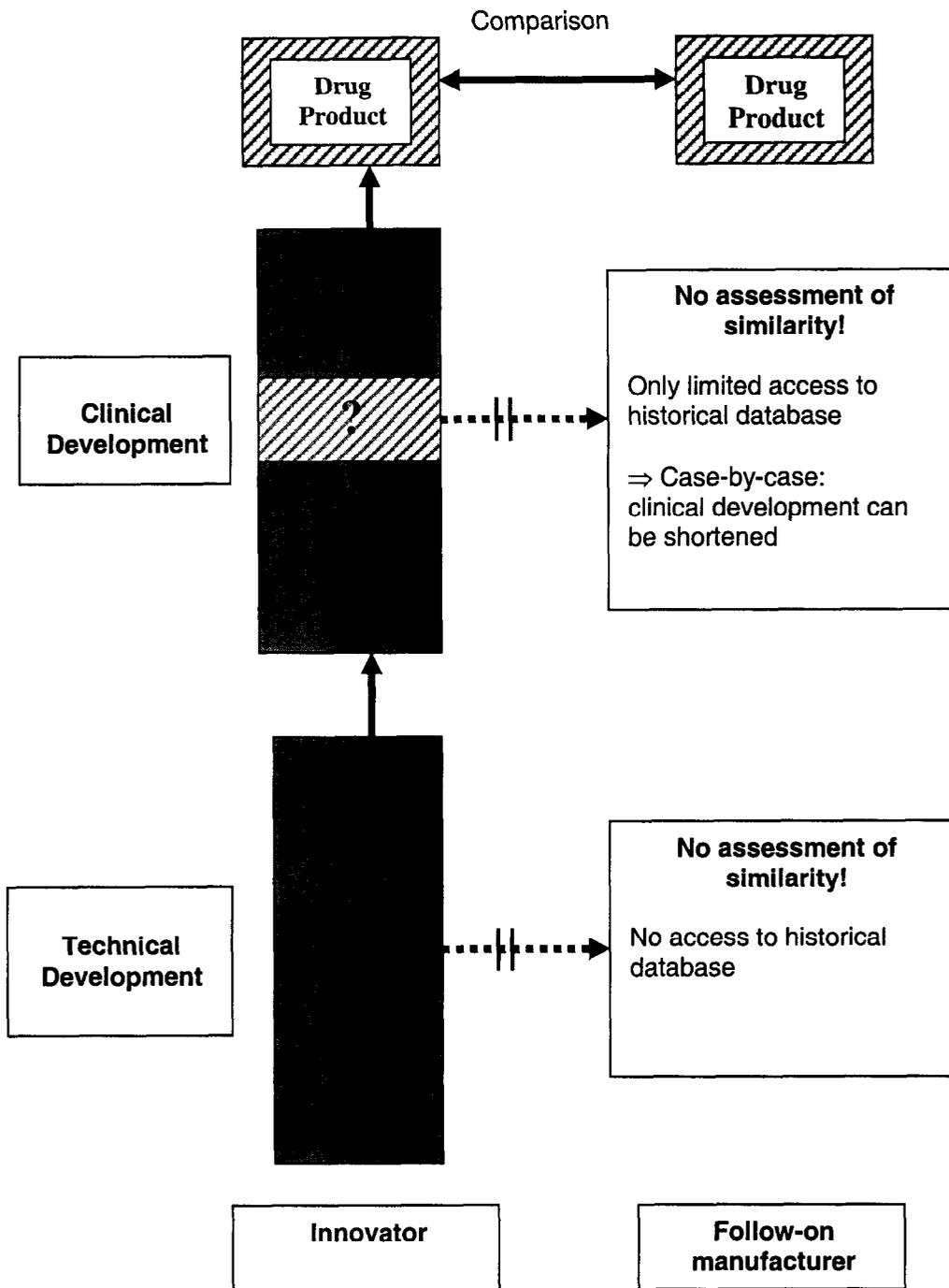
- **Comparability (from ICH Q5E):** A conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety or efficacy of the drug product occurred. According to ICH Q5E, comparability is used to assess impact of changes to a manufacturing process. There is no reference to application of comparability to assess materials generated from different processes. Accordingly, comparability is considered valid only for evaluating defined changes to an established process for a single compound. The data required to ensure that a comparability assessment is adequate to detect product differences depends on the magnitude and significance of the manufacturing change. For minor changes to an established manufacturing process, analytical data are generally sufficient to demonstrate comparability. For major changes, pre-clinical or clinical data may also be needed in order to assess the impact of the change on the quality, safety and efficacy of the post-change product.
- **Similarity:** In the context of FOBs, similarity refers to comparative assessment of drug products from *different* manufacturers/sources/processes. In general, a similarity assessment cannot be performed at the level of the manufacturing process for different manufacturers. Therefore, a similarity assessment must include all applicable clinical and pre-clinical data in addition to the available comparative physico-chemical data for the drug products in order to fully assess the impact of the differences in the processes and product on quality, safety and efficacy.



For all biological proteins, process development and pre-clinical/clinical development proceed in parallel such that there is ongoing feedback regarding the safety/efficacy of the protein product and associated process. Recent history and Roche's experience have demonstrated and validated the well-known observation that seemingly minor changes can have an important impact on a product's biological properties. By the time we at Roche submit a marketing application, we have generally identified critical process parameters and established the process consistency through both in-process controls and release specifications. Subsequent post-approval changes are also made with full knowledge of this process development history. In summary, comparability assessments at Roche, used during development or post-approval, are done in the context of extensive knowledge and experience on which changes to the manufacturing process are likely to be important, i.e. are likely to affect the biological properties of the molecule. This is a body of experience that has proven critical to maintaining product consistency at Roche and is unique to the innovator.

For an FOB, involving a new manufacturer, the process will be substantially different since there is no access to the innovator technology history. Accordingly, there is no basis for comparability assessment versus the current approved process. In-process controls and even release data will necessarily differ. Therefore, the only way to assess the significance of the differences on safety or efficacy is by generating appropriate clinical data for the "new" product.

In support of our position, consider the details of the innovator's pre-approval product development, provided in the Appendix to this submission. A graphical depiction of the points described above in terms of the differences in data available throughout drug development to the innovator and the FOB manufacturer is provided in the following schematic.



Legend:
 Unique grey: Trade secret of Innovator
 Hatched: Accessible for follow-on manufacturer

Additionally, to exemplify the importance of innovator knowledge and database on maintaining product consistency, the following two case studies from Roche global development are described. The first example supports the importance of access to a broad established database, the second example reflects the situation in which, while analytical comparability could be shown, *in vivo* characteristics revealed different results pre- and post-change.

Case 1: Roche performed a site-transfer for the manufacturing process of a monoclonal antibody. The transfer was associated with some minor changes to the manufacturing process which were necessary due to adaptations to the on-site available technical equipment. For this transfer an appropriate comparability strategy was designed including process validation, comprehensive analytical testing and stability testing. For assessment of comparability three representative batches of the API plus the reference standard of the original site were compared with the registration batches of the second site. The comparability exercise was successful with respect to the molecular, physicochemical and biological properties of the molecule, except for one parameter related to glycosylation. After assessment of a broader database reflecting the complete development history of the manufacturing process, it could be demonstrated that the assumed deviation within the one parameter fits within the intrinsic range of the manufacturing process. Therefore, with availability of a broad historical database from the clinical development of the manufacturing process, the designed comparability strategy could be applied successfully. Clearly, such a comparability assessment could not be done in the absence of the historical database. The comparability concept was accepted by the EU rapporteur, and EU approval was granted in 2003 in EU.

Case 2: After performing Phase III clinical trials for a recombinant protein Roche introduced several major changes, including a site-transfer of a starting material, process changes for a key reagent and scale-up of the drug substance. The comparability strategy was based on analytical and *in-vitro* functional testing. The database obtained from these analyses fit within the predefined specification for every investigated parameter. Due to the number of concurrently implemented changes, FDA requested that Roche perform a bioequivalence study. Although no deviation was observed within the analytical comparability, the bioequivalence study failed. During the subsequent investigations, it became obvious that one batch used in the study showed an out-of-trend distribution of the isoforms present in the product. In addition, the bioactivity of the individual isoforms was found to be different. Based on this new insight, the specification was tightened for this parameter. As shown in this example, differences of *in vivo* characteristics may occur although the analytical data and their original specifications indicated comparability. This example illustrates that when several major changes are introduced, they cannot be controlled at the level of comparability testing using physico-chemical analyses alone.

In-process controls are also critical to the manufacturing processes. If two products are manufactured by substantially different production processes, analytical testing of the finished product alone is insufficient to determine their similarity. The entire manufacturing process is monitored and controlled by carefully designed in-process controls, specifically set up for the needs of the process. These controls apply to both the protein's production and to the detection of agents and / or derivatives that may affect the activity or safety of the product. Product comparability, based on analytical testing, has only been demonstrated for incremental manufacturing changes performed by one manufacturer for its manufacturing process.

Characterization of Follow-on Biologics

At Roche, we have concluded that when an FOB is produced via a substantially different manufacturing process, it is not possible to use analytical data alone to assess for similarity between follow-on and reference biologic products. The substantially different manufacturing process for an FOB (compared with the innovator) requires extensive analytical, pharmacologic and clinical studies to demonstrate safety and efficacy.

It is not surprising that small changes to the manufacture of recombinant proteins often manifest in critical changes to the properties of the protein. Recombinant as well as natural proteins are very large and complex molecules produced by living cells. Their synthesis is complex and includes a multitude of biochemical synthesis steps, processing and transport events and possibly biochemical processes. Different cells and even different clones of one cell type may produce specific variants of products. Culture conditions may result in many by-products and the recovered product may be altered during downstream processing. The purification process and process development aim to minimize product variability, but complex mixtures are typical and, during development, we assume that all possible variants can exist in a final product preparation. A product consisting of a glycoprotein is a mixture of many individual molecular species. Data published for tissue type Plasminogen Activator (t-PA) show a large number of actual and potential chemical differences. For this molecule, more than 90 individual mechanisms are possible that may create molecules of a different chemical identity. If all permutations are calculated, the existence of 1.09×10^9 possible variants can be predicted and one cannot determine how many different molecules are actually present by using current analytical methods. For a non-glycoprotein, several thousand variants are possible as well. A similar calculation of the t-PA mutant molecule Reteplase, which is smaller in size and without glycosylation, still shows significant complexity (about 30 000 possible variants).

Current technologies are not capable of isolating and identifying each of these potentially existing variants. They are, however, suitable to characterize the detectable individual variations from fragments of the product and to monitor the consistency of such major variations. By using several different principles, one can create a monitoring program for tracking any changes of the identified isoforms. It is scientifically acceptable to track the identified species as markers for the non-identified species in the context of process validation. Through this approach the manufacturer is able to understand which events (e.g. modifications) may occur during each process step. The exact definition of process conditions will allow control of the microheterogeneity and the impurity profile of the product.

While we expect that the selectivity and sensitivity of technologies will improve, the general situation, i.e. that we continue to have complex mixtures of complex molecules, will remain unchanged. It is not technically possible to unambiguously identify and fully characterize such products by chemical analysis alone.

The evaluation of in-process data as well as the finished drug substance is necessary in order to compare product quality. For example, when an innovator is making changes, many parameters should be assessed including:

- In-process controls from the complete manufacturing process
- Removal data for impurities
- Release testing data
- Extended characterization
- Applicable functional assays
- Stability of drug substance / drug product

The difficulty for the manufacturer of an FOB is the inability to perform the in-process evaluation that is inherently part of assessments performed by the innovator.

Impurities

Product testing and consistency assessment together with the control of the process will enable the assurance of product quality. As stated above, such an assessment is not possible with chemical analysis of the final product alone, in large part because the existence of impurities cannot be adequately assessed.

When an FOB is produced through a different manufacturing process, it is not possible to use analytical data alone to assess for impurities or for similarity between follow-on and reference biologic products.

Specifically:

- An FOB has to be qualified within the same paradigm as an innovator product based on intrinsic data generated along the same procedure as described for an innovator.
- State-of-the art analytical methods provide a comprehensive database of the structural properties, but are inadequate to predict a specific correlation of these data to the safety and efficacy of a molecule, especially with regard to the existence of impurities.
- A similarity assessment is difficult, if not impossible, when two processes or products are compared. This is because data on the relationship between trace impurities and other unknowns are not available for the FOB manufacturer.

Immunogenicity Issues

Immunogenicity of therapeutic proteins is a concern for both innovator proteins and FOBs. Although attempts to develop *in vitro* assays capable of predicting immunogenicity in man continue, none of the available methods are validated. Preclinical toxicity testing in animals,

with special attention to detection of an antibody response in a relevant species, is required before entry into humans to ensure adequate exposure in the test species. The immunogenic potential of protein drugs in man must be assessed in pre-approval clinical studies and must also be monitored through post-approval surveillance (see below).

As with innovator products, there is a need for long term detailed risk assessment and risk management programs (RMP) to be developed for each FOB. A risk assessment program, which includes definitive requirements in the label for monitoring of immunogenic responses, will permit evaluation of the potential for immunogenic effects before and after each FOB product is marketed. The RMP should be developed prior to market approval and should include assays with appropriate sensitivity for evaluation of immunogenicity of the product.

The requirements of a clinical program to monitor rates of immunogenicity should be the same for both innovator and FOB manufacturer. The route of administration is an important factor influencing the incidence of an immunogenic response for a given biologic product. A validated assay for the assessment and characterization of anti-product antibodies should be used in all phase 3 studies and post marketing. A well-documented example of the need for well-validated assays to assess immunogenicity in clinical studies is the case of PRCA with a recombinant erythropoetin product.

Preclinical and Clinical Considerations for Streamlining a Program for FOBs

Preclinical Studies

Roche considers a thorough profiling of any biologic product using functional *in vitro* assays essential to assess the complex characteristics of proteins and their interaction with their intended targets. The use of *in vitro* functional assays for a “similarity assessment” is not acceptable as reagents and conditions will differ from those of the originator. Any alterations of the parameters can have consequences on the assessment of the characteristics of the product.

The original manufacturer of an innovative therapeutic protein generally has assayed this product in a large number of *in vitro* and animal models. These studies are usually done with several different molecules during lead identification and lead optimization. Once a molecule is selected, a large number of manufacturing lots of the protein are tested as well. Besides giving information on possible clinical settings for the later phases of development, these studies also contribute to the assessment of the functional characterization and consistency of the protein’s biological effect in animal systems.

Manufacturers of follow-on biologics do not have this broad historical database to assess their product. A follow-on manufacturer will not have available and cannot build a comparable database on functional characterization and consistency of their product in the preclinical phase. Before clinical studies in man are initiated, any manufacturer should demonstrate the functional (lot-to-lot) consistency of his product (i.e., consistency concerning the functional properties of the protein in an *in vivo* setting) and a stand alone preclinical development program.

We consider safety assays in animals for FOBs necessary according to the same criteria as applied for new substances before entering human studies. These assays include PK assays, since it is known that pharmacokinetics can vary significantly as a consequence of seemingly minor changes in protein modification (e.g., glycosylation differences) that cannot be detected reliably by *in vitro* assays and physicochemical analyses. Such tests should be carried out in a relevant

species that can respond mechanistically to the product tested (e.g. cross reactive to an antibody tested).

Clinical Studies

For the reasons given above, any FOB must be considered as a new protein drug and as such demonstration of safety and efficacy in each new indication and with each therapeutic dosage regimen is required.

Each FOB must establish its own safety database. Safety data obtained with the innovator product cannot be transferred to FOBs. The product labeling of an FOB will need to reflect the specific safety information from the FOB. Safety considerations also require studies in different indications for a product as effects such as immune response may differ according to the status of the patient.

Any product approval has to be supported by controlled trials to establish safety and efficacy of the product. If validated surrogate markers are available for the indication, these may be used instead of clinical endpoints to establish efficacy. Dose finding may not be required for FOBs provided that the exposure is similar to the reference compound, and no evidence of PD differences has been observed. For products with multiple indications, each indication should be supported by appropriate efficacy data since similarity with the innovator biologic cannot be assumed without experimental proof. This is particularly relevant when the biological mechanism of action is unknown or unclear. The product labeling for the FOB should be limited to the indications studied.

In many cases it will be unethical to conduct placebo-controlled studies with an FOB if approved medicines are available. At least in these cases, clinical studies should be conducted in a controlled, double-blind setting vs. the innovator drug in order to prove non-inferiority in relation to efficacy end points.

For FOBs, it is difficult, if not impossible, to assess the potential for immunogenicity without clinical data. The immunogenicity of FOBs therefore should be evaluated in appropriately sized clinical trials of adequate duration, particularly in cases when the likelihood of immunogenicity is high. Since in many cases, it will not be possible to assess the prevalence of immunogenicity with sufficient precision during development, a phase IV monitoring program, with a RMP, should be implemented. Until immunogenicity issues have been ruled out in adequately powered studies conducted post-approval, labeling of the FOB drug should indicate that there is a limited amount of data available on the prevalence and clinical consequences of immunogenicity.

Potency and Surrogates for Efficacy and Safety

Bioactivity and potency assays, while providing useful information to aid in the decision to allow a product into use in human clinical testing, cannot replace the requirement for complete clinical testing and should not be used as surrogates for establishing safety and efficacy to support the assessment of the benefit/risk of a biological product for marketing. As discussed in detail in the sections above, any *in vitro* and *in vivo* data can help establish that an FOB is exhibiting the appropriate response when compared with the reference product. However, bioactivity and potency assays are incapable of adequately predicting the clinical profile of a product from a different process. While information gained from such assays may aid the decision to approve use of the product in human clinical testing, but it cannot replace the requirement for complete clinical testing. Clinical studies of FOBs must include assessment of relevant surrogates or



clinical endpoints as required for any new product in that indication. Surrogate endpoints used to enable an accelerated approval for an innovator product cannot be used to support traditional approval of an FOB.

Terminology

In the interest of promoting communication among sponsors and health authorities in this complex environment and in order to minimize misunderstandings of both terms and concepts, Roche recommends harmonization of terminology between the US and Europe.

All protein products developed according to the proposals outlined above that are intended to be 'similar' to an originator product are by definition 'modified'. Second-generation protein products are those that are more extensively and selectively modified with the aim to differentiate the product characteristics. Both the FOB and the second-generation biologic will require safety management post marketing and will therefore need to be branded products, with distinct USAN names.

In conclusion, Roche appreciates the opportunity to comment on this complex discussion of the scientific expectations for bringing an FOB to market. We look forward to further scientific exchanges on these points at the upcoming February 14-16 workshop. If you have any specific questions about the content of this response, please contact the undersigned.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Michael Doherty" with a stylized flourish at the end.

Michael Doherty
Global Head – Pharma Regulatory Affairs
F. Hoffmann-La Roche AG

Appendix

Details of the innovator's pre-approval product development

During the **discovery phase**, tools and results are created that are relevant for the establishment of quality criteria for the in-process controls of the later process and the specifications of the later product. The critical information obtained is:

- Several functional in vitro assays/models to test the mechanism of intervention
- Several functional in vivo models to test for efficacy
- Assessment of qualitative and quantitative differences in such assays
- Data on variability of products from different expression systems
- Data on variability-function relationships
- Lab scale purification methods
- First methods for purity assessment

In the course of the **early development phase** a cell bank system, culture conditions and the first purification process are established. The process is monitored by in-process controls which allow assessment of the variability of product quality before and after the different process steps. The products obtained from this process are thoroughly tested in preclinical assays, in GLP toxicology studies, phase I and phase II trials to assess the safety of the compound and, if possible, the proof of mechanism in patients. The critical information obtained includes:

- Variability of product derived from different clones of a defined expression system
- Variability of product derived from a defined clone of an expression system
- Variability of product derived from different culture conditions of defined clones
- Product consistency for defined process conditions and process steps
- First standardized methods for in process controls and product quality
- Preclinical efficacy in various models
- Animal PK and metabolism
- Preclinical safety in GLP Tox studies
- Clinical safety and human PK/metabolism in phase I studies
- Proof of concept in patients from phase II studies

For the **late development phase** all relevant parameters are further defined and monitored. The relevant process scale, in-process-controls and quality criteria are established. A further step to control the process is a thorough validation of culture conditions, purification steps, methods for in process controls (IPCs) and for quality assessment. The established database and experience allows selecting the appropriate strategy for a comparability assessment. There are several cases documented in Roche experience in which analytical comparison did not provide sufficient information to show comparability. For other cases, one could observe differences of in vivo characteristics although the analytical data and their specifications indicated comparability. The critical information obtained during this phase includes:

- Standardized methods for in process controls and product quality
- Sufficient data from IPCs to assure process performance and robustness
- Sufficient data from removal experiments to assure acceptable limits for trace impurities
- Sufficient statistical sample of batches to assess product quality and consistency for the established process conditions and process steps
- Data from comparability assessments by analytical methods, preclinical efficacy studies in various models, potency and other functional assays
- Definition of the dose for the desired efficacy in patients from Phase II dose finding clinical trials
- Clinical safety (such as immunogenicity and other AEs) from Phase III studies
- Clinical efficacy in patients from Phase III studies

In our experience, we conclude that only in the context of full product development and manufacturing process development, including the establishment of methods and an historical database is it possible to determine the characteristics of a manufacturing process.