

November 12, 2004

Division of Dockets Management
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852**Re: Docket No. 2004N-0355, Federal Register: August 16, 2004 (Volume 69,
Number 157, Pages 50386-50388); Scientific Considerations Related to
Developing Follow-on Protein Products**

Dear Sir/Madam:

SICOR Inc., a subsidiary of Teva Pharmaceuticals Industries Ltd., is a biopharmaceutical company involved in the discovery, development, manufacturing and marketing of biopharmaceutical generic products (termed "follow on protein products" in Docket No. 2004N-0355). SICOR Inc. has been in this business for over 15 years and has invaluable experience with these products. This experience includes approval and distribution in over 17 countries, including interaction with the FDA and European Medicines Agency (EMEA).

SICOR Inc. appreciates this opportunity to comment on scientific considerations related to the development of biopharmaceutical generic products. In the September 14-15 FDA public workshop, the Agency requested data and information in the areas of manufacture, characterization, immunogenicity, preclinical, clinical, potency and surrogates for efficacy and safety, and terminology for these products. At this workshop, SICOR Inc. presented input to the Agency in these areas. This document serves to expand upon the presentations made by the company in the limited time period allotted during this workshop. Attached to this document is an Appendix containing analytical data presented during this meeting.

General Comments

SICOR Inc. believes that the approval of biopharmaceutical generics should be based on the totality of evidence gathered in the areas of quality, safety, and efficacy. A step-by-step approach should be taken where the extent of animal studies and clinical

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development programs are based on the ability to characterize the drug substance and drug product and comparability to the brand product. In some cases, it will not be necessary for a biopharmaceutical generic manufacturer to duplicate the animal and human studies conducted by the brand product. Extensive experience of the brand product in the therapeutic area will provide additional justification for abbreviated animal and human studies. Animal and human studies should not be conducted to prove what has already been proven.

This philosophy is supported by FDA's approach to the demonstration of comparability between biotechnology-derived products pre- and post-changes to the manufacturing process. The safety and efficacy of a product using a comparability protocol approach are defined by the chemical, physical, and biological attributes which can be assessed through analytical characterization. Analytical methods are available today to adequately characterize certain protein products. It has been recognized for at least a decade that a manufacturer of a biotechnology-derived product can change the production process and location and still have the same product if rigorous analytical exercises demonstrate comparability. Similarly, analytical comparability data in combination with a manufacturing process that is robust and reproducible, validated, and controlled can provide high confidence that a biopharmaceutical generic is of the same purity, potency, quality and as safe as the brand product.

Immunogenicity should always be addressed for biopharmaceutical generics as it is addressed for all biotechnological brand products. The presence of antibodies does not necessarily correlate with a negative clinical outcome or lessen the therapeutic viability of a recombinant protein drug. A risk assessment for immunogenicity should be performed based on known risk factors, such as the presence of protein aggregates and immunogenic profile of the brand product in the selected indication.

The terminology used to describe this product area is crucial. The term must convey trust, quality, and therapeutic equivalence as the term "generic" now implies for chemical drug products.

Specific Comments

1. Manufacturing issues

- a. What aspects of the manufacturing process determine the characteristics of a protein product whether produced through biotechnology or derived from natural sources?**
- b. What parts of the manufacturing process should the agency focus on when assessing similarity between products?**

Specific aspects and parts of the manufacturing process do not determine the characteristics of a protein product. The biopharmaceutical generic is developed to be comparable to the biotechnology-derived brand product. The power of current analytical methodology, combined with modern concepts of quality management, reinforced by in-process controls and validation, allow for a high confidence level that a biopharmaceutical generic is comparable to the brand.

FDA has vast experience with the scientific review and approval of biotechnology-derived products. The vast knowledge that Agency reviewers have was recently highlighted in the white paper on the Critical Path Initiative.¹ The scientific rationale behind decision making in two areas should be closely reviewed as it can provide knowledge to apply to policy making in the area of biopharmaceutical generics. These two areas are the review and approval of Human Growth Hormone (HGH) and scientific assessments of comparability of biotechnology products prior and subsequent to major changes in the manufacturing process. FDA policy making and decisions in these areas have been a great success for patients by bringing much needed drugs to market as soon as possible and maintaining an adequate supply of these drugs.

Regardless if a biotech product is a brand product or a biopharmaceutical generic, certain features of the manufacturing process need to be maintained in order to insure the identity, potency, purity, quality and safety of the final product. These features include robustness and reproducibility, validation, controls, and testing. There is a strong relationship between analytical characterization and these features of the manufacturing process. Bringing these capabilities together give confidence that the final product produced by a biopharmaceutical generic manufacturer is comparable to the brand product.

Human Growth Hormone products

HGH products manufactured via biotechnology have been distributed in the US market for over 17 years². Six immediate release products have been approved and five are currently distributed on the market today – Humatrope® (Lilly), Norditropin® (Novo Nordisk), Saizen® (Serono), Genotropin® (Pharmacia), Nutropin® (Genentech), and Tev-Tropin™ (Teva/Bio-Technology General; approved, but not yet marketed).

The manufacturing process for each HGH product is different as each company considers details of their process to be confidential. These separate manufacturing processes become even more discrete as cell lines and Master Cell Banks are different. In fact, one product is derived from a mammalian cell line while the other five products are derived from bacterial cell lines. As there is little similarity among these manufacturing processes, this can be considered the ultimate manufacturing change when viewed from a comparability exercise perspective (see discussion below). Yet, these different manufacturing processes yield the same product. Therefore, HGH serves as an example of how the “process = product” dogma is not applicable for certain protein products and provides support for a “product = product” comparability approach for biopharmaceutical generics.

All of these products are identical in primary structure. They are all 191 amino acids in length with a molecular weight of approximately 22 kilodaltons. As the approved labeling states, the amino acid sequence for each product is identical to pituitary-derived

¹ <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

² Center for Drugs Evaluation and Review (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>)

human growth hormone (pit-HGH), the natural protein product extracted from human tissue. Pit-HGH was on the market at the time when the first recombinant DNA-derived HGH product was submitted to FDA for approval. Therefore, if all these products are identical in primary structure to pit-HGH, they are identical in structure to one another. This argument can be extended further than the amino acid sequence. The approved labeling for one of these products states that in addition to the primary structure being identical, the secondary and/or tertiary structure is also identical to pit-HGH.

Further, FDA has recognized the identical nature of all six of these recombinant protein products by assigning the same generic (established) name "somatropin". This established name is also assigned to the natural protein product, pit-HGH. The FD&C Act grants authority to the Secretary to designate an official (established) name if such action is necessary or desirable in the interest of usefulness and simplicity. Established names are statements of the identity of the drug³ and are assigned to drugs that are identical in chemical structure and pharmacological action and which are substantially identical in strength, quality and purity⁴.

Somatropin was also adopted by the USAN Council of which FDA is a member. The USAN term is selected based on chemical information including the chemical name, structure, molecular formula, and molecular weight; pharmacologic action; and therapeutic indication/method of action.⁵

These products were also considered the "same" under the Orphan Drug Act. The first of these six drugs approved was Humatrope in March, 1987. Humatrope was granted Orphan Drug exclusivity on that date. FDA issued Not Approvable letters to all other HGH manufacturers. These letters indicated that the active moiety of these products was chemically equivalent to Humatrope and the only manner in which exclusivity could be broken was an enhanced safety profile. Because these products were considered the same by FDA, exclusivity could only be broken for a HGH product with an improved safety profile.

In order for FDA to make determinations of identical structure and sameness, adequate analytical methods must be available. For Humatrope, a variety of techniques were employed including peptide maps and fast atom bombardment mass spectrometry, sequencing, amino acid analysis, RP-HPLC, Raman and circular dichroic spectra, electrophoresis, and bioassay. These were comparative studies with the recombinant product and its natural counterpart, pit-HGH, an already marketed product. These data collectively confirmed that Humatrope was structurally, chemically, and biologically equivalent to pit-HGH. Its identity, potency and purity appear to have been well established⁶. Thus, 15 years ago, analytical methods were available to adequately characterize a protein product manufactured using biotechnology as well as a natural protein product extracted from human tissue. Many of these same analytical techniques

³ Title 21 of the Code of Federal Regulations, § 201.50

⁴ Federal Food, Drug, & Cosmetic Act, § 508

⁵ USAN Council (<http://www.ama-assn.org/ama/pub/category/3032.html>)

⁶ Humatrope, Medical Officer's Review of Original Submission, February 19, 1987

are used today in comparability exercises of specified biotechnological products manufactured by the brand industry. With more advanced analytical methods available today than when Humatrope was approved, characterization of protein products can provide even more assurance in terms of physicochemical structure and biological properties.

Prior to the Humatrope approval in 1987, FDA made the decision that abbreviated safety and efficacy clinical trials can be performed in 50-100 patients for 6 months. The rationale for this decision was that HGH is a simple protein that can be adequately characterized; identity, potency, and purity of HGH products are well established; and there was a product already on the market to which identity, safety, and efficacy could be compared. All HGH products were approved through this abbreviated clinical program. The adequacy of this approach has been demonstrated by the consistent track record on the safe use of the six HGH products for the past 17 years.

During FDA review of each product post-Humatrope approval, a decision was made that the only possible circumstance under which another recombinant HGH product could supercede Humatrope's exclusivity would be for the new product to have a superior safety feature. The only safety issue concerning HGH was immunogenicity - the anti-HGH antibody incidence. For all five HGH products approved after Humatrope, immunogenicity profiles were consistent with Humatrope. There was no clinically significant advantage over the currently protected product to break exclusivity. Considering that all these products were manufactured using a different manufacturing process, including different cell lines, this provides strong evidence that different manufacturing processes do not yield products which elicit varying adverse antibody response in patients.

Approved labeling for these products state that they are therapeutically equivalent to the natural protein product, pit-HGH. Therefore, FDA has criteria in place to determine therapeutic equivalence for protein products. Labeling for Humatrope, Nutropin, and Tev-Tropin state that in vitro, preclinical, and clinical testing has demonstrated that the product is therapeutically equivalent to human growth hormone of pituitary origin. Equivalent pharmacokinetic profiles in normal adults to pit-HGH has also been demonstrated for Humatrope and Tev-Tropin. For Genotropin, therapeutic equivalence, including similar pharmacokinetic profiles, is extended to other recombinant human growth hormone products. For Nutropin, similar efficacy to pit-HGH has been established using clinical endpoints.

Most endocrinologists view these HGH products as equivalent. Companies must differentiate themselves from competing products by pursuing unique indications, developing patented delivery systems that service the needs of patients, providing patient services & value-add programs, establishing relationships with prescribers & nurses, and providing influence through patient advocacy organizations.

FDA has the ability to use knowledge gained from their experience with products in the approval process and marketed products and through published literature. This

knowledge is applied in the evaluation of safety and efficacy. For Humatrope, the FDA Medical Officer concluded that the drug is fully active in promoting growth, with growth acceleration values consistent with past experience with pit-HGH and recombinant methionyl-HGH, an approved product containing natural sequence human growth hormone with an extra N-terminal methionine amino acid residue attached. The reviewer further states that “the results obtained are essentially consistent, qualitatively as well as quantitatively, with previous clinical data, obtained either through publications during the last quarter of a century, as well as data submitted to the FDA by various producers of pit-HGH and recombinant DNA growth hormones, natural or synthetic.” Therefore, FDA made the determination of safety and efficacy of Humatrope based on literature and clinical trial data submitted for the natural protein product and other recombinant HGH products. It is likely that these data supplemented the data obtained through the abbreviated clinical trial program.

For Genotropin, the Medical Officer concludes that growth hormones “of recombinant origin have been in use since 1984-85. One of these products (Humatrope, Lilly) is chemically identical, although differences exist in its final formulation. It is my impression that the world wide experience with” growth hormone “is applicable to this particular product. I believe that” Genotropin “is identical in all respects to this product”. Results of clinical trials were found to be comparable to historical data using growth hormone from pituitary sources or to other recombinant growth hormone products. The design and outcome of those trials can be compared to those of any approved growth hormone product. Similar growth velocities as obtained with other GH formulations were maintained. Genotropin had the “expected effectiveness” and patients that were receiving other growth hormone formulations and switched to this formulation maintained similar growth velocities to those seen with the previous products. “In our evaluation of natural sequence GH products, we relay (*sic*) in part on 30 years experience with GH therapy.”... “The sponsor has produced data that show this GH product to be safe and effective as any other GH product”.

For Norditropin, the Medical Officer concludes that efficacy results “are comparable to those observed with other somatotrin preparations. Adverse reactions were all minor and confined to those expected” for other somatotrin preparations. “It can be concluded that Norditropin is at least comparable in safety and efficacy to Humatrope”. Efficacy results were all consistent with previously reported results using either pituitary-derived or recombinant HGH products. “Efficacy of Norditropin appears to be equivalent to that of Humatrope”.

For Tev-Tropin, the Medical Officer concluded that the product is comparable to the marketed product. The Chemistry, Manufacture and Controls (CMC) reviewer concluded that the potency and purity of the drug substance and limits compare with Humatrope.

These comparisons to other growth hormone products pre- and post-approval are extended to immunogenicity. As mentioned above, in order to break Orphan Drug exclusivity a HGH product was required to have a statistically significant change in the safety profile in regard to anti-HGH antibody formation. All HGH products evaluated

and approved after Humatrope required a comparison to approved products in this regard. All products approved had similar frequencies of antibody formation against growth hormone that was consistent to clinical trial data and data collected for marketed products.

In conclusion, different manufacturing processes can yield structurally identical and equivalent products. The ability to adequately characterize protein products was available at least 17 years ago, as demonstrated for Humatrope. Immunogenicity should always be considered. The immunogenic profile of the brand product should factor into risk-based decision making. An abbreviated clinical program was adopted by FDA for HGH due to the ability to adequately characterize the protein, well established use of HGH products, and a brand product already on the market to which identity, safety, and efficacy could be compared. These abbreviated trials resulted in products that have maintained consistent safety and efficacy profiles even today. These protein products are labeled as therapeutically equivalent to another protein product; therefore, FDA has criteria in place to determine therapeutic equivalence for biopharmaceutical generics.

Use of scientific protocols to determine comparability between biotechnology-derived products

Historically, biological products have been complex mixtures with low purity that were difficult to characterize. Because of this limited ability to characterize the product, a biological product was defined by its manufacturing process. FDA considered that changes to the manufacturing process, equipment or facilities could result in changes to the biological product. In order to determine if this change had an effect on safety and efficacy, human studies were required. FDA generally required new clinical data, often from a small number of patients, whenever manufacturing changes were implemented.

In the early 1990s, FDA examined the policy on comparability for biotechnology and other well-characterized biological products. This assessment led to a change in the "process=product" belief. This change was due to the experience that the Agency and industry had gained with products manufactured via biotechnology; improvements in production methods; and test methods for characterization, the manufacturing process, and controls. FDA recognized that small clinical trials were less likely to determine any product differences than rigorous analytical characterization. If a manufacturer could demonstrate that a product made after a manufacturing change was comparable to the product made before the manufacturing change then animal and/or human studies would not be necessary. These changes may be implemented individually, simultaneously, or in tandem. Comparability could be established through analytical and functional testing of the product. This initiative allowed increased flexibility in bringing important and improved products to patients more efficiently and expeditiously.

The policy on comparability was formalized in FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Biotechnology-derived Products issued in 1996 which clarified the philosophy of "product=product". It was a well-acknowledged fact that these types of evaluations had

been done by FDA on a case-by-case basis in the past and the Guidance document was published to clarify inconsistencies and ambiguities. A number of manufacturing changes were approved based on analytical comparability data including the move of production from one site to another; increase from pilot scale production to commercial scale production; and changes to fermentation, purification, and formulation. These decisions were made by FDA scientists who used their knowledge and experience in the evaluation of the product pre- and post-manufacturing process change.

FDA acknowledged that the most important factor for the Agency in the evaluation of product comparability is the anticipation of if these manufacturing changes will result in significant changes in product safety and efficacy. The Agency encouraged manufacturers to carefully evaluate the product resulting from these changes for comparability to the pre-existing product.

A comparability exercise is a stepwise approach to evaluating a product pre- and post-manufacturing changes. Comparable does not mean identical as minor product differences, for example a change in impurities, is allowable if no change in the safety profile can be justified based on the existing knowledge. In many cases, more than one manufacturing change may be made and all changes may be included in one exercise. A determination of comparability is first made through extensive chemical, physical and bioactivity testing with side-by-side comparisons of each product. If comparability is established, the exercise stops at this point. However, if comparability cannot be established, additional testing is performed which might include non-clinical testing and clinical safety and efficacy studies. In reality, this additional testing is a rare occurrence.

This scientific support led to the success of the FDA comparability exercise approach. This success was acknowledged by EMEA in 2001 when the scientific body of this regulatory agency, the Committee for Medicinal Products for Human Use, formerly the Committee for Proprietary Medicinal Products (CPMP), adopted Guidance in this area.⁷ However, this body took this approach one step further and acknowledged that comparability exercises can be performed to demonstrate that a biotechnology-derived product is similar to an already approved biotechnology-derived product. The CPMP Guidance acknowledges that the manufacturer of a biotechnology-derived product similar to one already authorized would not have all the data and information as the brand manufacturer. The design of the comparability exercise will depend on the complexity of the molecular structure as well as the possible differences as compared to the reference product.

The concept of comparability and methodology was subsequently adopted by the International Conference on Harmonization (ICH). ICH brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. Comparability was further refined in the Q5E guidance (Step 2) completed

⁷ Note For Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance, CPMP/BWP/3207/00, London, 20 September 2001

in 2003.⁸ This document states that effects of manufacturing changes on the product can initially be evaluated by quality assessments using a series of analytical analyses. Additional animal and human studies are needed only when there is uncertainty regarding the outcomes of analytical studies. In many cases, analytical studies alone are adequate to demonstrate that the changed manufacturing process does not have adverse impact on the safety and efficacy of the product.

This comparability policy has implications for the US biopharmaceutical generic industry. FDA has accepted for more than 15 years that in most cases manufacturing changes to biotechnological products can be assessed by analytical testing alone. Human studies are not necessary to demonstrate that the product derived from the modified process is comparable to the product derived from the non-modified process. Changes to the manufacturing process may include changes in manufacturing site, Master Cell Bank, fermentation, purification, etc. These changes may be implemented individually, simultaneously, or in tandem and are important to improve efficiency, quality, and economics. Even in situations where some human studies must be performed, those studies are in general confirmatory and limited in scale. FDA has accepted over the past 15 years that analytical characterization was suitable for the demonstration of comparability after manufacturing changes. Analytical tests have become increasingly sophisticated over the past 15 years and the ability to characterize proteins, including glycoproteins; tertiary structure; and aggregation has improved greatly. Knowledge of the product and manufacturing process is necessary to anticipate potential changes to the product. However, experience with the product is not limited to the brand manufacturer as the biopharmaceutical generic manufacturer will also have extensive experience (see below). Furthermore, this experience with the manufacturing process does not imply that the process need be the same as the brand manufacturer.

FDA has vast experience with scientific protocols to compare a biotech product derived from a modified manufacturing process to the one derived from the previous manufacturing process. Biopharmaceutical generics are developed to be comparable to the brand biotechnology-derived product. The ability to analytically characterize these products has been well demonstrated by the brand industry and accepted by FDA through the success of the comparability program. Comparability between the biopharmaceutical generic and brand product can be established using scientific knowledge available today. As FDA did prior to issuance of comparability Guidance in 1996, the Agency should look to their vast experience with comparability protocols to develop policy for biopharmaceutical generics.

The power of current analytical methodology, modern concepts of quality management, in-process controls and validation allow for a high confidence level that a biopharmaceutical generic is comparable to the brand

⁸ Q5EB, Step 2 Note for Guidance on Biotechnological/Biological Products Subject to changes in their Manufacturing Process (CPMP/ICH/5721/03)

Regardless if a biotech product is a brand product or a biopharmaceutical generic, certain features of the manufacturing process, such as robustness and reproducibility, validation, controls, and testing need to be maintained in order to insure the identity, potency, purity, quality and safety of the final product. There is a strong relationship between analytical characterization and these features of the manufacturing process. Bringing these capabilities together give confidence that the final product produced by a biopharmaceutical generic manufacturer is comparable to the brand product.

SICOR Inc. is a biopharmaceutical company involved in the discovery, development, manufacturing and marketing of biopharmaceutical generic products. The company has been in this business for 15 years. Drug substance and drug product are produced in state-of-the-art facilities devoted to the production of biotechnology products. These facilities were designed and constructed according to current cGMP standards of both the European Union and United States. These facilities are located in Lithuania and Mexico and have received GMP certificates from the Therapeutic Goods Administration (TGA), Australia.

SICOR Inc. currently manufactures multiple biopharmaceutical generics; therefore, the company is in a strong position to comment on the scientific approach for approval of such products. One of these products, IFN alfa-2b, has been manufactured for over 15 years. At least 9 million doses have been given in 17 countries. As one may expect, over this time period changes have been made to the manufacturing process. All changes to the manufacturing process were conducted using the comparability protocol approach. To date, through all these changes, safety and efficacy remain consistent. All SICOR Inc.'s products are manufactured using a process that is robust and reproducible, validated, and controlled. In-process control testing and end product testing adds additional assurance that the manufacturing process is producing a product that is pure, safe, potent, and of high quality. In addition, testing of the drug substance and drug product provides assurance that the product is comparable to the Interferon alfa-2b Chemical Reference Standard (*European Pharmacopoeia*), and/or the National Institute of Biological Standards and Controls (WHO international standard). The production of IFN alfa-2b will serve as an example of how the features mentioned above are important.

Each step of the manufacturing process must be controlled to establish with a high level of confidence that the final product will meet all specifications. Quality, safety and effectiveness must be built and designed into the manufacturing process. Final product testing insures that quality goals are met. SICOR Inc.'s mature quality management groups insure that the manufacturing process is consistent through the release or rejection of all intermediate, drug substance, and final product. An active internal audit program insures compliance with cGMPs. In addition, through the Vendor Approval and Qualification Program, which includes on-site audits, the high quality of raw materials and manufacturing components and compliance with cGMPs is assured.

Annual product quality reviews verify the consistency of the IFN alfa-2b manufacturing process. These reviews include trending and evaluation of in-process controls and critical testing results; critical systems and programs, to include water, HVAC, and

environmental monitoring; all batches not meeting established specifications; equipment failures; critical deviations and related investigations; change management; stability programs; returns, complaints, and recalls, if any; and adequacy of corrective actions. In addition, changes to dossiers and any adverse events are reviewed to insure adequate feedback and communication to all production and Quality Unit staff.

Qualification and validation is performed for all procedures, processes, equipment, materials, and systems that may affect the quality of the product. Process validation demonstrates the reproducibility and efficiency of the manufacturing process. Reproducibility provides a high degree of assurance that the drug substance and drug product consistently meet all established specifications. Monitoring of critical process parameters assesses the reproducibility of the manufacturing process. Process validation includes the validation of fermentation, recovery, formulation, and fill/finish.

Characterization and validation of the Master Cell Bank (MCB) and Working Cell Bank (WCB) are important to insure a consistent source of high quality and safe starting material for each production lot. IFN alfa-2b is manufactured using a validated and characterized MCB and WCB. The MCB was produced from a clone from the bacterial cell line and selected on the basis of efficient production of IFN alfa-2b, expression vector integrity and stability, and identity of the protein. Both MCB and WCB have been characterized for the absence of contamination by extraneous microorganisms, identity of the cells by phenotypic features, and viability. The structure and copy number of the expression vector have been investigated at the working seed stage and at the end-of-production and shown to be identical to that determined for the MCB. The quality and safety of this starting material, coupled with a robust, reproducible, controlled manufacturing process provides assurance of the quality and safety of the final product.

Controls maintain the consistency of the manufacturing process. Limits are set to monitor this consistency. Limits are justified based on critical information gained from the entire manufacturing process spanning the period of development through commercial scale production. Process controls are established during all stages of manufacture to insure drug substance and drug product quality. In-process testing is performed at critical decision making steps and at other steps where data serve to confirm reproducibility of the process during the production of drug substance and drug product. The manufacture of IFN alfa-2b is representative of other biotechnology products manufactured from bacterial cell culture. In process controls monitored throughout the production process include absence of contamination by extraneous microorganisms, stability of expression vector, expression level of protein, identity of IFN protein, medium sterility, culture purity, total soluble cell protein, dry weight of intermediate, IFN protein quantity, total protein quantity, purity, content of soluble protein, protein activity, identity of plasmid structure, time, and optical density. On-line controls of production equipment include pH, temperature, conductivity, pressure, flow rate, pO₂, optical density, speed, time, shaking rate, conductivity, feed pressure, gradient, and UV-absorption.

The biopharmaceutical generic product produced using a reproducible and robust manufacturing process is demonstrated to remain within its established specifications of identity, potency, safety, quality, and purity during storage through a stability program. This program also serves to detect changes in the product over time. Stability studies are performed under real-time, accelerated, and stress conditions to support a proposed expiration dating period and to determine the physical or chemical degradation profile of the drug substance and drug product.

Tests for identity, purity, and potency of the drug substance and drug product should be sensitive, quantitated, and validated. Assays selected for this purpose are selected from those used in analytical characterization and are specifically validated for this purpose. A subset of these tests are also identified as stability-indicating and used for stability assessment. Scientifically-sound limits and specifications are established for in-process controls and intermediates which are quantitative and justified based on the manufacturing history of the biopharmaceutical generic. Specifications for the drug substance and drug product should be based on data obtained from validation lots used to demonstrate the reproducibility of the manufacturing process. As mentioned above, data obtained from stability lots also factor into the setting of specifications.

As described in ICH Q5E, step 2, evaluation of the manufacturing process in relation to manufacturing changes does not imply that the process has to be comparable before and after the manufacturing changes. Instead, the evaluation is intended to provide assurance that the new process is as validated and controlled as before the manufacturing changes. For SICOR Inc.'s biopharmaceutical generic products marketed today, the manufacturing process is different than the manufacturing process for the comparable brand. Although publicly available information is used in the design of this process, a biopharmaceutical generic company does not have access to confidential information on the manufacture of the brand. Analytical procedures measuring quality attributes of the manufacturing process also evolve with product development. Manufacturing procedures and testing methods employed by biopharmaceutical generics will more than likely be more advanced than the brand product as state-of-the-art procedures and methods used today are more advanced than those used decades ago when the brand was approved. Therefore, the manufacturing process, test methods, and specifications for a biopharmaceutical generic must be evaluated separately from the brand product. Although the process is not the product, one recognizes the importance of the manufacturing process in assuring the quality of the final product.

Biopharmaceutical generic manufacturers should submit a full Chemistry, Manufacturing and Controls (CMC) section to their application to insure that FDA has the data and information to determine that the drug substance and drug product is safe, pure, potent and of high quality. The CMC section should include full analytical characterization, a description of the manufacturing process and test methods, and stability data. Analytical characterization should include a molecule-to-molecule comparison to the brand product to demonstrate comparability.

2. Characterization

- a. What is the capability of current analytical technology to adequately characterize protein products?
- b. What factors, including quality attributes, impurity profiles, and changes in the manufacturing process, should be considered when assessing similarity of different protein products?
- c. Is it possible to accurately predict safety and efficacy from analytical studies?

Analytical methods are available today to adequately characterize certain protein products. The power of current analytical methodology, combined with modern concepts of quality management, reinforced by in-process controls and validation, allow for a high confidence level that a biopharmaceutical generic is comparable to the brand. Analytical test methods are far more precise and sensitive in detecting potential product differences than are preclinical or clinical studies. Analytical characterization has shown that the biopharmaceutical generic has the same chemical, physical and biological characteristics as the brand product. Since safety and efficacy are defined by these attributes it is anticipated that the biopharmaceutical generic will have a comparable safety and efficacy profile to the brand product.

Analytical methods are available today to adequately characterize certain protein products and demonstrate comparability

SICOR Inc. manufactures and distributes IFN alfa-2b in 17 countries and G-CSF in two countries. In order for approval to be gained, the product must be demonstrated to be safe, pure, potent, and of high quality. The ability to characterize the product and demonstration of comparability serve as the foundation for the design of animal and human studies.

For the purposes of this section only, the term "biogeneric" is the same as "biopharmaceutical generic". SICOR Inc.'s product is noted as the biogeneric. Figures are contained in the attached Appendix.

The analytical techniques employed for a comparability assessment to characterize a biopharmaceutical generic must demonstrate, within the specified limits established for the brand product or scientifically justified acceptance criteria, that the biopharmaceutical generic exhibits:

- (i) comparable protein structure,
- (ii) comparable physicochemical properties,
- (iii) comparable biological properties, and
- (iv) comparable level of impurities

in a side-by-side, molecule-to-molecule evaluation. Among the quality attributes for establishing comparability, protein structure and biological activity related to product identity are the most essential while the safety aspect of new or higher levels of impurities can be qualified by non-

clinical studies. The outcome of this analytical comparability exercise will be considered in the design of animal and human studies.

As established historically, protein characterization is routinely addressed in a step-wise fashion moving from elucidation of the primary structure, then secondary and tertiary, and finally finishing with purity assessment.

Following this scheme, using G-CSF as an example, the primary structure was demonstrated to correspond to the theoretical primary structure, and that of the brand product, using:

- (i) mass spectrometry,
- (ii) peptide mapping,
- (iii) amino acid terminal sequence data,
- (iv) HPLC analysis.

Electron spray mass spectrometry appears to be the most powerful technique (as well as other currently available MS techniques) in precisely characterizing the molecular structure of the compound. Precision in molecular mass estimation routinely is below 1 Dalton, to allow the detection of minute alterations in the molecule of the protein product. The overlay of the spectra of the biopharmaceutical generic G-CSF from 3 different manufacturing batches and that of the brand product revealed no differences between the two molecules or discrepancy with the theoretically expected molecular mass. The results provide proof of the primary structure of the protein since no other technique could overcome the power of these MS results (see Figure 1).

Nevertheless the classic peptide mapping procedure was applied to characterize and compare 3 different batches of the biopharmaceutical generic G-CSF and brand product. The overlay of HPLC-chromatographic profiles of the protein digests obtained with *Staphylococcus aureus* V8 protease revealed no detectable differences between the biopharmaceutical generic and brand preparations (see Figure 2).

N-terminal partial amino acid sequence analysis is routinely used to characterize proteins for identity and homogeneity purposes. Five batches of the biopharmaceutical generic G-CSF were subjected to such analysis to prove that all of these batches matched the expected 15-residue long N-terminal amino acid sequence (see Figure 3).

Combination of reverse phase and size exclusion HPLC analysis provides additional proof of the structure and comparability of the two proteins, if performed in head-to-head fashion.

RP-HPLC reveals the hydrophobicity of the protein as well as is a powerful tool to detect minor isoforms of the principal compound. In the analysis of 3 independent batches of the biopharmaceutical generic G-CSF and 3 different samples of brand product, the identical hydrophobicity of the two preparations was established, and actually, similar, if not identical, impurity profile was demonstrated (see Figure 4).

The SE-HPLC, which monitors the aggregation status of the protein molecule, provides additional proof that 3 independent batches of the biopharmaceutical generic G-CSF and 3 different samples of brand product exhibit an indistinguishable monomeric state, as well as very close higher aggregate formation profile (see Figure 5).

The totality of the results of investigation of the primary structure presented above prove unequivocally that the biopharmaceutical generic G-CSF and brand product possess an identical primary molecular structure.

The next phase in characterization and comparison is elucidation of conformational elements of the two molecules. Numerous techniques are currently available, but two were selected. The conformational elements of biopharmaceutical generic r-metHuG-CSF were demonstrated to be comparable with those of the brand product, using:

- (i) 2nd-order fluorescence emission spectroscopy,
- (ii) HPLC analysis (see previous data).

Direct and 2nd-order fluorescence emission spectra of the two molecules are indistinguishable. This suggests that Trp and Tyr residues exist in identical solvent exposure environments. This further suggests indistinguishable secondary and tertiary structures of the two molecules. If there would be a detectable amount of the molecular species characterized with altered conformation, such as distorted disulphide bonds, it would be immediately detected as demonstrated for the green color labeled trace of the misfolded intermediate (see Figure 6). The combination of this spectroscopy technique with previously discussed RP- and SE-HPLC, where hydrophobicity and monomer/aggregation state of the molecule is determined, respectively, allows with extremely high degree of confidence to conclude that the two molecules under investigation possess indistinguishable conformational structure.

The establishment and comparison of impurity profiles of the two preparations is the most challenging part of an analytical comparability exercise. Techniques involved in such a study are essentially the same as those used in structural identity studies. For instance, SE-HPLC, when applied to analysis of different batches of the biopharmaceutical generic G-CSF and to one batch of brand product, revealed the content of higher molecular species (dimers, aggregates) not exceeding 0.1% for both preparations – well below what is routinely regarded as a safe level of 0.5% for many biopharmaceuticals (see Figure 7).

Very similarly, RP-HPLC is a method of choice to characterize and quantify product-related substances, such as oxidized, deamidated or misfolded species. Results of such analysis applied to different batches of the biopharmaceutical generic G-CSF and to one batch of brand product revealed that the purity of the biopharmaceutical generic product far exceeded the 99% value established for the particular lot of brand product. Again, this level of purity appears to be far superior to that of 95% that is routinely regarded to be safe for many biopharmaceuticals (see Figure 8).

Potency measurements, an inseparable and crucial part of characterization of a brand product as well as a biopharmaceutical generic, are a complex issue. For certain protein products, this is due to the lack of availability of proprietary cell lines for the bioassay and proof of the suitability of the biopharmaceutical generic manufacturer's assay when access to the brand manufacturer's cell line is not possible. An example to be considered is a year-long targeted study that was undertaken by SICOR Inc. to prove that the bioassay system, which is a cell proliferation-type assay, works comparably to that established by the brand manufacturer. As is clear from the presented data, different batches of the biopharmaceutical generic G-CSF exhibited a specific biological activity comparable to that of the brand product both in terms of the mean value and with respect to fiducial limits of the estimation (see Figure 9).

Evaluation of the level of process-related impurities is an integral part of characterization of any product derived via biotechnological means. Obviously, no direct comparison to the relevant characteristics of the brand product could be made (due to the differences in the manufacturing process), so the biopharmaceutical generic manufacturer has to restrict their efforts to maintain the purity of the product within the range of generally accepted limits. The two critical parameters of process-related impurities are host-cell proteins (HCP) and host-cell DNA (HC DNA).

Assay methods specific to the biopharmaceutical generic product had to be developed and the results of their application revealed that a series of batches of G-CSF contained significantly less than 100 ppm of HCP (in fact, around 20 ppm)(see Figure 10), and less than 200 ppm of HC DNA (see Figure 11).

The same comparability exercise can be performed for IFN alfa-2b. The primary structure of IFN α -2b was demonstrated to be comparable to the theoretical primary structure, and that of the brand product, using:

- (v) mass spectrometry,
- (vi) peptide mapping,
- (vii) amino acid terminal sequence data,
- (viii) HPLC analysis.

ESI mass spectrometry experiment, used in a similar format shown above for G-CSF, proved unequivocally that the two molecules, the biopharmaceutical generic IFN α -2b and the brand product, have an indistinguishable molecular mass (see Figure 12).

Tryptic peptide mapping procedure was applied to characterize and compare 3 different batches of the biopharmaceutical generic IFN α -2b and Chemical Reference Substance (CRS) preparation from *European Pharmacopoeia (Eur. Ph.)* (it is important to note, that in this case the CRS is in fact the drug substance coming from the brand product's manufacturing process). The overlay of HPLC-chromatographic profiles of the protein digests obtained with trypsin revealed no detectable differences between the two preparations (see Figure 13).

It is important to stress that the peptide mapping study is supplemented with orthogonal application of mass spectrometry. Namely, each peptide is isolated and subjected to MS analysis to establish its molecular mass. Then from the mass spectrometry data and gene sequence information, the assignment of each peptide to a specific amino acid segment is made to cover ultimately the entire polypeptide sequence of the product. In addition, such orthogonal MS application is performed for peptides produced under thiol-reducing and non-reducing conditions to establish the disulphide bond presence and location within the molecule structure.

N-terminal partial amino acid sequence analysis is presented from the manual Edman degradation experiment. The principal purpose is to demonstrate the ability of the technique to detect subtle differences between the biopharmaceutical generic product and the brand. In the separate enlarged window of the slide one can clearly see that the brand product has a substantial part of methionine as the first amino acid residue of the polypeptide chain while the biopharmaceutical generic IFN α -2b is free of such impurity (however, extensive safety studies performed by the brand manufacturer demonstrated that the addition of a methionine group does not pose any risk to the patients)(see Figure 14).

The combination of RP-HPLC and SE-HPLC completes the proof that both the biopharmaceutical generic IFN α -2b and the brand product have indistinguishable primary structures (see Figures 15 and 16).

The next phase in characterization and comparison is elucidation of conformational elements of the two molecules. Numerous techniques are currently available, but two were selected. The conformational elements of IFN α -2b were demonstrated to be comparable with those of the *Eur. Ph.* CRS material, using:

- (iii) 2nd-order fluorescence emission spectroscopy,
- (iv) HPLC analysis (see previous slides).

As in the previous case study, obtained results allow with extremely high degree of confidence to conclude that the two molecules possess indistinguishable conformational structure (see Figure 17).

Potency estimation for the IFN α -2b product is a more complicated issue since the molecule is known to have a pleiotropic action in humans; however, well-established cell and virus lines are available from reputable sources for the biopharmaceutical generic manufacturer to develop its bioassay systems. In addition, established international potency standards are available.

Both the biopharmaceutical generic IFN α -2b and the brand product exhibited the viral cytopathic inhibition and antiproliferative activities indistinguishable from one another (see Figure 18).

For the establishment and comparison of impurity profiles of the two preparations an approach very similar to that in the previous case study was used. The *Eur. Ph.*

monograph for IFN α -2 as well as the *Eur. Ph.* CRS material were used for certain experiments.

For instance, the electrophoretic homogeneity of the biopharmaceutical generic IFN α -2b was established, following recommendations of the *Eur. Ph.* By eye one can see the presence of product-related substances up 0.2% (see Figure 19).

Control of charge isomers of IFN α -2b is achieved by isoelectrofocusing technique, again following the format recommended by *Eur. Ph.* No differences from the *Eur. Ph.* CRS materials were detected for the biopharmaceutical generic IFN α -2b product (see Figure 20).

The RP-HPLC is a method of choice to characterize and quantify product-related substances, mainly oxidized forms, for IFN α -2b. Results of such analysis applied to approximately 30 batches of the biopharmaceutical generic IFN α -2b product revealed that the purity of the biopharmaceutical generic product far exceeded the 97% and 95% limits, established for the singular impurity and the sum of impurities, respectively, according to *Eur. Ph.* (see Figure 21).

The critical parameters of process-related impurities are HCPC and HC DNA. Assay methods specific to the biopharmaceutical generic product had to be developed, and the results of their application, as well as of that for general bacterial endotoxins, revealed that a series of batches of IFN α -2b contained significantly less than 5 ng/mg of HCP (in fact, around 0.5 ng/mg), less than 50 pg/mg of HC DNA (in fact, around 20 pg/mg), and less than 100 EU/mg of bacterial endotoxins (in fact, around 10-15 EU/mg), all below the level which is generally accepted as safe for IFN α -2b and many other biopharmaceutical generics.

In conclusion, analytical methods are available today to adequately characterize certain protein products. The rigorous analytical characterization exercises presented above have shown that the biopharmaceutical generic has the same chemical, physical and biological characteristics as the brand product. Since safety and efficacy are defined by these attributes it is anticipated that the biopharmaceutical generic product will have the same safety and efficacy profile as the brand product. Analytical data as presented above would permit the Agency to make a scientific decision on abbreviated animal and human studies.

Biopharmaceutical generic manufacturers should submit a full Chemistry, Manufacturing, and Controls (CMC) section to their application to insure that FDA has the data and information to determine that the drug substance and drug product is safe, pure, potent and of high quality. The CMC section should include full analytical characterization. Analytical characterization should include a side-by-side, molecule-to-molecule comparison to the brand product to demonstrate comparability.

Data and information for the CMC section are available from many sources. Industry quality trends are usually known for impurity levels- levels that are known to be generally safe. In some cases, compendial monographs are available to provide for essential quality requirement threshold information. Biopharmaceutical generic product

manufacturers perform the same development programs as the brand biotechnology product. It takes many years of development and batches of product to develop a biopharmaceutical generic product that is safe, pure, potent, and of high quality. As a result, the biopharmaceutical generic manufacturer assembles a massive data set on their product as well as an understanding both of the product and the impact of the manufacturing process on the product.

The power of current analytical methodology, combined with modern concepts of quality management, reinforced by in-process controls and validation, allow for a high confidence level that a biopharmaceutical generic is comparable to the brand.

Regardless if a biotech product is a brand product or a biopharmaceutical generic, certain features of the manufacturing process need to be maintained in order to insure the identity, potency, purity, quality and safety of the final product. These features include robustness and reproducibility, validation, controls, and testing. There is a strong relationship between analytical characterization and these features of the manufacturing process. Bringing these capabilities together give confidence that the final product produced by a biopharmaceutical generic manufacturer is comparable to the brand product. (see above)

Animal studies and clinical development programs should be based on the ability to characterize the drug substance and drug product and comparability to the brand product.

Analytical characterization has the ability to demonstrate that the biopharmaceutical generic has comparable chemical, physical and biological characteristics as the brand product. Since safety and efficacy are defined by these attributes it is anticipated that the biopharmaceutical generic will have a comparable safety and efficacy profile to the brand product.

3. Immunogenicity

- a. **How, and to what extent, should immunogenicity be evaluated for a follow-on protein product?**

A risk assessment for immunogenicity should be performed based on known risk factors, such as the presence of protein aggregates and immunogenic profile of the brand product in the selected indication.

Immunogenicity is only a concern when there are clinical consequences that may result from the presence of antibodies. The presence of antibodies is not always harmful. Many biotechnology-derived products generate antibodies with no clinical consequence. For example, some patients develop antibodies to interferon-alpha or HGH with no impact on the clinical safety and efficacy of the products. Fabry disease represents a small patient population that has been studied extensively over a period of several years during treatment with Fabrazyme®. While 89% of the patients have antibodies, these antibodies

did not effect the safety and efficacy of the protein. After continued treatment the antibodies to Fabrazyme disappeared in most patients, possibly through a tolerance mechanism. A similar situation was observed in Gaucher's disease where patients were treated with Cerezyme®. Approximately half of patients developed antibodies to Cerezyme, which peaked at six months, but with continued treatment substantially decreased by 12-24 months. The antibodies to Cerezyme also had no effect on the safety and efficacy of the product.

The presence of antibodies should not be minimized as there are cases where antibodies with clinical consequences have been a concern. For example, antibodies that affect the pharmacokinetics of the protein, antibodies that diminish therapeutic efficacy, and perhaps the most serious example, are antibodies that crossreact with endogenous protein. In these specific cases immunogenicity is a valid concern. However, the generation of antibodies to a protein should not always be an issue. Antibodies with clinical consequences are rare. Many antibodies to therapeutic proteins are transient and most patients with antibodies to the protein continue on therapy with no clinical consequence. In fact, in a review article published in 2001, immune responses to all approved biotechnology-derived hormones, enzymes, cytokines, antibodies, growth factors, and interferons were evaluated. The author concluded that "the presence of antibodies has not been detrimental to clinical efficacy" and "early fears of anaphylactic responses... have not been borne out".⁹

Although anaphylactic-like reactions have been observed after administration of some biotechnology-derived products, it is not known whether these were true anaphylactic reactions to the protein. These incidences are rare and there is no analytical, preclinical or clinical predictor of hypersensitivity reactions. It is important to recognize that hypersensitivity reactions are not unique to biotechnology-derived products and there are a number of drugs that cause hypersensitivity reactions, such as those used in radiological imaging and antibiotics. Drug products which are known to induce hypersensitivity reactions in some patients have been approved with no requirement for immunogenicity testing.

Manufacturers of biotechnology-derived products, including biopharmaceutical generic manufacturers, should take a risk management approach in which resources are focused on assessing product factors with the greatest risk of inducing an immune response. Based on more than 20 years of clinical use of hundreds of therapeutic proteins, aggregation is the main product factor associated with immunogenicity.^{10,11} For example, aggregates of interferon alfa-2a and human serum albumin were shown to be the cause of immunogenicity. When the aggregation problem was resolved the immunogenicity of

⁹ Porter S, 2001. Human Immune Response to Recombinant Human Proteins. *Journal of Pharmaceutical Sciences* 90:1-11

¹⁰ Hermeling S, Crommelin DJ, Schellekens H, Jiskoot W. Structure-immunogenicity relationships of therapeutic proteins. *Pharm Res.* 2004 Jun;21(6):897-903.

¹¹ Cleland JL, Powell MF, Shire SJ. The development of stable protein formulations: a close look at protein aggregation, deamidation, and oxidation. *Crit Rev Ther Drug Carrier Syst.* 1993;10(4):307-77.

IFN alfa-2a was decreased.¹² While there may be other factors with a possible association with immunogenicity, such as novel epitopes, impurities other than aggregation, glycosylation changes, oxidation, etc., these actually pose a very minimal risk. In fact, many of the factors often cited as a possible cause of immunogenicity are merely theoretical risk factors and have never been demonstrated to be actually associated with an immune response.

Since aggregates are the primary product factor associated with immunogenicity, analytical testing of all biotechnology-derived products, including biopharmaceutical generics, for aggregation could minimize the potential for immunogenicity. Today there is improved methodology available to measure aggregates such as light scattering, size exclusion chromatography, etc. Often techniques to adequately measure aggregation did not exist at the time that the brand product was approved. Aggregates should be measured as an aspect of drug product characterization, on stability, and after reconstitution of a lyophilized product. Immunogenicity of biotechnology-derived products could be minimized if aggregation is monitored systematically.

For all biotechnology-derived products, a complete understanding of immunogenicity and its possible consequences is not usually possible until after approval. This is due to the greater patient exposure numbers needed to detect rare events. The limitations of small clinical comparator studies to detect true differences in immunologic profiles between two products need to be recognized. If extensive analytical testing demonstrates comparability between the biopharmaceutical generic and the brand, the chance for increased immunogenicity is minimized. Clinical trials done solely to evaluate differences in immunogenicity are of limited utility. This is distinct from the evaluation of antibodies to biotechnology-derived proteins as part of clinical development. A clinical trial must be designed to answer a sound scientific question. The answer to addressing immunogenicity lies in a robust post-marketing surveillance program. Eprex® provides a good example. Reports of epoetin-associated pure red-cell aplasia (PRCA) were received by FDA for Eprex, Epogen®, and Neorecormon®. 92% of these reports were in patients receiving Eprex.¹³ Eprex has been associated with PRCA at an incidence of 1 in 10,000 patients. Clinical trials could not have detected the immunogenicity that developed due to formulation and container/closure changes (in addition to other potential causes identified by the company, such as storage conditions in the distribution chain). However, extensive analytical testing did detect product differences so that the problem could be resolved. Analytical testing, beyond routine product release testing, is generally warranted. Analytical assays for all biotechnology-derived products need to be updated periodically to be assured that any product differences can be detected.

Immunogenicity should be a concern only when there are clinical consequences. All immunogenic responses are not harmful. A risk-based approach taking into consideration product factors that are most associated with immunogenicity, such as protein aggregates,

¹²Hochuli E. Interferon immunogenicity: technical evaluation of interferon-alpha 2a. J Interferon Cytokine Res. 1997 Jul;17 Suppl 1:S15-21

¹³ Bennet, CL, *et al.* Pure Red-Cell Aplasia and Epoetin Therapy. N Engl J Med. 2004 Sep; 351(14):1403-1408.

should be pursued for all biotechnology-derived products, including biopharmaceutical generics. If extensive analytical testing demonstrates comparability between the biopharmaceutical generic and the brand, the chance for increased immunogenicity is minimized. Clinical trials have limitations in detecting immunogenicity differences between a brand product and the biopharmaceutical generic. Immunogenicity concerns should not be a hurdle in the development of biopharmaceutical generics as an evaluation of the immunogenic profile of any biotechnology-derived product is included in the drug development process.

4. Preclinical and Clinical

- a. **When and how would it be appropriate to streamline or eliminate certain animal or human studies during development of a follow-on protein product?**

The need and extent of animal and human studies should be based on the ability to characterize the drug substance and product and comparability to the brand product with the concept that the more one knows about the protein characterization and the greater the comparability to the brand product, the less the need for animal and human studies.

A biopharmaceutical generic that is demonstrated to be comparable to a brand product through analytical testing and for which an indication is being sought where there is extensive experience with the brand product may require none or less extensive toxicity testing than the brand product. This philosophy is prescribed in the International Conference on Harmonization for safety pharmacology of biotechnology-derived pharmaceuticals.¹⁴

Toxicity is an intrinsic property of any biotechnology-derived product, including a biopharmaceutical generic. With most biotechnology products, any toxicities observed are a reflection of the exaggerated pharmacological action of the product. The primary goals of preclinical safety animal studies are the determination of an initial safe dose and of the subsequent dose escalation schemes in humans. The role of toxicology studies in animals during drug development is to identify interactions with potential target organs and communicate these risks to the clinician before initiating human trials. Acute and short term repetitive studies are done before first dosing in humans, whereas repetitive dosing studies for extended periods should be performed before exposing larger populations or exposing special populations such as women of child bearing age, infants, the elderly or impaired patients.

The identification of potential target organs of biotechnology-derived products serves both to assess the risk, as well as to assist clinicians in their design of monitoring strategies during the human trial. For example, the clinician may choose to include nonroutine markers of inflammation when there is an indication for pro-inflammatory effects or additional markers for liver toxicity when findings in the animal toxicology studies raise such concerns. The toxicology study also assesses the severity of the

¹⁴ ICH Topic S6, Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, Step 4, consensus guideline, 16 July 1997

findings, their mode of action and reversibility. These are important toxicological endpoints that should be properly communicated.

Once safety data in humans becomes available, it supersedes the preclinical safety data in animals, not only because it measures the actual target population, but also since the clinical trials are larger. The small number of animals used in toxicology studies also limits the power of these studies to detect subtle differences between related products.

Therefore, once the safety and efficacy profile is established for a biotechnology-derived product, there is no scientific need to repeat the pre-clinical evaluation for a biopharmaceutical generic unless analytical comparability is questionable.

If analytical comparability is questionable, the extent of the pre-clinical program should then be determined on a case-by-case basis taking into consideration general safety concerns. In either situation, if a biopharmaceutical generic is demonstrated to be comparable to the brand product or if comparability is questioned, all safety considerations outlined under ICH S6 must be addressed in the application. The rationale for preclinical safety testing strategy should be justified.

When designing pre-clinical studies in animals the current sentiments against experimentation in animals should also be considered. One of the principles for reduction of animal experimentation is to avoid studies that duplicate previous work. Repeating preclinical animal studies for biopharmaceutical generic products violates this principle, unless there is a concrete scientific or safety issue that needs to be addressed.

In some cases, it will not be necessary for a biopharmaceutical generic to duplicate all human safety and efficacy studies conducted by the brand product. The extent of human trials is dependent on the ability to characterize the product and comparability of the biopharmaceutical generic and the brand product. In addition, extensive clinical experience of the brand product in the therapeutic area will provide additional justification for the design and extent of human trials. Studies should not be conducted to demonstrate what has already been demonstrated.

Clinical trials are less likely to detect subtle differences than state-of-the-art analytical methodologies available today. In order to clinically detect subtle differences between the biopharmaceutical generic and the brand product, human studies must be powered for the expected differences, thus requiring unreasonably high patient numbers. These patient numbers are frequently higher than that required to demonstrate safety and efficacy of the brand product.

For a biopharmaceutical generic that is demonstrated to be comparable to the brand product, a phase I study to establish comparable PK and/or PD may be the only human trial necessary for approval. The study should be of a crossover design using the same dose as well same route of administration.

The following biotechnology-derived products are examples in which such a human trial is possible:

- Insulin: PK is possible and PD (glucose level) is available.
- hGH: PK is possible, PD (IGF-1) is available.

- GCSF: PK is possible and PD (Absolute Neutrophil Counts – ANC) is available. ANC is also considered as a surrogate marker for febrile neutropenia (in addition to temperature elevation) and severity of neutropenia.

Once therapeutic equivalence has been demonstrated in a selected indication, therapeutic equivalence should also be extended to other indications. This justification is based on the fact that once it is shown that a biopharmaceutical generic is pharmacokinetically and pharmacodynamically comparable to the brand product, this study does not need to be replicated for all other indications as the study protocol design will be the same for each indication. Demonstration of therapeutic activity may be done by using clinical outcomes as endpoints or by using surrogate markers if validated either for the indication or for the brand product.

Safety must be closely monitored on an ongoing basis for all biotechnology-derived products. Immunogenicity should be a concern only when there are clinical consequences. All immunogenic responses are not harmful. A risk-based approach taking into consideration product factors that are most associated with immunogenicity, such as protein aggregates, should be pursued for all biotechnology-derived products, including biopharmaceutical generics. If extensive analytical testing demonstrates comparability between the biopharmaceutical generic and the brand, the chance for increased immunogenicity is minimized. Preapproval clinical trials have limitations in detecting immunogenicity differences between a brand product and the biopharmaceutical generic due to their small patient numbers. Rare adverse events should be monitored during the post-marketing phase when products are exposed to a larger patient population.

The approval of biopharmaceutical generics should be based on the totality of evidence gathered in the areas of quality, safety, and efficacy. A step-by-step approach should be taken where the extent of animal and human studies are based on the ability to characterize the drug substance and drug product and comparability to the brand product. Animal and human studies should not be conducted to prove what has already been proven. Immunogenicity should always be addressed for biopharmaceutical generics as it is addressed for all biotechnological brand products. A risk assessment for immunogenicity should be performed based on known risk factors, such as the presence of protein aggregates and immunogenic profile of the brand product in the selected indication.

5. Terminology

- a. **Please comment on the appropriateness of this notice's working definition of "follow-on protein" as a protein that is intended to be a similar version or copy of an already approved or licensed protein pharmaceutical product.**
- b. **Please comment on this notice's working definition of a "second-generation protein product" as a product similar to an already approved or licensed product but which has been deliberately modified to change one or more of the product's characteristics (e.g., to provide more favorable pharmacokinetic parameters or to decrease immunogenicity).**

The term "follow-on protein" is not an appropriate term. If "similar" is equal to "comparable" scientifically, then "similar" may be an appropriate term to use in the working definition. The term "copy" should be removed.

The term "follow-on protein" suggests that data and information on the scientific and technical development, other than preclinical and clinical, and manufacture of the brand product is shared with the biopharmaceutical generic manufacturer. The biopharmaceutical generic manufacturer then develops a product that "follows" the brand product. At this time, this is not the case. Biopharmaceutical generic product manufacturers do not have access to confidential information on the manufacture of the brand product. The manufacturing process for a biopharmaceutical generic is designed using publicly available information in the same manner as the brand biotechnology industry develops its products. As mentioned above, it takes many years of development and batches of product to develop a biopharmaceutical generic product that is safe, pure, potent, and of high quality. This results in the biopharmaceutical generic manufacturer having a massive data set on their product as well as an understanding both of the product and the impact of the manufacturing process on the product.

The manufacturing processes for SICOR Inc's marketed biopharmaceutical generics are different from the manufacturing processes for the comparable brand product. Yet, as demonstrated above, these different manufacturing processes yield biopharmaceutical generics that are comparable to the brand product. Analytical procedures measuring quality attributes of the manufacturing process evolve with product development and some of these methods will be developed specifically for the biopharmaceutical generic product.

The terminology used to describe this product area is crucial. The term must convey trust, quality, and therapeutic equivalence as the term "generic" now implies for chemical drug products. If the term "similar" is used in the definition of this product area, it should scientifically be the same as "comparable" as the philosophy and science behind comparability protocols will be followed in the determination of biopharmaceutical generic "similarity" to the brand product. The term "copy" should be removed from the definition. Under comparability guidelines, the term "copy" does not appear – a product is deemed "comparable" to another product. The product post-manufacturing changes is not required to be a "copy" of the product pre-manufacturing changes.

As a side-by-side, molecule-molecule analytical comparison will be conducted between the biopharmaceutical generic and the brand product to demonstrate comparability, the term and definition for "second generation protein product" is not necessary.

Conclusion

Specific aspects and parts of the manufacturing process do not determine the characteristics of a protein product. The biopharmaceutical generic is developed to be comparable to the biotechnology-derived brand product. The power of current analytical methodology, combined with modern concepts of quality management, reinforced by in-

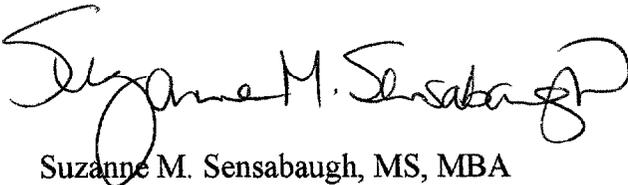
process controls and validation, allow for a high confidence level that a biopharmaceutical generic is comparable to the brand.

Analytical methods are available today to adequately characterize certain protein products. A step-by-step approach should be taken where animal studies and clinical development programs are based on the ability to characterize the drug substance and drug product and comparability to the brand product. Analytical characterization can demonstrate that the biopharmaceutical generic has the same chemical, physical and biological characteristics as the brand product. Since safety and efficacy are defined by these attributes then it is anticipated that the biopharmaceutical generic will have a comparable safety and efficacy profile to the brand product.

Immunogenicity should always be addressed for biopharmaceutical generics as it is addressed for all biotechnological brand products. The presence of antibodies does not necessarily correlate with clinical outcomes and lessen the therapeutic viability of a recombinant protein drug. A risk assessment for immunogenicity should be performed based on known risk factors, such as the presence of protein aggregates and immunogenic profile of the brand product in the selected indication.

SICOR Inc. recognizes the complexity of issues surrounding the development and approval of biopharmaceutical generics. The company appreciates the opportunity to comment on these issues and looks forward to working with FDA in the development of guidance for industry.

Sincerely,

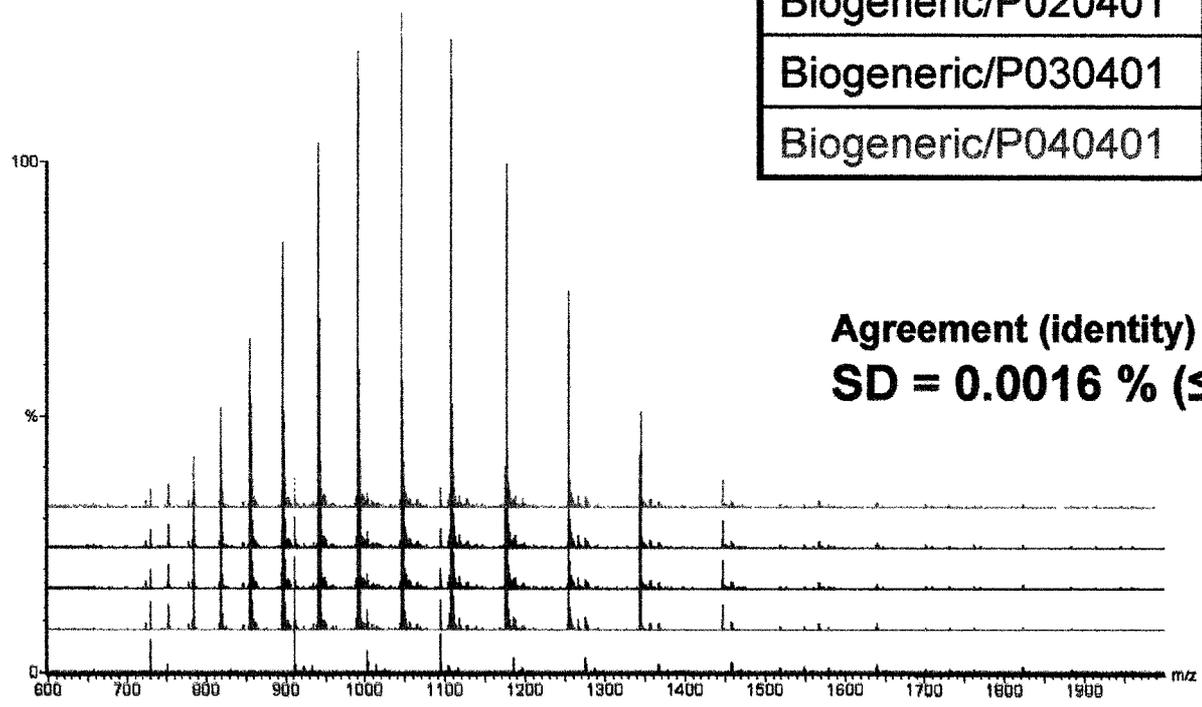


Suzanne M. Sensabaugh, MS, MBA

VP, Regulatory Affairs, SICOR Inc., Biotechnology Division

ESI-Mass Spectrometry

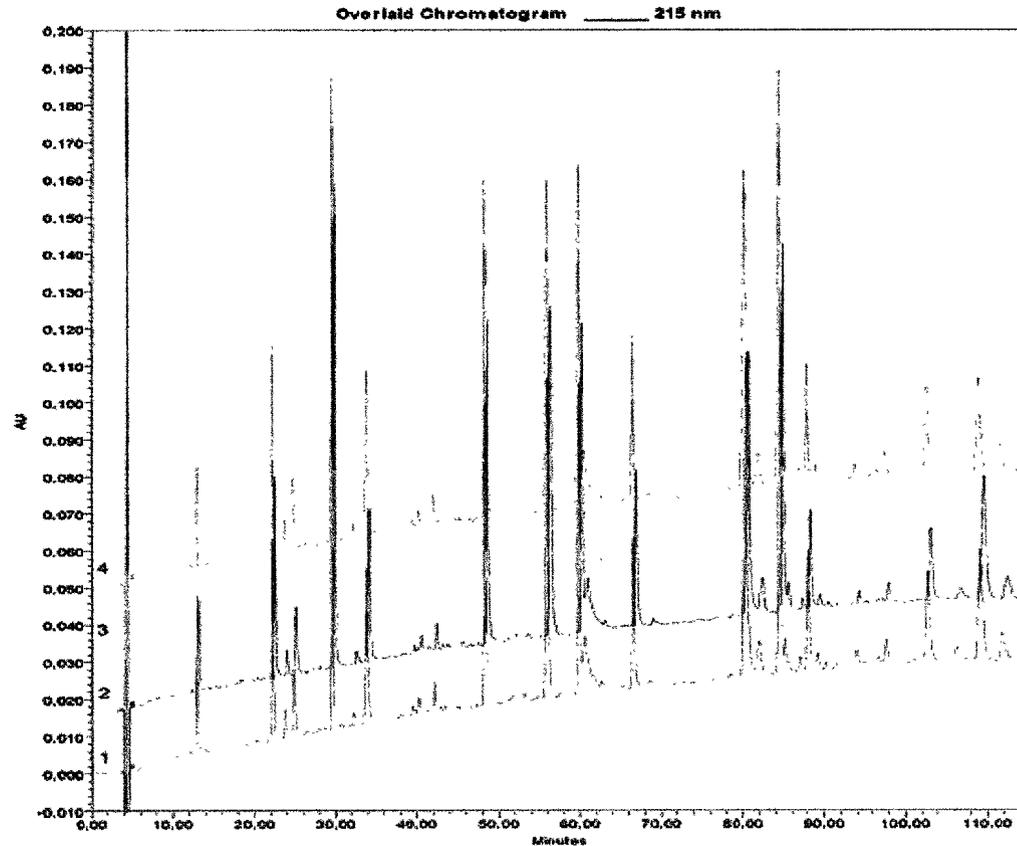
Product/batch	Mr, Da	SD
Theoretical	18,797.89	
Brand/B1033	18,798.18	0.082
Biogeneric/P020401	18,798.27	0.035
Biogeneric/P030401	18,798.11	0.081
Biogeneric/P040401	18,798.31	0.182



Agreement (identity) = 99.9987 %
SD = 0.0016 % (≤ 0.5 Da)

Figure 1

Peptide maps



Bottom red profile - brand sample (Lot B 1025)
Three top profiles – biogeneric r-metHuG-CSF, different batches of production

Figure 2

N-terminal amino acid sequencing of different batches of r-metHuG-CSF

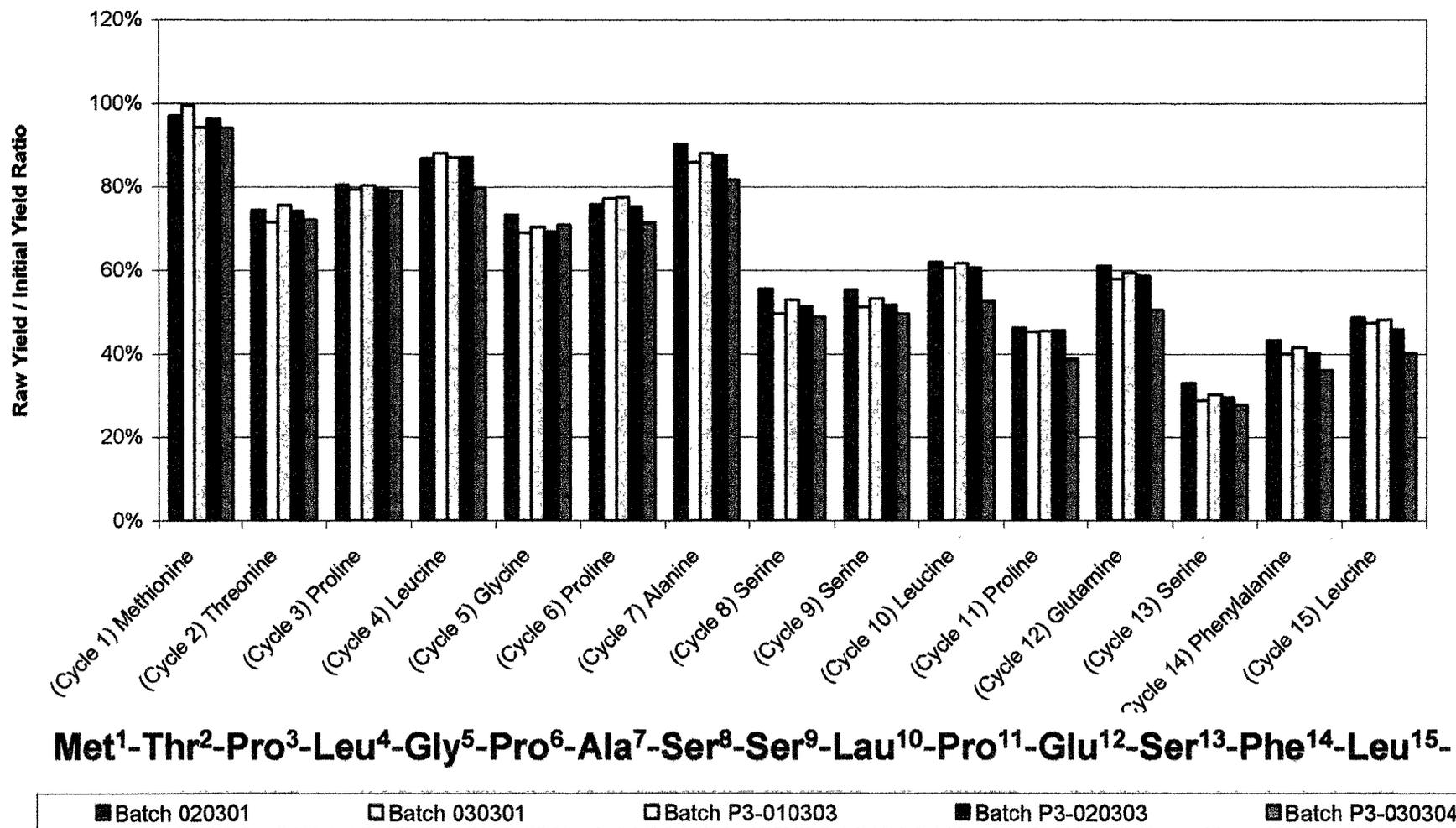


Figure 3

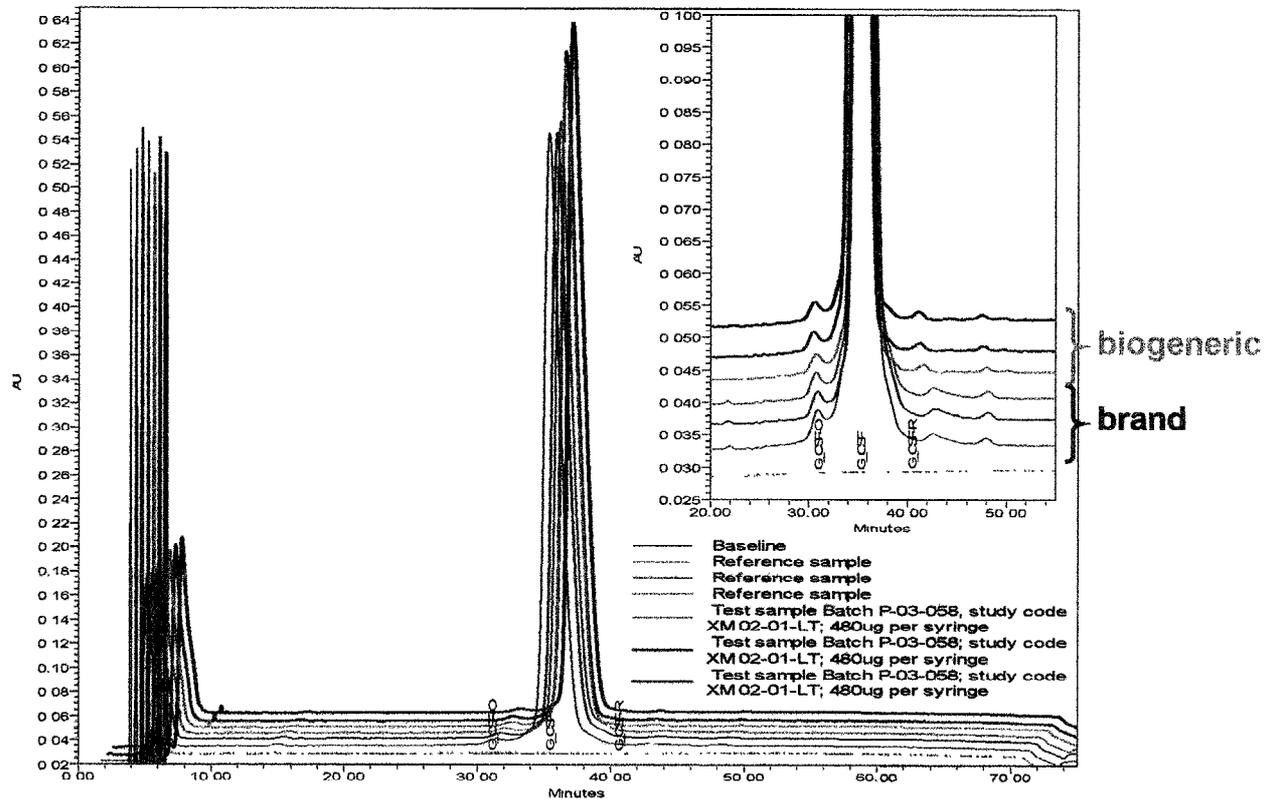
RP-HPLC Comparison of G-CSF

SICOR BIOTECH UAB

SAMPLE ANALYSIS REPORT

Reported by User: linag

Project Name: G-CSF



Report Method: Summary Report Overlay_3

Printed 10:39:09 AM 11/20/03

Figure 4

SE-HPLC Comparison of G-CSF

sicor
BIOTECH UAE

SUMMARY REPORT

Reported by User: Lina Gelunate (Lina)

Project Name: G-CSF_Gelfiltrator

FILGRASTIM bulk solution and final formulation

DETERMINATION of PURITY and presence of AGGREGATED FORMS of G-CSF by SE-HPLC

Method description

Sample Set Name G-CSF_XM_02_syri_test2003_11_

Injection Volume: 20.00 ul

Sample Type: Unknown

Column_name

Column_temp 22°C

Mobile_phase 35mM Na phosphate, pH7.0 / 4.5%

Propanol-2

Acq Method Set G-CSF_SEC_08_flow_4_5%_2_prop

Date Acquired 11/17/2003 8:12:00 - 11/18/2003 12:22:56

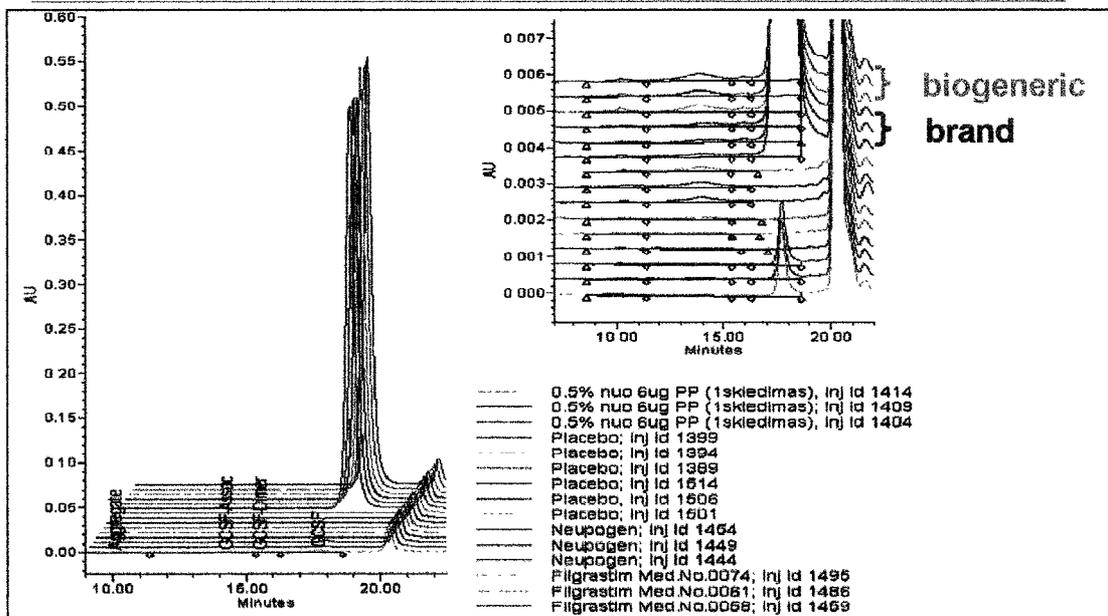
ColumnID 3SWX08EE6106VZ

PrecolumnID 3WXdE1439

Run Time: 50.0 Minutes

Flow_rate 0.6ml/min

Overlaid Chromatograms



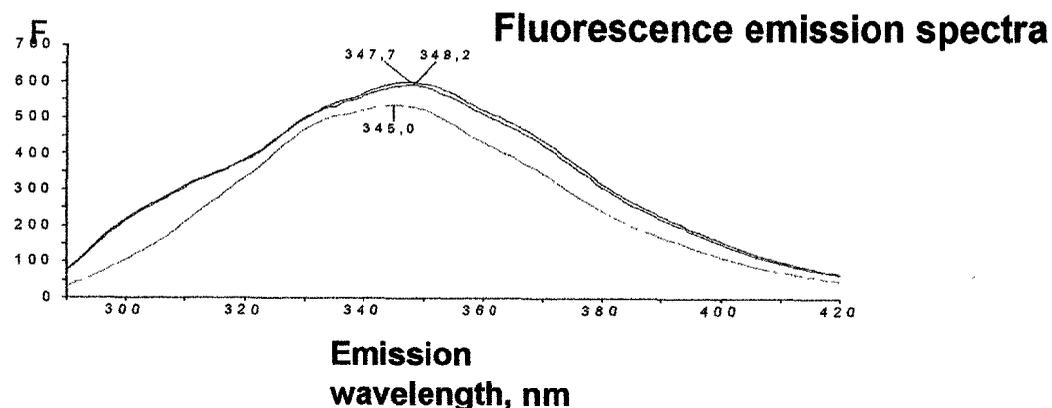
Report Method: G-CSF_SEC_LQ_Corr_Over_Prot_1

Printed 5:11:31 PM 11/19/2003

Figure 5

2nd-order fluorescence emission spectroscopy to elucidate conformation of G-CSF

Direct and 2nd-order fluorescence emission spectra of the two molecules are indistinguishable - to suggest that Trp and Tyr residues exist in identical solvent exposure environments. This further suggests indistinguishable secondary and tertiary structures of the two molecules.



-----Brand	0.05 mg/ml, Batch B1030 MFD 02/2003
-----r-metHuG-CSF, biogeneric	0.05 mg/ml, Lot 039
-----r-metHuG-CSF, biogeneric	0.027 mg/ml, misfold intermediate

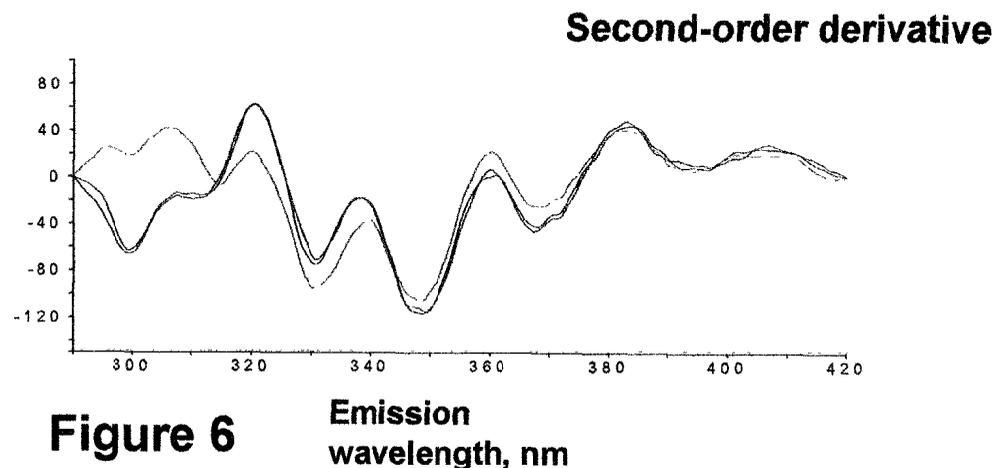


Figure 6

Emission wavelength, nm

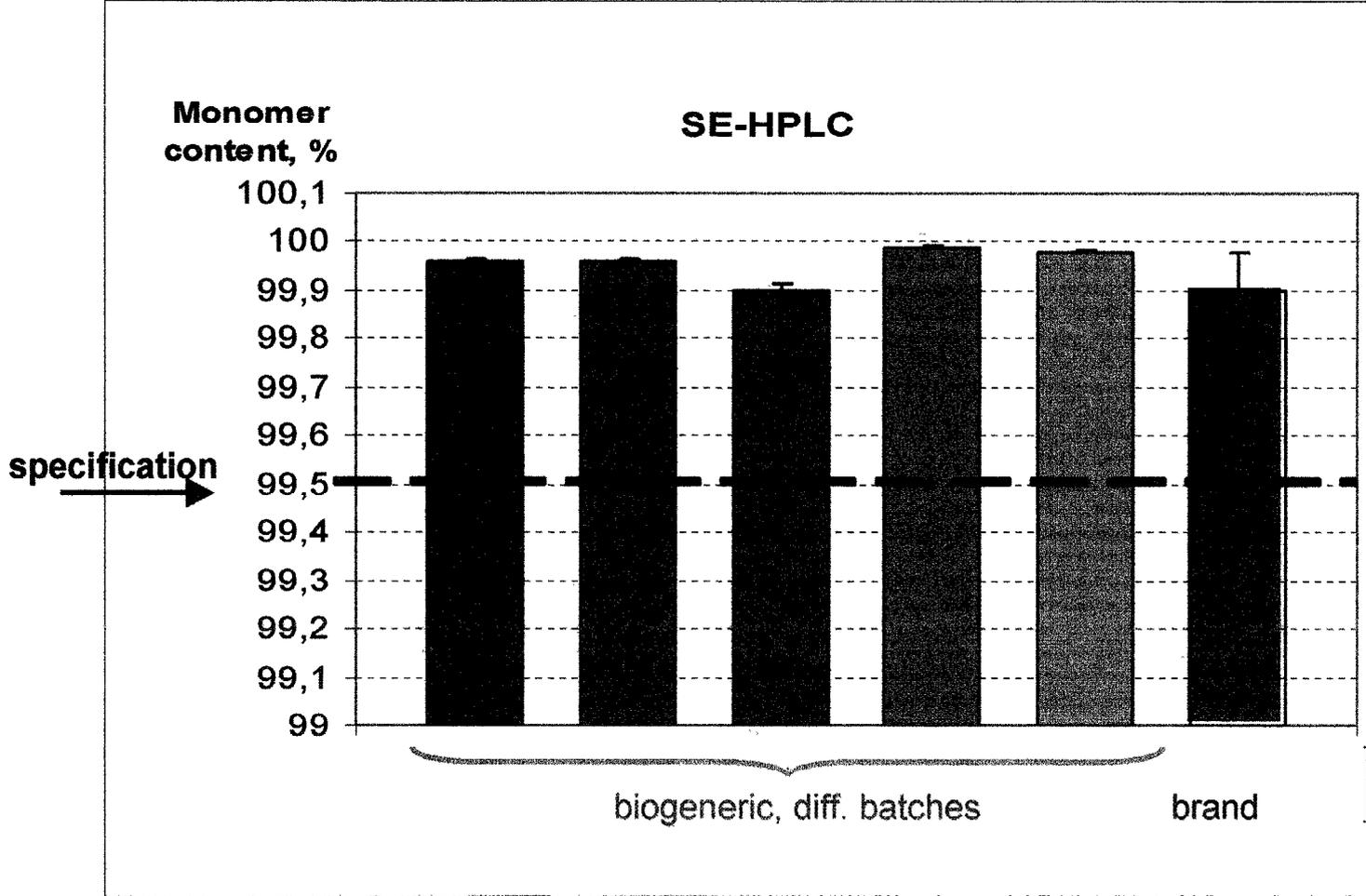


Figure 7

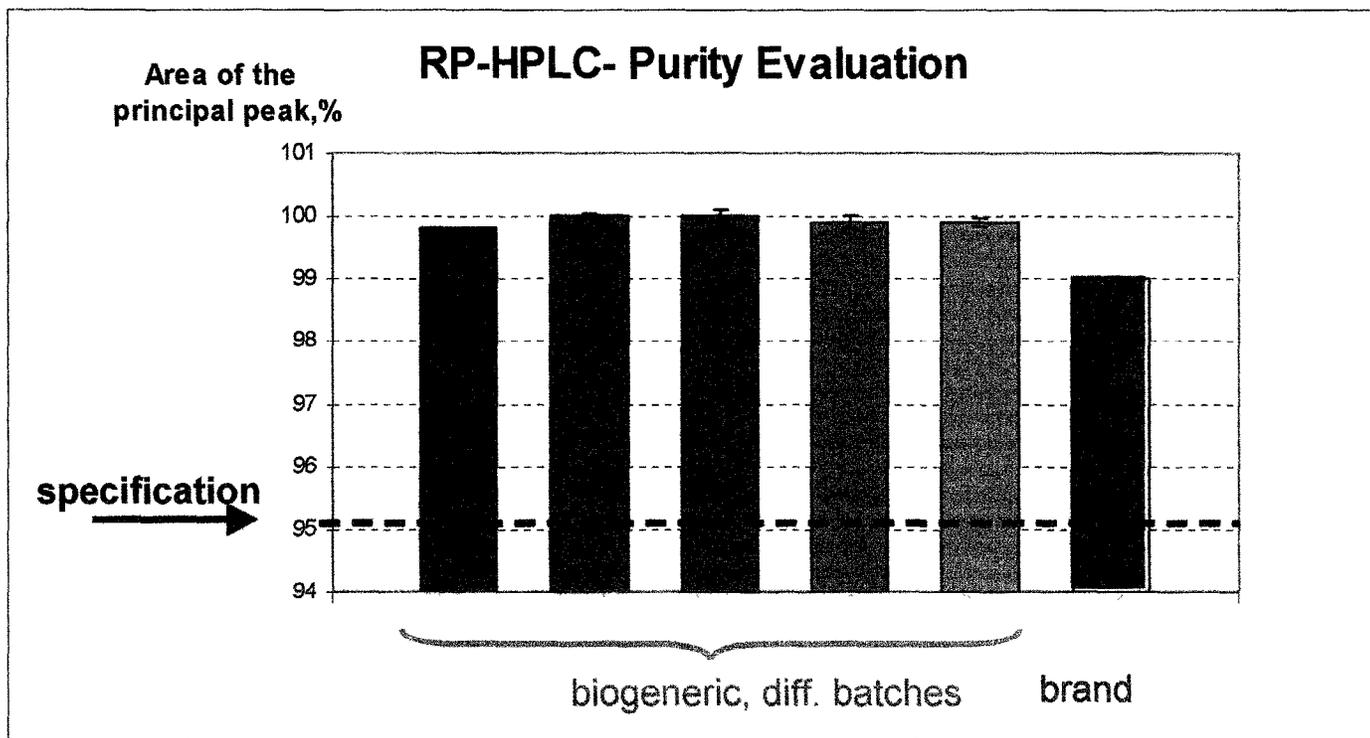


Figure 8

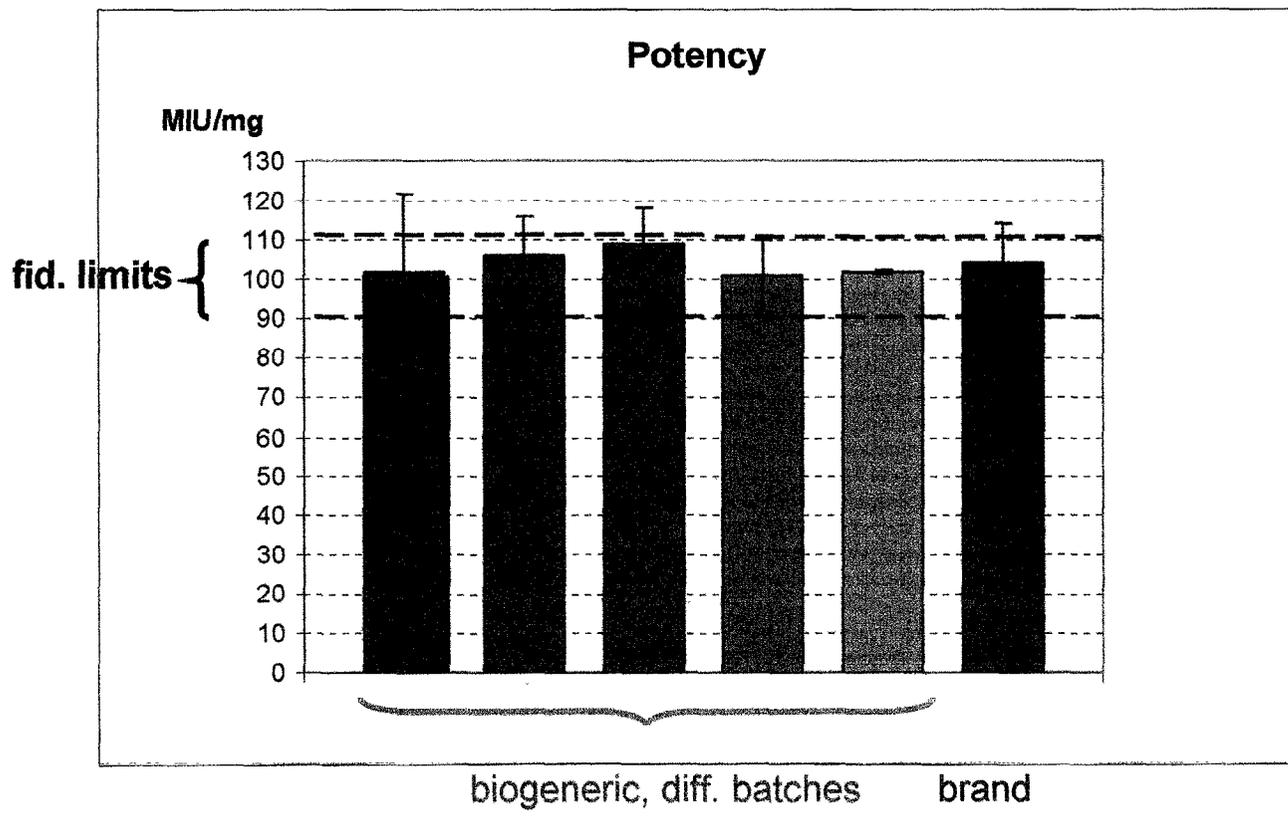
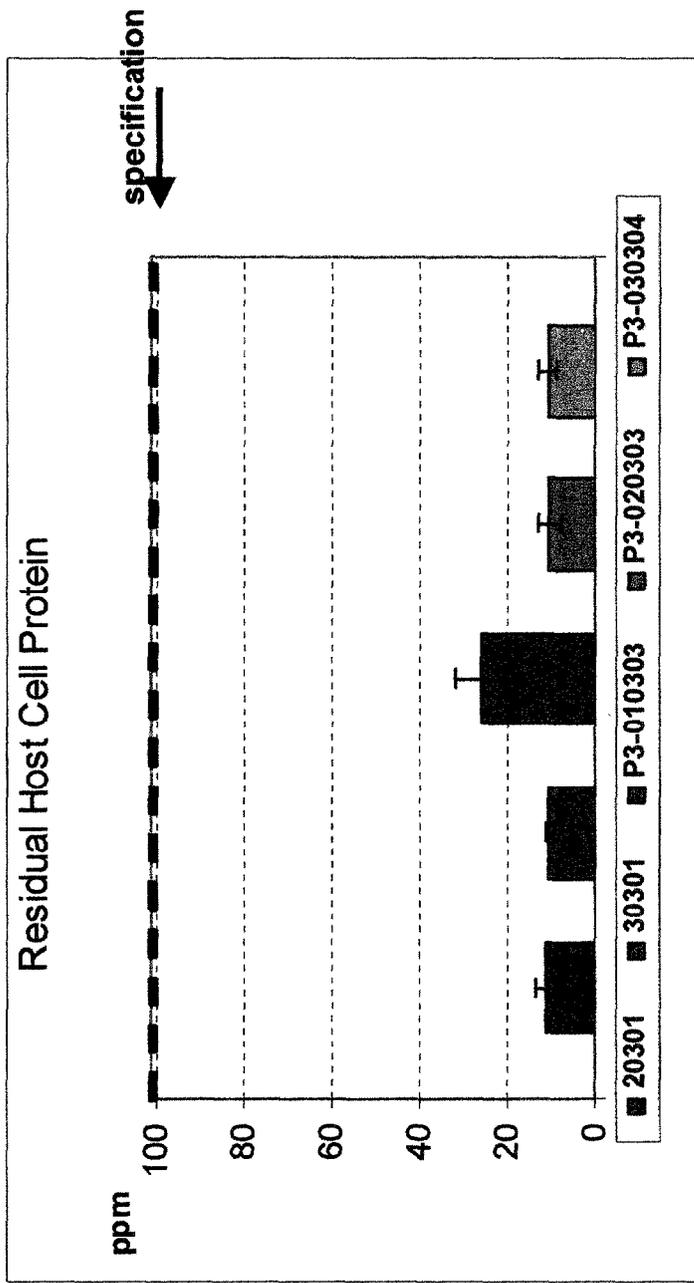


Figure 9



biogeneric, diff. batches

Figure 10

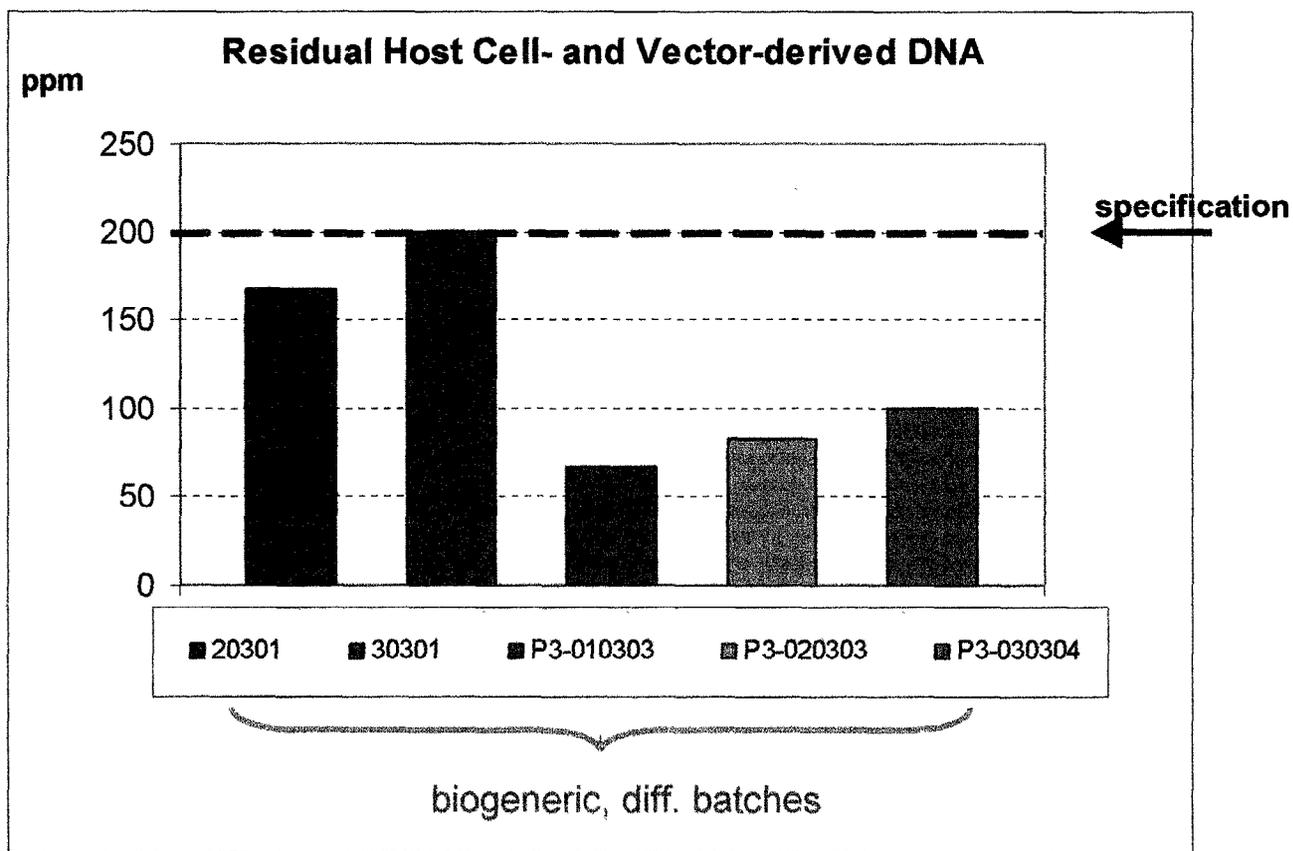
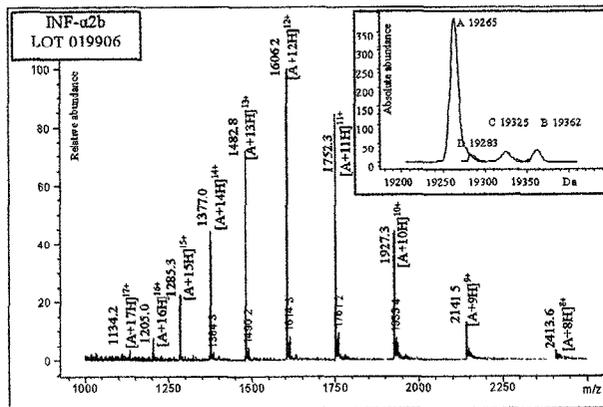


Figure 11

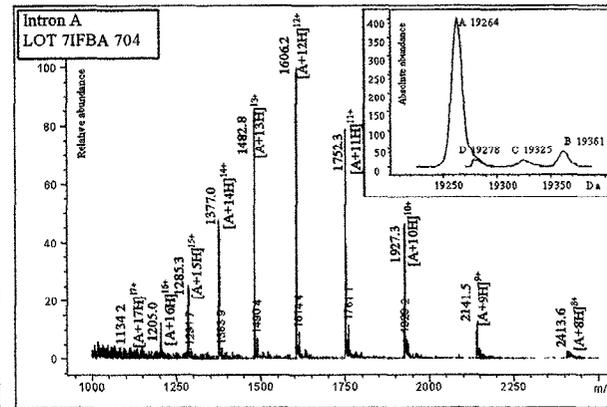
ESI-Mass Spectrometry

Biogeneric product



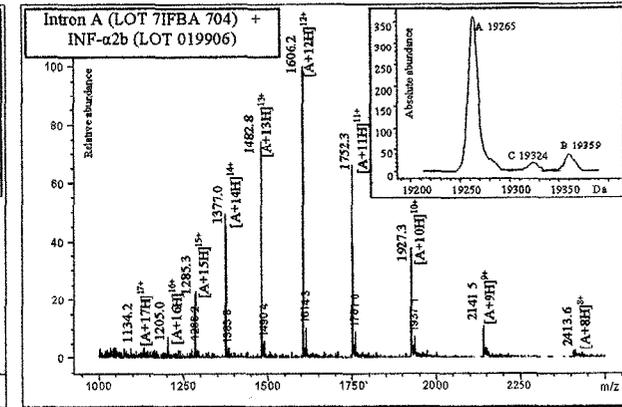
curve fitted mass, 19264.92.

Brand



curve fitted mass, 19264.46.

Biogeneric product : Brand,
1:1 mixture



curve fitted mass, 19264.79.

The molecular masses of the two molecules – the biogeneric product and that of brand – are indistinguishable

Figure 12

Biogeneric IFN- α 2b is indistinguishable from *Eur Ph* CRS by peptide mapping

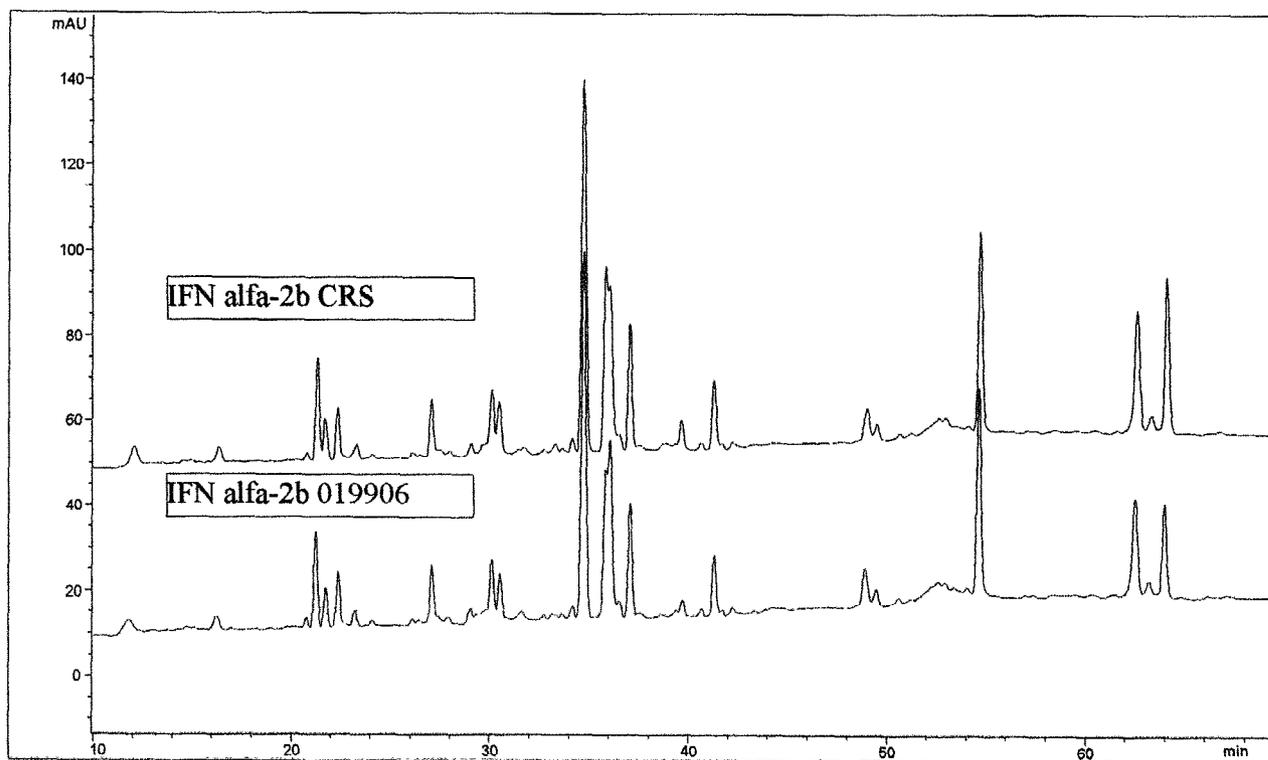
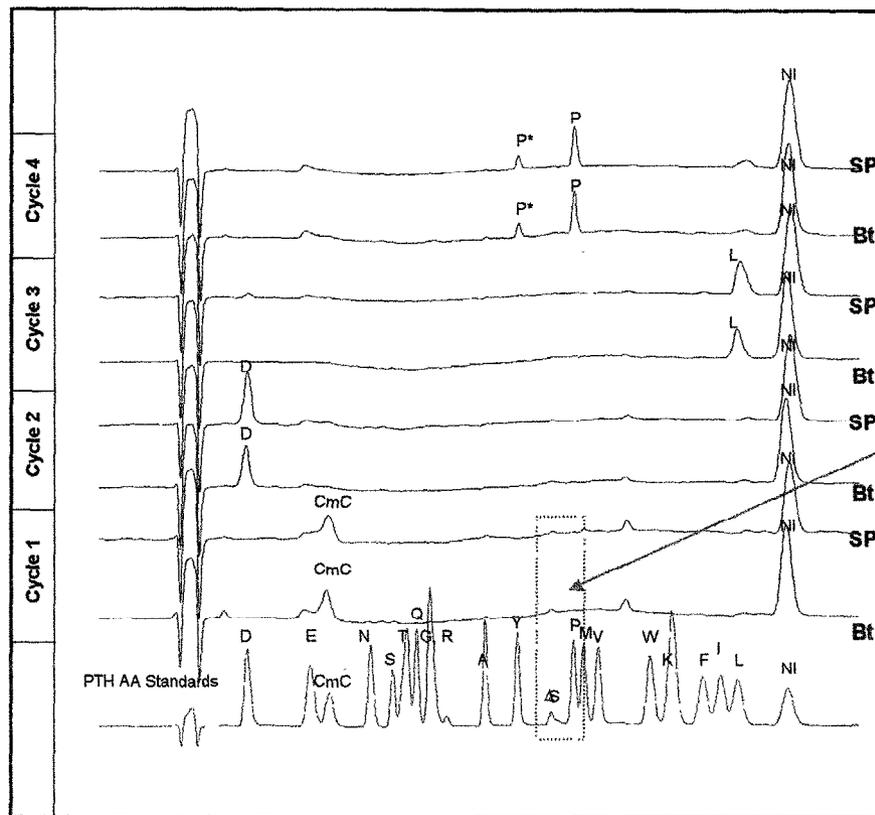


Figure 13

Comparative N-terminal amino acid sequencing data



1st cycle – biogeneric IFN- α 2b does not exhibit any traces of Met¹, while brand does.

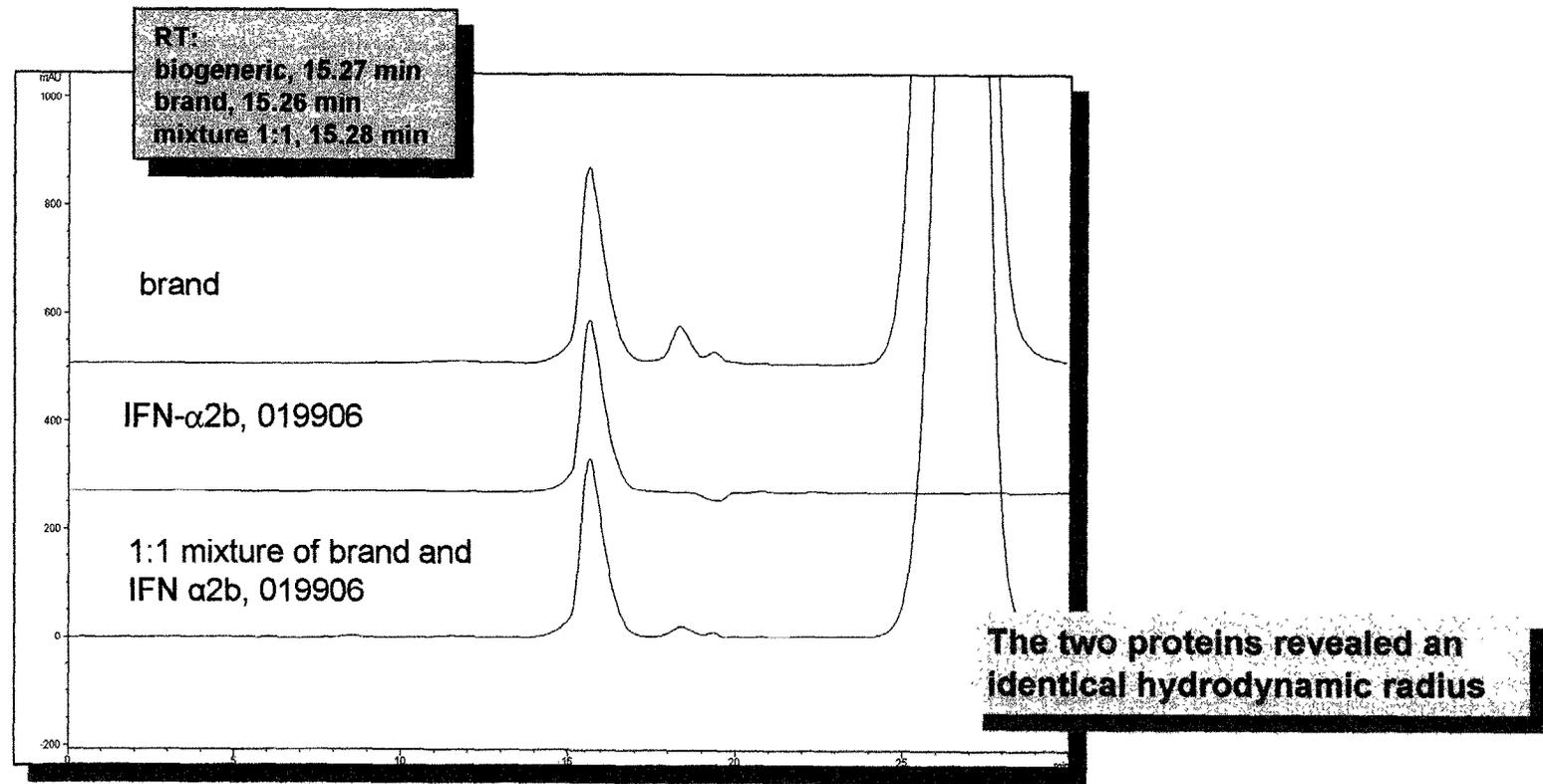
**Experimentally determined N-terminal amino acid sequence:
CmCys¹- Asp²- Leu³- Pro⁴- ...**

Bt – biogeneric lot 019906
SP- brand lot 9-I0K-111

NI, norleucin
CmC, carboxymethyl-Cys.

Figure 14

Comparative HPLC gel-filtration analysis of biogeneric IFN- α 2b and brand



Column: Bio-Sil TSK 250; 300x7.5 mm

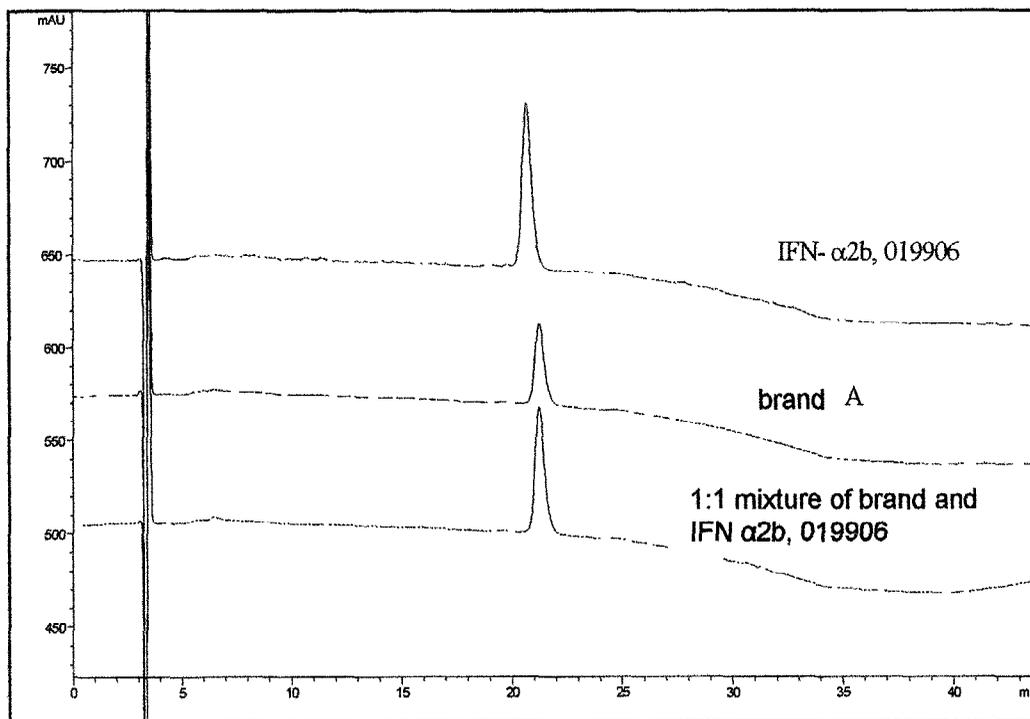
Samples of 100 μ l containing 0.102 mg/ml of indicated proteins were analyzed.

All the samples were analyzed without pretreatment, therefore the excipient peak is recorded at retention time of 25-28 min.

Brand sample was obtained from the finished product, batch No. 9-I0K-111, mntg. 09/14/99.

Figure 15

Comparative reverse phase HPLC analysis of biogeneric IFN- α 2b and brand



The two proteins revealed an indistinguishable RT (20.93 ± 0.27), to suggest similar hydrophobicity

RP-HPLC column RP-318, 250*4.6 mm, 300 Å, Bio-Rad

Samples of 30 μ l containing 0.1 mg/ml of indicated proteins were analyzed.

All the samples were purified onto reversed phase column, collected peak lyophilised and dissolved in mobile phase, before subjecting them to analysis.

Brand sample was obtained from the finished product, batch No. 9-10K-111, mnfg. 09/14/99.

Figure 16

Comparative fluorescence spectroscopic analysis of biogeneric IFN- α 2b and Ph Eur CRS IFN- α 2b

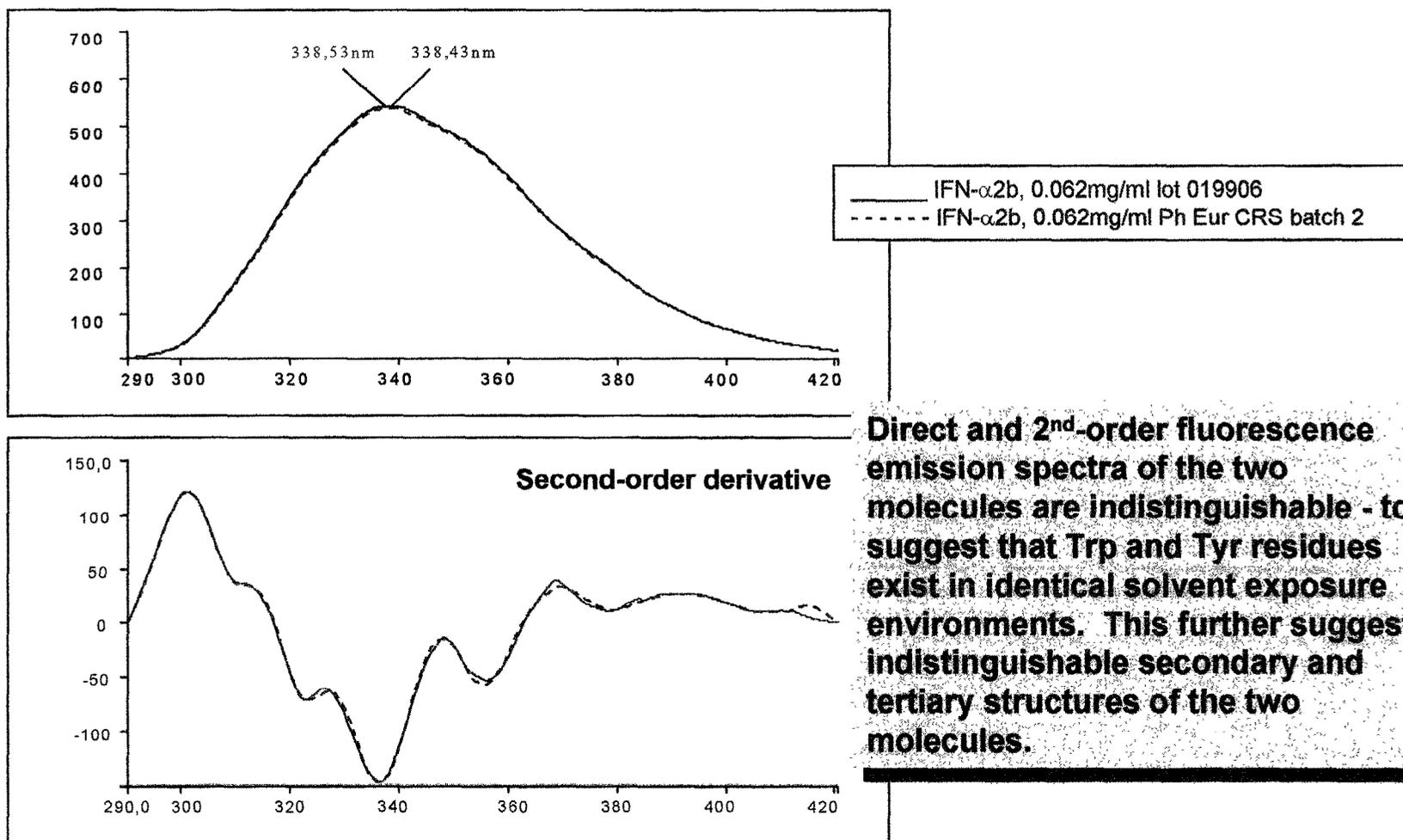
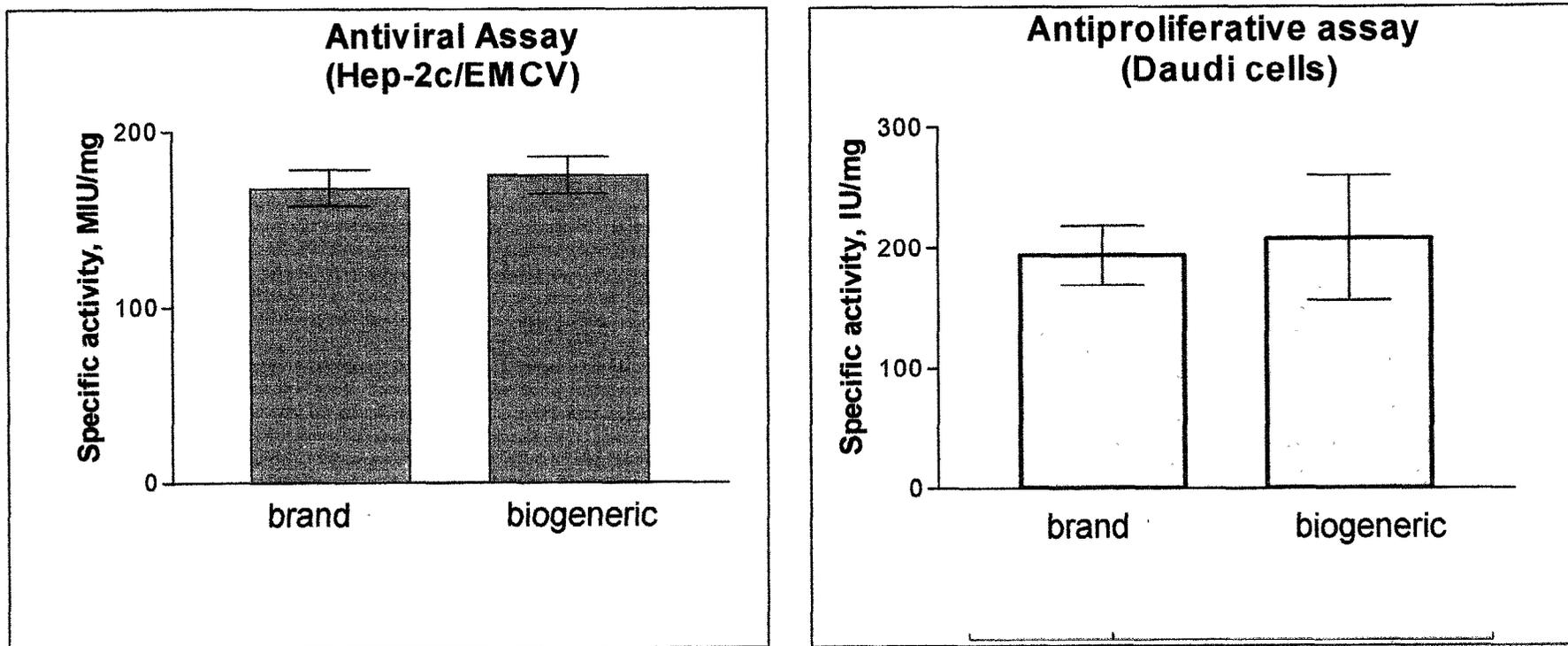


Figure 17

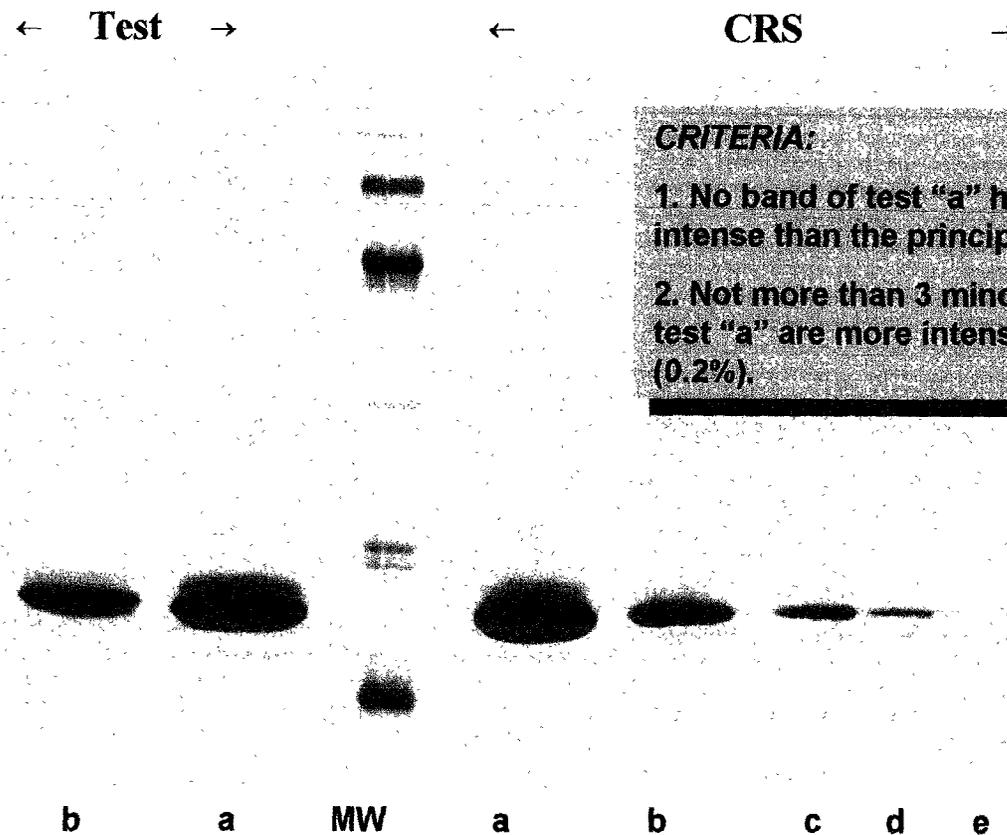
Specific bioactivity of the IFN- α 2b protein is indistinguishable in biogeneric product and brand



Protein measured by RP-HPLC

Figure 18

Impurities of molecular masses differing from that of IFN- α 2b by SDS-PAGE under non-reducing conditions, Eur Ph.



CRITERIA:

1. No band of test "a" higher than the principal band is more intense than the principal band in reference "d" (1%);
2. Not more than 3 minor bands higher than the principal band of test "a" are more intense than the principal band in reference "e" (0.2%).

RESULTS:
consistent with the criteria.

CONCLUSION: COMPLIES

Figure 19

Biogeneric IFN- α 2b is indistinguishable from *Eur Ph* CRS by IEF

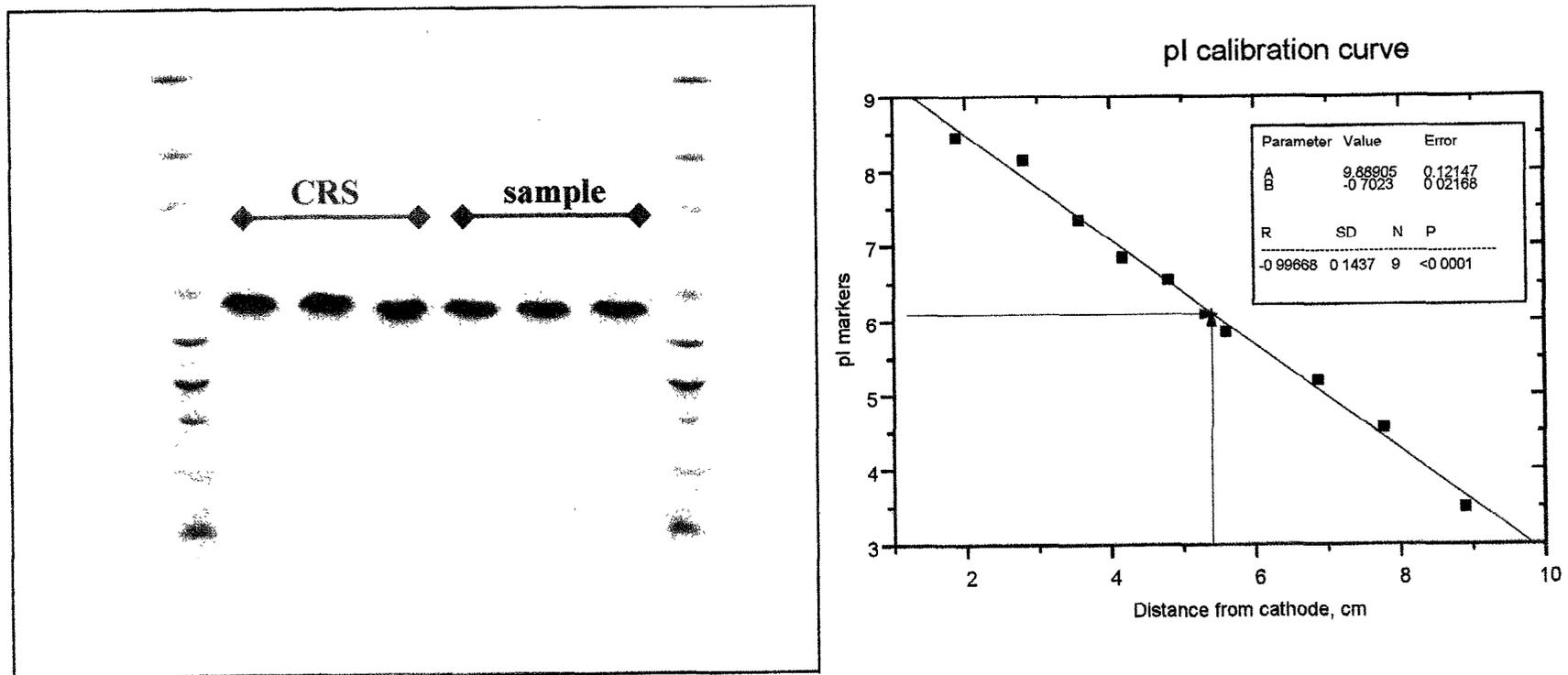


Figure 20

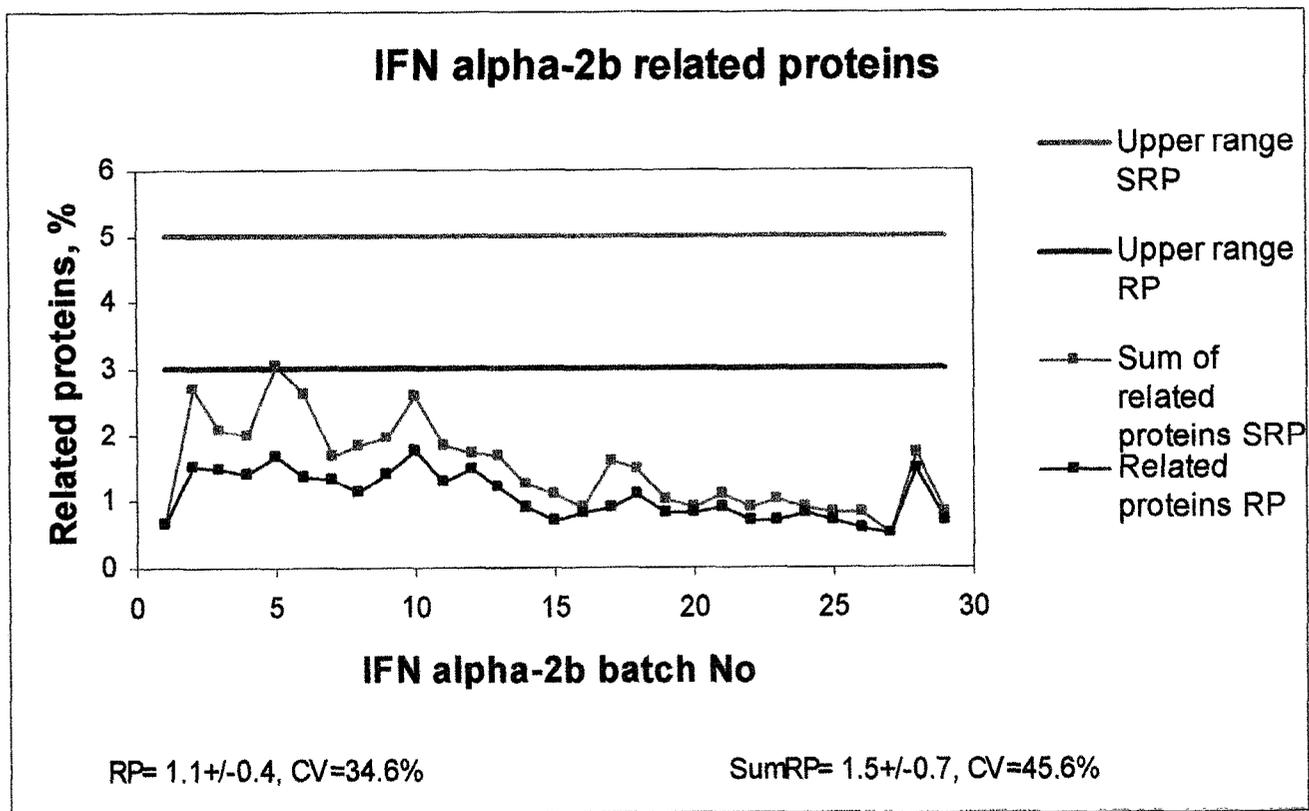


Figure 21

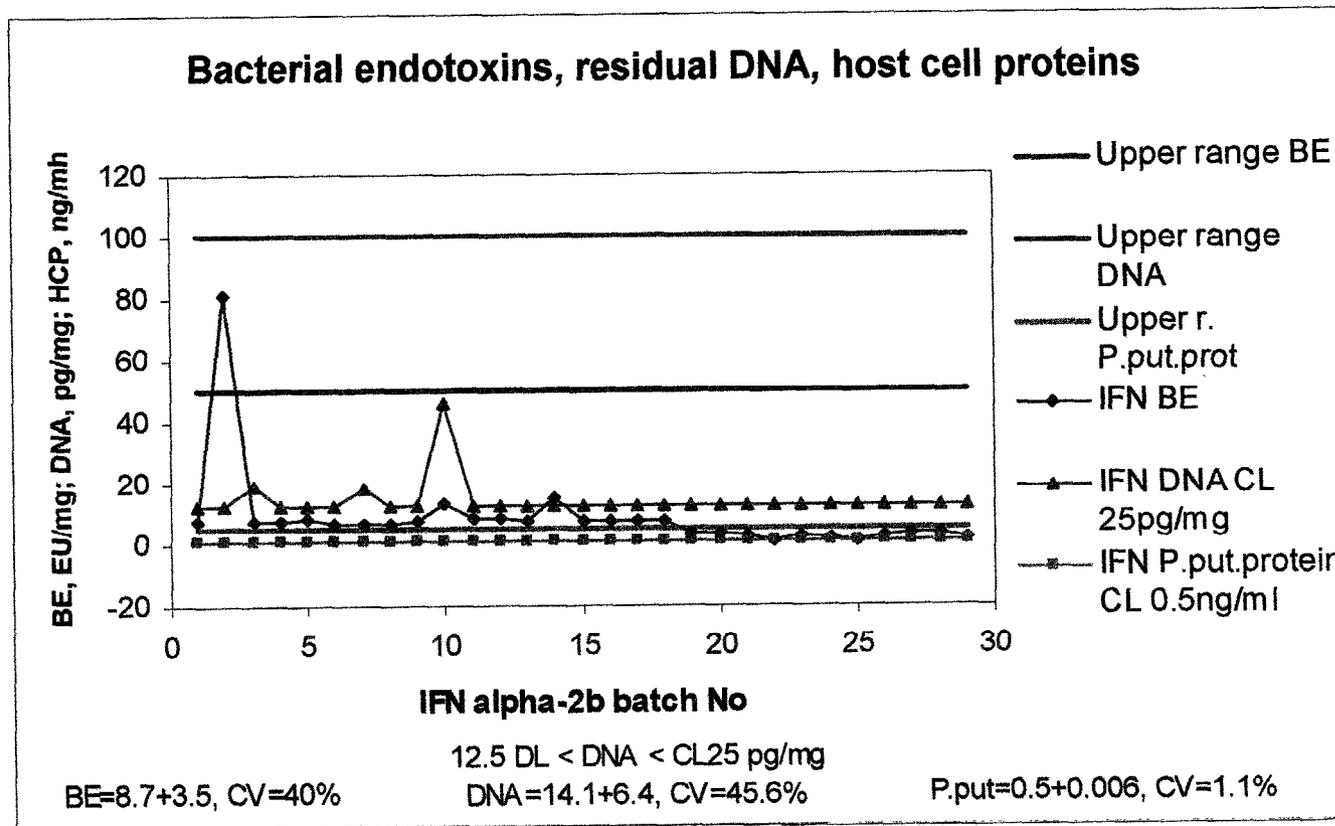


Figure 22