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Before the

Government Oversight and Reform Committee

Hearing On

“Safe and Affordable Biotech Drugs – The Need for a Generic Pathway”

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Chairman Waxman, Ranking Member Davis, and members of the Committee, thank you for inviting me to testify today. My name is Inger Mollerup and I am Vice President for Regulatory Affairs at Novo Nordisk A/S. Novo Nordisk is a healthcare company with an 80-year history of innovation and achievement in diabetes care. In addition to diabetes care, Novo Nordisk has a leading position within areas such as hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk's business is driven by the Triple Bottom Line: a commitment to economic success, environmental soundness, and social responsibility to employees and customers. Our global headquarters are in Denmark and our U.S. headquarters are in Princeton, New Jersey.

For approximately 30 years, I have been involved in the design of manufacturing processes and development programs for a number of recombinant proteins for Novo Nordisk. With this background, in December 2005, I presented before the European Medicines Agency (EMEA) as part of a panel on guidelines for biosimilar insulins (biosimilars is the term for follow-on biologics in Europe) and then

presented before the World Health Organization INN Committee in November 2006 on the topic of naming biosimilars. Novo Nordisk wants to work closely with Congress as it considers the best way to establish a legal and regulatory pathway for biosimilars, or follow-on biologics as they are called in the United States.

The creation of an entirely new approval pathway for a new class of drug products not presently on the market is an enormous undertaking with serious consequences for literally millions of patients. Novo Nordisk believes any pathway for follow-on biologics should be rooted in the best science, preserve innovation, respect proprietary information, and most importantly be constructed to protect patient safety. Based on my experience with all of the therapeutic proteins I have worked with over the years, it is clear that biological medicines are both individual and complicated. Any pathway must take into account the fact that biological medicines are distinctly different from chemical drugs or we will fail in our responsibility to ensure patient safety and product efficacy.

Characterization Doesn't Tell the Whole Story

Biological medicines are complicated – but we have a long track record showing that they can be developed and characterized, and all the same tools are available for the development of follow-on biologics. However, while some of the best known peptide molecules – like insulin – can be largely characterized with today's technology, we do not yet have the tools and models that enable us to predict safety and efficacy from that characterization without undertaking human clinical trials.

Any pathway should fully address the patient safety considerations of medicines that are "similar to" or "comparable to" instead of "same as" the reference product. Given that proposals currently before Congress go far beyond the science in an effort to deem products having "minor differences in amino acid sequence" as "highly similar," I would like to share with you an experience we had at Novo Nordisk with two potential therapeutic proteins with just one amino acid difference.

Case Study: Minor Differences Can Have Major Health Consequences

Our goal was to create a fast acting insulin analogue that would enable patients with diabetes to use the medicine in close connection with a meal to control mealtime rise in blood glucose (and thus ease the

problem of too much or too little insulin at mealtime - a regular patient safety issue prior to the advent of the fast acting insulins). To pursue this goal, Novo Nordisk's strategy was to make a change in the amino acid sequence. We developed a number of drug candidates that were put into an extensive chemical, preclinical and clinical program. The candidate that we took to the market has only one change to the amino acid sequence from its precursor: in position B28 threonine is exchanged for aspartic acid. This change has resulted in an analogue (NovoLog) with significantly shorter time of action than human insulin (Novolin® R) and a unique safety profile. Significantly, an earlier candidate, also with only one amino acid substitution, similarly showed a positive effect on the timing of action but in full pre-clinical animal toxicological studies, this drug candidate also created a significantly increased tumourigenic (tumor growth response) potential in rats. This led to a decision by Novo Nordisk to immediately discontinue this program. As this experience shows, a seemingly "minor" difference can have enormous consequences for important safety characteristics.

Preclinical and Laboratory Tests Not Sufficient to Determine Immunogenicity and Other Issues

Mr. Chairman, this leads me to my next point. Based on our experience as I'll describe below, we believe clinical data is necessary to ensure that a follow-on biologic is safe. We are not advocating for a full package similar to that required of innovators, but comparable clinical data, albeit abbreviated, should be required to ensure drug safety.

In 2002, Novo Nordisk approached the FDA about creating a second generation manufacturing process for our fast acting insulins. Such upgrades are important because they ensure that our manufacturing technology processes are up-to-date and that our production capacity is adequate to meet demand. The changes involved in creating this second generation process included the use of a new precursor DNA; a new production strain and cell bank of the original host cell (*S.ccerivisiae)*; optimized fermentation, recovery and purification; and a new complete production facility. Any follow-on biologic manufacturer would have to do no less than (and most likely significantly more) to develop their unique manufacturing process than what was included in this undertaking for Novo Nordisk.

In order to implement these changes, the FDA required us to supply comparability data (comprising quality data on the structure, impurity

profile, stability and in-process characteristics), and clinical data encompassing phamcokinetics/pharmacodynamics (PK/PD) data as well as human immunogenicity data. To clarify, immunogenicity is how our body naturally responds to foreign substances – by developing antibodies. In our discussions with the FDA, they expressed confidence in our ability to detect and characterize impurities in this newly constructed medicine. However, FDA stated that no general safety threshold, even one as low as 0.1%, could be applied for new impurities because proteins can be immunogenic at very low concentrations and it is not known when "low" is "low enough." Because the immunogenic potential of a protein cannot be predicted from laboratory or preclinical investigations, the FDA required immunogenicity data from an appropriate clinical study. In response, Novo Nordisk submitted data showing comparable immunogenicity between the new and the older processes in a study of several hundred patients.

FDA Authority Should Not Be Constrained

Another example that may assist the Committee in their evaluation of how to establish a pathway that ensures that potential follow-on therapeutic proteins are both safe and effective can be illustrated by

the challenges Novo Nordisk faces in the investigation of a second generation process for the production of rFVIIa, a coagulation (clotting) factor used for the treatment of hemophilia patients with inhibitors. By moving from the current mammalian cell line derived from baby hamster kidneys to one derived from a Chinese hamster ovary (CHO) cell line, a more robust cell line for large scale manufacturing will be obtained.

At an early process step we identified a low level impurity (well below 0.1% in the drug substance) from the CHO cell line, which we proceeded to isolate and characterize. When we tested our experimental rFVIIa material in a repeat dose animal toxicity study we found a large number of animals developing antibodies directed against this impurity, indicating that it was very immunogenic in monkeys. Because this impurity is a foreign protein both to monkey and man, it implied a significant risk that our new product could lead to similar immunogenicity in humans with potential safety implications. Therefore we implemented additional process steps which succeeded in reducing this impurity to extremely low levels.

This example points out the need for the FDA to have the authority to require any safety studies it deems necessary to protect the public

safety. The fact is that a follow-on manufacturer, even after characterizing a product, would have a different cell line from the innovator, different processes, different raw materials, and no matter how well characterized, would not be able to be sure of the immunogenic effect of its product without clinical trials. Imagine the impact on patient safety if a follow-on manufacturer took a product to market not realizing that there were such impurities in the product from the host cell – and had not done clinical trials because Congress had not allowed FDA to require it.

Indeed, when we discussed this cell change program with the FDA at a pre-IND meeting, the FDA made it clear that rFVIIa produced in the new host cell line would be seen as a new product, which would need to stand on its own quality, safety and efficacy documentation including substantial clinical work and requiring submission of a full new BLA.

Multiple Indications Require Appropriate Data

Congress should reject proposals that would give a follow-on biologic based on a limited comparative clinical trial in one indication all indications of the innovator. Safety issues in different patient

populations treated with the same drug are not necessarily the same. RFVIIa® serves as a useful example here. RFVIIa® is a coagulation factor – meant to stop bleedings – and hence events associated with excessive clotting or formation of thrombi (blood clots) pose potential safety concerns. The risk of thrombus formation in a population of hemophilia patients with inhibitors (for which the product is approved) can be very different from the risk for patients with a normal coagulation system (for which the product has been/is being investigated in clinical trials). Similarly, the safety concerns for growth hormone treatment of children with growth hormone deficiency are different from those for adult patients with AIDS wasting for which growth hormone is also indicated. Because of the nature of the underlying conditions, subtle differences between a follow-on and innovator product that may not be evident in one patient population (i.e., may be considered a “minor” difference in that group of patients) may express itself more dramatically and detrimentally when the follow-on product is administered to a different patient population. Furthermore, adequate clinical and post-marketing safety experience in the use of a product in any indication should be established with the innovator product before a follow-on version (with reduced amount of safety data) can be approved.

Current Science Doesn't Support Interchangeability

Because of the potential difference in immunogenicity and other drug-specific adverse events, and because a follow-on biologic product cannot be determined to be the same as the innovator product, these products should not be allowed to be interchangeable. The European system recognizes that "by definition similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established." *(Guideline on Similar Biological Medicinal Products (CHMP/437/04))* There is a further requirement that the products are clearly identified to support post-market monitoring. In addition, there is no evidence to support interchangeability in existing biologics, let alone a new class of biologics with different safety standards. For example, there are currently three different companies who manufacture 9 different types of insulins in 23 different presentations – and they are not interchangeable. Indeed, the FDA expressed its concerns with interchangeability in September, 2006: "With protein products, as of today, the FDA has not determined how interchangeability can be

established for complex proteins. Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response." *(http://www.fda.gov/cder/news/biosimilars.htm)*

Traceability Important to Protect Safety

Congress should also carefully consider the issues involved in traceability, as Europe has done. Because these products are similar, but not the same, all protein drugs should be prescribed and given to the patient based on a unique name. To reference the regulations implemented in Europe, "in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified." *(Guideline on Similar Biological Medicinal Products (CHMP/437/04))* Different names will underscore that the products are, indeed, not "the same" and will help prescribers and dispensers avoid mistakes. Even extensive pre-approval clinical testing may be insufficient to detect rare, but potentially serious, side effects including immunogenicity. Such effects are often specific to one product but not another. Assurance of safety depends, even more than for typical small molecule drugs, on pharmacovigilance and other

post-marketing surveillance measures which allow the tracing of adverse events to a specific product – all of which are much more difficult if products from different manufacturers bear the same name (e.g. USAN or INN).

Conclusion

In summary, our experiences at Novo Nordisk have repeatedly shown that even small impurities or differences in molecular structure can lead to very important changes in properties of the product. These changes are not always detectable by standard analytical methods or predictable by animal tests, and therefore going beyond simple bioequivalence studies and requiring appropriate clinical investigations to document safety in patients is necessary.

Members of the Committee, the development of a follow-on biologics pathway is a complicated issue because of the significant scientific and public health issues involved. However, Novo Nordisk believes a pathway for follow-on biologics is possible provided it is rooted in the best science, preserves innovation of life-saving medicines for millions of patients across the globe, respects proprietary information, and

most importantly is constructed to protect patient safety. Novo Nordisk stands ready to assist Congress as this issue moves forward.