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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

The Novartis Group of companies (Novartis) submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of the Food and Drug Administration (FDA) take the action requested below.

A. Action Requested

Novartis respectfully requests that, to encourage and protect the safe and rational use of all medicines, FDA require that a biosimilar, be identified by the same international nonproprietary name[1] (INN) as the reference product. A biosimilar, by definition of its approval, has successfully met FDA's demanding standard of high similarity to a reference product and, further, the Agency has concluded that the totality of the evidence demonstrates that there will be no clinically meaningful differences in terms of safety, purity and potency between it and the reference product.

B. Summary

The United States enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2010 to establish a pathway for FDA to approve biologic products as biosimilar to already-approved biologics. Under the statute, a biosimilar must demonstrate to the satisfaction of FDA that it is highly similar to an originator reference product and, further, to demonstrate the safety, purity, and potency of the proposed biosimilar. The biosimilar will be considered interchangeable with its reference product if the applicant provides sufficient information to show that the biosimilar can be expected to produce the same clinical result as the reference product in any given patient.

The BPCIA is appropriately silent about the nomenclature FDA should apply to biosimilars, as such nomenclature should be self-evident from FDA's current practice. Nevertheless, the question of whether biosimilars should share an international non-proprietary name (INN) with their reference product has been the subject of much public debate.[2, 3] Such debate has confused the concept and current utilization of INN by departing from the INN's intended purpose of facilitating the identification of pharmaceutical substances. Instead the current dialogue has implied that the INN is intended to facilitate the identification of a specific product. This implication is untrue and has resulted in confusing an otherwise straightforward issue. Many products, including biologics, currently marketed in the United States share INNs (see Table 1

below). But INNs are not, and cannot be, the only or even the primary tools used for tracking and tracing. Indeed, despite their shared INNs, these products have been successfully traced for pharmacovigilance purposes.

Moreover, assigning unique INNs to biosimilars that FDA concurs are highly similar to a reference product would imply that INNs are intended to communicate more than just molecular characteristics and a pharmacological class.[4] It would imply that INNs are intended to communicate an aspect of the regulatory status itself, such as interchangeability or lack thereof. FDA has clearly argued against unique INNs for biosimilars when it stated: "INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist."[5] Indeed, many biologic products on the market today share INNs even though they have never been compared directly to each other, and should a demonstration of "sameness" be required by FDA retrospectively today, many of these products would fail to meet it. Nevertheless, and most importantly, the fact that these products share INNs has not resulted in any safety issues being identified.

Assigning different INNs to products approved as biosimilars would introduce unnecessary confusion into the healthcare system and could unintentionally communicate increased caution, unfounded risk, or other regulatory reservations that are purely hypothetical. Significantly, it would put into question years of FDA's practice of using the well-established analytical standard of high similarity[6] to approve major manufacturing changes of originator biologic products without a parallel change in the originator INN, despite the fact that the manufacturing changes have altered, sometimes substantially, the originator biologics' molecular structures.[7] Using the high similarity standards, FDA has in these cases satisfied itself that the altered originator biologic would produce the same clinical result in terms of safety, purity and potency as its pre-manufacturing change version, and applied this reasoning multiple times for the same product with the same confidence.[8] Similarly, FDA will use these same standards to satisfy itself that the biosimilar would produce the same clinical result as the reference product. Requiring separate INNs for biosimilars but not originator biologics would undermine FDA's own approval decisions, which in both cases require FDA's determination that the compared product (biosimilar or the post-manufacturing change originator biologic) produces the same clinical outcomes as its comparator (respectively, the reference product or the pre-manufacturing change biologic).[9, 10]

Novartis submits that imposing unique INNs on biosimilars would not improve any aspects of patient safety, pharmacovigilance or tracking, and would instead undermine the safe use of all biologics by introducing unfounded confusion into the healthcare system. Novartis therefore respectfully requests that, rather than imposing unique INNs on biosimilars, FDA instead require them to be identified by the same international nonproprietary name as the reference product to encourage and protect the safe and rational use of all medicines.

C. Statement of Grounds

I. INNs are not, and cannot, be the primary tool relied on for tracking and tracing.

The World Health Organization (WHO) administers an international naming convention, known as the International Non-proprietary Naming system. INNs are intended to facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients by health care

professionals worldwide.[11] They are granted based only on molecular characteristics and pharmacological class of active ingredients. In the United States, a sponsor may obtain a United States Adopted Name (USAN), and USANs have been generally consistent with the INN naming convention. INNs are by definition non-proprietary and therefore not designed to identify a specific product; indeed, once an INN is established, it identifies ALL products matching the respective molecular characteristics.

Novartis agrees that for pharmacovigilance purposes all drug products and biologics must be tracked. However, a tracking system does not require, nor would it be helped by, unique INNs for biosimilars. As INNs were designed to be shared among products, they were never intended to function as the basis – and certainly not the sole basis - for tracking and tracing specific products. It is the proprietary, or trade name of a product that is more useful in that regard. And even trade names comprise only a part of the track and trace tool portfolio as products are also traced by national drug codes (NDCs), manufacturer names, and batch and lot numbers.

Despite the suggestions to the contrary, there is no indication that this system will not work for biosimilars. Although no product has been approved as a biosimilar under the BPCIA to date, FDA has set the regulatory precedent by approving numerous biologics which appropriately share INNs even though they were approved under separate approval pathways and are manufactured by different manufacturers. (See Table 1 below). While a few of these products have been discontinued (but unless taken off the market due to safety or efficacy reasons can still be a reference product, hence they are included in the table[12]), the products that have not been discontinued are currently being marketed under separate brand names, and the fact that they share INNs has not resulted in any unique traceability issues.

If there are any weaknesses in the current system with regard to the traceability of a specific product to an adverse event, such weaknesses are not related to the INN and must be addressed for all currently approved products. Indeed, Novartis would support a vigorous enhancement of track and trace methods, and education of physicians and pharmacists.

Furthermore, there are compelling data from other highly regulated jurisdictions confirming that different INNs are not necessary as a mechanism for tracking and tracing. In Europe, where biosimilars have been on the market since 2006, they share the same INNs[13] (see attached Table 2) with their corresponding reference products', and in each case the individual biosimilar product is identified by a brand name[14]. A recent study of the identification of biosimilars in the European Union pharmacovigilance system found that the naming convention for biosimilars has a successful product identification rate of 96.2% across all three marketed biosimilar classes (somatropin, filgrastim and epoetin).[15] There is no reason to expect that the United States' pharmacovigilance system cannot achieve similar or even higher product identification rates given that, unlike the European Union, the United States has the advantage of a singular, nationwide NDC product identification system for tracking.

II. Assigning different INNs to products approved as biosimilars would unnecessarily put into question years of FDA's practice of approving manufacturing changes of originator biologic products without a resulting change in the originator INN.

FDA reviews and approves manufacturing changes in biological products using comparability approaches that use the same highly similar standard that has been written into the biosimilar legislation enacted by U.S. Congress. Both similarity exercises are based on the highly

similar concept as used in the BPCIA and described in FDA's draft guideline on the quality of biosimilars, as well as the International Conference on Harmonization Q5E guideline (ICH Q5E). ICH Q5E focuses on assessing quality of the altered molecule pre- and post-manufacturing change, and when the magnitude of the change so requires, on assessing preclinical and clinical data as well. This approach has been coordinated among regulatory authorities across the highly regulated markets,[16] and also in the form of guidance by WHO for biosimilars in other, emerging markets where patient access is critically important.[17]

FDA has confirmed this approach. When discussing the biosimilar review process, FDA commented that "[its] experience with biologics provides important relevant knowledge. Since the mid-1990s, for example, physicochemical and functional assays have been used to characterize changes in manufacturing processes for some biologics, and then animal or clinical studies are used to resolve any remaining uncertainties about the comparability of the products created before and after such changes and to provide sufficient confidence that safety and efficacy are not diminished."[18] Indeed, data published in peer-reviewed scientific literature demonstrate that, while originator products do change over time, they are well controlled between manufacturing changes, and, even after manufacturing changes, the clinical attributes of the products are acceptable.[19]

Given the fact that the comparability assessment of biological products pre- and post-manufacturing changes not only mirrors, but is in fact the very basis for assessment of biosimilarity, requiring different INNs for biosimilars would unnecessarily put into question years of FDA practice in reviewing and approving such changes without requiring new INNs for post-manufacturing change biologics, whose molecular structure, variant composition or impurity profile has been altered, sometimes substantially, by the manufacturing change. If an identical, consistent naming system is not adopted, patients and physicians may - and should - ask why they were not notified of the change in the originator biologic, which continued to be identified by the same INN and brand name and whose label did not reflect the manufacturing change or the corresponding change in the product itself. The practice of maintaining the same INNs for post-manufacturing change originator biologics is well founded in law, health authority guidelines and science, and should apply equally to naming considerations for biosimilars.

There is no need to introduce confusion and doubt through an unequal application of naming conventions when FDA has such in-depth understanding of all the biologics that they have reviewed and licensed for the United States market, which by definition comprise the entirety of the reference products for biosimilars in the United States.[20] If FDA applies regulatory science consistently, such that the highly similar standard for manufacturing changes is the same as the highly similar standard for biosimilars, then patients can be confident that a biosimilar will generally be as similar to its reference as that reference is to itself over its lifetime, and more importantly, that in both cases any minor differences between them will be in clinically inactive components only.

III. Assigning different INNs to products which conform to an established compendial monograph in the US would be inconsistent with the current regulations governing USP names.

The United States Pharmacopeia (USP) General Notices specify how the compendial standards, including monographs for particular drug substances and drug products, are developed. The current USP and National Formulary (NF) standards are then publically listed and referenced

in the Federal Food, Drug, and Cosmetic Act (FDCA).[21] FDA is therefore responsible for the enforcement of USP standards.

The FDCA states that drugs, including biologics,[22] will be deemed adulterated[23] or misbranded[24] if they do not conform to recognized compendial standards relating to nonproprietary naming and identity, and strength, quality and purity. Therefore, if USP has a monograph for a biologic product, which would be applicable to a biosimilar, such biosimilar will be deemed misbranded unless its label bears the official title recognized in USP-NF.[25] Of course, FDA has the authority to change a USP name[26] in the interest of usefulness and simplicity, but first it must submit its act to public notice and comment and provide the opportunity for judicial review.[27]

IV. Far from advancing it, unique INNs for biosimilars would be detrimental to patient safety.

Assigning unique INNs to biologics, which were proved to be highly similar to their reference products, would send a signal that INNs are intended to communicate more than the molecular characteristics and the pharmaceutical class of the active ingredient. It would send a signal that, instead of simply being used as a global cataloguing mechanism for products with a related active ingredient, INNs are somehow intended to communicate an aspect of the regulatory review and approval itself, such as pharmacologic interchangeability or lack thereof in products with the same active ingredient(s).

A determination of pharmacologic interchangeability of products with the same active ingredient(s) must be made by regulatory agencies based on credible scientific data.[28] For example, in the United States, FDA must make an affirmative determination that two products bearing the same INN are therapeutically equivalent, i.e., that in FDA's judgment they are expected to have equivalent clinical effect.[29] It is this determination by FDA and the subsequent listing of the products as therapeutically equivalent – **and not the products' INN** – that informs physicians, pharmacies, state agencies and other stakeholders that the products can be substituted with the full expectation that they will produce the same clinical effect and safety profile. Similarly, FDA will have to make a separate determination of interchangeability with respect to a biosimilar, and it will be that determination and its reflection on the biosimilar's label that will inform of the biosimilar's interchangeability with its reference product.

FDA previously expressed concern at the potential confusion that could be created by the implication that assigning the same INNs to products was tantamount to a determination of pharmacological interchangeability, as opposed to a high degree of similarity.[30] This concern was echoed in a number of stakeholder letters to the Agency.[31] Representative of these comments are those from a letter authored by the American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) submitted to FDA's Draft Guidances Relating to the Development of Biosimilar Products docket:

> "Unique INNs for common active ingredients may generally increase confusion, leading to increased safety concerns and possibly medication errors. Physicians are already pressed for time, and therefore it is imperative that there are no additional and unnecessary obstacles that hinder them from timely decision-making, especially in cases of urgent care. The use of different INNs would increase the burden of being able to distinguish which products are biosimilar and interchangeable with which reference drug and may pose

difficulties in recognizing the best alternative drug for therapeutic use in a timely manner. Such confusion may lead to medication errors such as therapeutic duplication."[32]

The determination of safety, efficacy, and in appropriate cases, interchangeability, is and should remain beyond the scope of any naming convention. If FDA were to assign different INNs to products with the same active substance for the purpose of preventing inappropriate substitution, it would necessarily create an equally inappropriate implication that all products with the same INNs are by definition interchangeable. This implication could have potentially negative effects on patient safety; especially if such an implication were to be applied to products which share INNs but which have never been compared with each other and which may even have been licensed by FDA for different indications. However, it must be remembered in this context that FDA already allows different recombinant and naturally-derived products from different manufacturers to share INNs, even though such products have been approved by FDA under separate Biologics License Applications (BLAs) and have never demonstrated comparability. The fact that they share INNs has not resulted in any safety issues, but an implication that the same INNs indicate that they are all interchangeable would indeed negatively impact the safe and rational use of these and other medicines which share INNs.

The corollary is also true. Requiring different INNs for biosimilars, and presumably other biologics produced by different sponsors that share active ingredients, would suggest that prescribing by INN could be as appropriate in the future as brand name prescribing is today – after all biologics would essentially have two unique names going forward. Anticipating that such an argument could be made, we tested a recent FDA decision to require that one of the biosimilars approved in Europe with the INN filgrastim to be licensed in the US with the interim established name[33] of TBO-filgrastim. See the MedERRs report summarized in Figure 1 below. Historically, in the context of Brand names, FDA has recommended against the use of pre-fixes and suffixes because of their ability to lead to confusion[34] and this policy is confirmed in the analysis conducted for TBO-filgrastim. Whether or not such confusion will result in practice has yet to be determined as the product in question has not yet been launched in the US.

Figure 1: Med-ERRS® Report for TBO-filgrastim found a "high vulnerability" for medication errors

Proposed name	Score	Vulnerability	Issues
tbo-filgrastim	2	high	Look-alike name(s) Sound-alike name(s) misinterpretation of prefix

Strong look-alike and strong sound-alike similarity was noted with filgrastim (NEUPOGEN, others: used in the treatment of chemotherapy-induced neutropenia), especially if the "tbo" prefix is separated from the rest of the name, missed or misinterpreted. Filgrastim is an injectable product that is used for the same indication as tbo-filgrastim. The dose, dosage strengths, clinical setting for use and patient population all are the same. Both drugs would be ordered by the same type of practitioner (eg., oncologist). Both filgrastim and tbo-filgrastim are stored in the refrigerator. If confusion occurred, the risk of harm generally is moderate due to the bone pain and fever associated with the use of filgrastim. However, due to the clinical similarities between the two drugs, the harm is likely to be negligible.

Slight sound-alike similarity was noted with pegfilgrastim (NEULASTA; used in the treatment of chemotherapy-induced neutropenia). Pegfilgrastim is an injectable product that is used for the same

indication as tbo-filgrastim. The clinical setting for use and patient population are the same. Both drugs would be ordered by the same type of practitioner (e.g., oncologist). Both pegfilgrastim and tbo-filgrastim are stored in the refrigerator. Pegfilgrastim is given at a different dose than tbo-filgrastim. If confusion occurred, the risk of harm generally is moderate due to the bone pain associated with the use of pegfilgrastim. However, due to the clinical similarities between the two drugs, the harm is likely to be negligible, unless pegfilgrastim is administered on a daily basis as if it were tbo-filgrastim, in which case the harm would be increased.

A number of misinterpretations were noted for the "tbo" prefix. These include "to be ordered," "TVO" for "telephone verbal order," "the," "Hb" for the abbreviation for hemoglobin, "TB" for the abbreviation for tuberculosis and "TKO" for the abbreviation "to keep [vein] open." If any of these misinterpretations occurred, the practitioner would likely dispense and/or administer a filgrastim product rather than a tbo-filgrastim product.

INNs are assigned based on the molecular structure and pharmacological class of products and have been utilized successfully as one component of pharmacovigilance monitoring. INNs are used in national and regional pharmacovigilance systems, along with other key identifiers such as brand name, to facilitate the detection of new safety information related to pharmaceutical substances on a global level. They allow the aggregation of safety data, detection of class effects, and appropriate and timely response to safety alerts. These significant safety benefits would be undermined if products with the same active ingredients were assigned different INNs, especially when such products have been shown to produce the same clinical result in terms of safety, purity and potency by credible scientific data. Different INNs (USANs) will necessarily decouple biosimilars approved in the United States from safety data of the same products elsewhere in the world, where consistent INNs are currently used, and vice versa. This could contribute to the breakdown of the current international system with ramifications for public health more broadly than just in the US.

V. Conclusion

The BPCIA was enacted to provide a pathway for approval of products that reference already-approved biological molecules. It is for FDA to determine whether an applicant under the BPCIA meets the demanding standards of high similarity to the reference biological molecule. If it does not demonstrate high similarity, it is for FDA to simply not approve it as a biosimilar. Approving it under a separate INN would run counter to the very purpose of the BPCIA, a major goal of which is to create competition in the marketplace for biologics and expand access to, and increase the affordability of, these critical medicines. This goal of providing patients and providers with access to high quality, lower cost alternative products and incentivizing innovation in the field of medicine should never compromise patient safety. It is the FDA review process, however, and not separate INNs, that will ensure patient safety is never compromised. Indeed, assigning separate INNs to biosimilars will undoubtedly undermine this objective by creating confusion in the healthcare system and unnecessarily casting doubt on FDA's robust and well-established practice of reviewing the relevance of differences in originator products after manufacturing changes. As unfortunate as such a result would be, it will only be compounded unnecessarily and equally tragically by thwarting the congressional intent of increasing patient access to affordable biologics. Therefore, Novartis submits that imposing unique INNs on biosimilars would not improve any aspect of patient safety, pharmacovigilance or tracking, and would instead undermine the safe use of all biologics by introducing unfounded confusion into the healthcare system. Novartis therefore respectfully requests that, rather than imposing unique INNs on biosimilars, FDA instead require

them to be identified by the same international nonproprietary name as the reference product to encourage and protect the safe and rational use of all medicines.

D. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R § 25.30.

E. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only at the request of the Commissioner.

F. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted on behalf of the Novartis Group of Companies

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Acronyms:

APhA = American Pharmacists Association
BLA = Biologics License Application
BPCIA = Biologics Price Competition and Innovation Act
FDA = Food and Drug Administration
FDCA = Federal Food Drug and Cosmetic Act
ICH = International Committee on Harmonization
INN = International Nonproprietary Name
NACDS = National Association of Chain Drug Stores
NCPA = National Community Pharmacists Association
NF= National Formulary
Novartis = Novartis Group of companies
USAN = United States Adopted Name
USP = United States Pharmacopeia
USP-NF= United States Pharmacopeia – National Formulary
WHO = World Health Organization

Table 1: Examples of FDA Approved/Licensed biologic products that share INNs (listed alphabetically by INN; products shaded in blue are currently discontinued, but not withdrawn for safety or efficacy reasons)

Brand/Trade Name	**Common Name (established, generic, INN, USAN)**	Sponsor	Original Approval Date	FDA Application Number
Myozyme®	**Alglucosidase Alfa**	Genzyme	April 28, 2006	BLA 125141
Lumizyme®		Genzyme	May 24, 2010	BLA 125291
Kogenate FS®	**Antihemophilic Factor (Recombinant)**	Bayer Corp	June 26, 2000	BL 103332
ReFacto®		Genetics Institute	March 6, 2000	BL 980137
Recombinate®		Baxter Healthcare Corporation	January 21, 2010	BL 103375
Advate®	**Antihemophilic Factor (Recombinant) - Plasma/Albumin Free**	Baxter Healthcare Corporation	July 25, 2003	BL 125063
Xyntha®		Wyeth Pharmaceuticals, Inc.	February 21, 2008	BL 125264
Miacalcin®	**Calcitonin Salmon**	Novartis	August 17, 1995	NDA 20313
Calcimar®		Sanofi Aventis US	April 17, 1978	NDA 17760
Calcitonin Salmon (Generic)		Apotex Inc	November 17, 2008	ANDA 076396
Calcitonin Salmon (Generic)		AstraZeneca	Unknown	ANDA 073690
Calcitonin Salmon (Generic)		Par Pharm	June 8, 2009	ANDA 076979
Tripedia®	**Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed**	Sanofi Pasteur, Inc	July 31, 1996	BL 103922
Infanrix®		GlaxoSmithKline Biologicals	January 29, 1997	BL 103647
Daptacel®		Sanofi Pasteur, Inc	May 14, 2002	BL 103666
VAQTA®	**Hepatitis A Vaccine, Inactivated**	Merck & Co, Inc	August 11, 2005	BL 103606
Havrix®		GlaxoSmithKline Biologicals	October 17, 2005	BL 103475
Engerix-B®	**Hepatitis B Vaccine (Recombinant)**	GlaxoSmithKline Biologicals	July 7, 1998	BL 103239
Recombivax HB®		Merck & Co, Inc	August 27, 1999	BL 101066
Wydase®	**Hyaluronidase**	Baxter	March 22, 1950	NDA 006343
Vitrase®		Ista Pharms	May 5, 2004	NDA 021640
Amphadase®		Amphastar Pharm	October 26, 2004	NDA 021665
Hydase®		Akorn Inc	October 25, 2005	NDA 021716

Fluzone®, Fluzone High-Dose and Fluzone Intradermal®	**Influenza Virus Vaccine**	Sanofi Pasteur, Inc	September 4, 2002	BL 103914
Fluarix®		GlaxoSmithKline Biologicals	August 31, 2005	BL 125127
Fluvirin®		Novartis Vaccines and Diagnostics Ltd	September 14, 2005	BL 103837
Flucelvax®		Novartis Vaccines and Diagnostics Ltd	November 20, 2012	BL 125408
FluLaval®		ID Biomedical Corp of Quebec	October 5, 2006	BL 125163
Afluria®		CSL Limited	September 28, 2007	BL 125254
Agriflu®		Novartis Vaccines and Diagnostics S.r.l.	November 27, 2009	BL 125297
Iletin® I	**Insulin Pork**	Eli Lilly	June 17, 1966	NDA 017931
Insulin and Regular Insulin		Novo Nordisk	Unknown	NDA 017926
Iletin® II and Regular Iletin® II	**Insulin Purified Pork**	Eli Lilly	December 5, 1979	NDA 018344
Regular Purified Pork Insulin		Novo Nordisk	March 17, 1980	NDA 018381
Velosulin®		Novo Nordisk	Unknown	NDA 018193
Exubera®	**Insulin Recombinant Human**	Pfizer	January 27, 2006	NDA 021868
Humulin® BR		Eli Lilly	April 28, 1986	NDA 019529
Humulin® R and Humulin® R Pen		Eli Lilly	October 28, 1982	NDA 018780
Novolin® R		Novo Nordisk	June 25, 1991	NDA 019938
Velosulin® BR		Novo Nordisk	July 19, 1999	NDA 021028
Humulin® 70/30 and Humulin® 70/30 Pen	**Insulin Recombinant Human; Insulin Suspension Isophane Recombinant Human**	Eli Lilly	April 25, 1989	NDA 019717
Novolin® 70/30		Novo Nordisk	June 25, 1991	NDA 019991

Mixtard® Human 70/30	**Insulin Recombinant Human; Insulin Suspension Isophane Semisynthetic Purified Human**	Bayer Pharms	March 11, 1988	NDA 019585
Novolin® 70/30		Novo Nordisk	Unknown	NDA 019441
Novolin® R	**Insulin Recombinant Purified Human**	Novo Nordisk	Unknown	NDA 018778
Velosulin® BR Human		Novo Nordisk	Unknown	NDA 019450
Insulin Insulatard NPH Nordisk	**Insulin Suspension Isophane Purified Pork**	Novo Nordisk	Unknown	NDA 018194
NPH Lietin® II (Pork)		Eli Lilly	December 5, 1979	NDA 018345
NPH Purified Pork Isophane Insulin		Novo Nordisk	July 30, 1981	NDA 018623
Humulin® N	**Insulin Suspension Isophane Recombinant Human**	Eli Lilly	October 28, 1982	NDA 018781
Novolin® N		Novo Nordisk	July 1, 1991	NDA 019959
Insulatard® NPH Human	**Insulin Suspension Isophane Semisynthetic Purified Human**	Novo Nordisk	Unknown	NDA 019449
Novolin® N		Novo Nordisk	Unknown	NDA 019065
Protamine Zinc and Iletin® II	**Insulin Suspension Protamine Zinc Purified Beef**	Eli Lilly	June 12, 1980	NDA 018476
Protamine Zinc Insulin		Bristol Myers Squibb	Unknown	NDA 017928
Lente®	**Insulin Zinc Suspension Purified Pork**	Novo Nordisk	March 17, 1980	NDA 018383
Lente Iletin® II		Eli Lilly	December 5, 1979	NDA 018347
Humulin® L	**Insulin Zinc Suspension Recombinant Human**	Eli Lilly	September 30, 1985	NDA 019377
Novolin® L		Novo Nordisk	June 25, 1991	NDA 019965
Avonex®	**Interferon Beta-1A**	Biogen	May 17, 1996	BLA 103628
Rebif®		Serono Inc	March 7, 2002	BLA 103780
Betaseron®	**Interferon Beta-1B**	Bayer Healthcare Pharms	July 23, 1993	BLA 103471
Extavia®		Novartis	August 14, 2009	BLA 125290

Asellacrin® 10, Asellarcrin® 2	**Somatropin**	EMD Serono	July 30, 1976	NDA 017726
Crescormon®		Genentech	April 6, 1979	NDA 017992
Accretropin®	**Somatropin Recombinant**	Cangene	January 23, 2008	NDA 021538
Bio-Tropin®		Ferring	May 25, 1995	NDA 019774
Genotropin® and Genotropin® Preservative Free		Pharmacia and Upjohn	August 24, 1995	NDA 020280
Humatrope®		Eli Lilly	March 8, 1987	NDA 019640
Norditropin® Flexpro and Norditropin® Nordiflex		Novo Nordisk	June 20, 2000	NDA 021148
Nutropin® and Nutropin® AQ		Genentech	Nov. 17, 1993 and Dec. 29, 1995	NDA 020168 & NDA 020522
Omnitrope®		Sandoz	May 30, 2006	NDA 021426
Saizen®		EMD Serono	October 8, 1996	NDA 019764
Serostim®		EMD Serono	August 23, 1996	NDA 020604
Tev-Tropin®		Ferring	May 25, 1995	NDA 019774
Valtropin®		LG Life	April 19, 2007	NDA 021905
Zorbtive®		EMD Serono	December 1, 2003	NDA 021597

Table 2: Examples of EU Approved biosimilars and their INNs (all are shared between the biosimilar and its reference, with the exception of Epoetin zeta and that was at the election of its sponsor)

Trade Name	Common Name (INN)	Biosimilar Sponsor	Reference Product	Decision	Biosimilar Approval Date
Omnitrope®	**Somatropin**	Sandoz	Genotropin®	Approved	April 12, 2006
Valtropin®		BioPartners	Humatrope®	Approved	April 24, 2006
Binocrit®	**Epoetin alfa**	Sandoz	Eprex®	Approved	August 28, 2007
Epoetin alfa Hexal®		Hexal	Eprex®	Approved	August 28, 2007
Abseamed®		Medice	Eprex®	Approved	August 28, 2007
Retacrit®	**Epoetin zeta**	Hospira	Eprex®	Approved	December 18, 2007
Silapo®		STADA	Eprex®	Approved	December 18, 2007
Biograstim®	**Filgrastim**	CT Arzneimittel GmbH	Neupogen®	Approved	September 16, 2008
Filgrastim Ratiopharm®		Ratiopharm GmbH	Neupogen®	Approved	September 16, 2008
Ratiograstim®		Ratiopharm GmbH	Neupogen®	Approved	September 16, 2008
Tevagrastim®		Teva Generics GmbH	Neupogen®	Approved	September 16, 2008
Zarzio®		Sandoz	Neupogen®	Approved	February 6, 2009
Filgrastim Hexal®		Hexal	Neupogen®	Approved	February 6, 2009
Nivestim®		Hospira	Neupogen®	Approved	June 6, 2010
Remisima®	**Infliximab**	Celltrion	Remicade®	Positive Opinion	June 28, 2013
Inflectra®		Hospira	Remicade®	Positive Opinion	June 28, 2013

Endnotes

[1] For the sake of simplicity, the term "international nonproprietary name" or "INN" is used throughout this paper, though of course in the United States the applicable term is "United Stated Adopted Name" or "USAN".

[2] See e.g., FDA, Part 15 public hearing on approval pathway for biosimilar and interchangeable biological products November 3, 2010, transcript available at http://www.fda.gov/downloads/Drugs/NewsEvents/UCM289124.pdf (accessed Oct. 18, 2013); FDA, Center for Drug Evaluation and Research, Office of Medical Policy, Part 15 public hearing on draft guidances relating to the development of biosimilar products May 11, 2012, transcript available at http://www.fda.gov/downloads/Drugs/NewsEvents/UCM310764.pdf (accessed Oct. 18, 2013); Richard Dolinar, *It's All About the Name: What Is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?*, FDLI's Food and Drug Policy Forum, 2 (22) (Nov. 28, 2012); Steve Miller, *Is it Necessary to Depart from International Naming Conventions for Biosimilars in the US to Ensure the Safety of Biologic and Biosimilar Therapeutics?: A Response to 'It's All About the Name: What is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?'* FDLI's Food and Drug Policy Forum, 3 (1) (Jan. 9, 2013).

[3] McCamish, Gallaher, Orloff "Biosimilar by Name and Biosimilar by Nature", RPM Report, June 28, 2013.

[4] WHO, "International Nonproprietary Names," available at: http://www.who.int/medicines/services/inn/en/ (accessed Oct. 18, 2013).

[5] FDA paper submitted to WHO, "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (Sept. 2006) (attached below as an Appendix).

[6] ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CMPM, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Oct. 18, 2013). The guidance defines comparable as follows:

> A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

[7] Schiestl, M et al., *Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals*, Nature Biotechnology, 29 (4): 310-312 (Apr. 2011).

[8] Schneider C. "Biosimilars in Rheumatology The Wind of Change", Am Rhem Dis March 2013, available at http://ard.bmj.com/content/72/3/315.full.pdf (accessed Oct. 18, 2013). While the data on the number of manufacturing changes is provided for Europe, similar changes will have been undertaken for the US, but the use of comparability is not made public in the US.

[9] BPCIA definition of biosimilar/biosimilarity is that "there are no clinically meaningful differences between the biological product and the biosimilar in terms of safety purity and potency of the product." PHS Act § 351(i)(2).

[10] ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CMPM, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Oct. 18, 2013).

[11] WHO, "International Nonproprietary Names," available at: http://www.who.int/medicines/services/inn/en/ (accessed Oct. 18, 2013).

[12] Such was the case with the hyaluronidases where the reference product, Wydase®, was no longer commercially available.

[13] The one exception is Hospira's epoetin zeta, a biosimilar to Eprex®, but it must be pointed out that a separate INN was requested at the sponsor's own initiative.

[14] As Novartis has previously stated in the context of this discussion, it expects that biosimilars would have unique brand names in the United States. Indeed, Novartis would support a FDA requirement that all biosimilars must have unique brand names.

[15] Presentation by Niels Vermeer "Traceability of biopharmaceuticals in spontaneous reporting systems," (May 25, 2012), at the European Medicines Agency, Fifth stakeholder forum on the implementation of the new pharmacovigilance legislation, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127934.pdf (accessed Oct. 18, 2013), and also presentations available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2012/05/event_detail_000582.jsp&mid=WC0b01ac058004d5c3 (accessed Oct. 18, 2013).

[16] ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CMPM, Dec. 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted April 26, 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Oct. 18, 2013).

[17] WHO, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) (2009), available at: http://www.who.int/entity/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf (accessed Oct. 18, 2013).

[18] Kozlowski, S et al., *Developing the Nation's Biosimilars Program*, N Engl J Med 365(5):385-388 (Aug. 4, 2011).

[19] Schiestl, M et al., *Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals*, Nature Biotechnology, 29 (4): 310-312 (Apr. 2011); *see also* Dörner et al., *The role of biosimilars in the*

treatment of rheumatic diseases, Ann Rheum Dis, published online Dec. 19, 2012, doi:10.1136/annrheumdis-2012-202715; Christian K Schneider, *Biosimilars in rheumatology: the wind of change*, Ann Rheum Dis, 72 (3): 315- 318 (Mar. 2013)(looking at the number of manufacturing changes for certain European biologics, and finding these products have undergone up to 37 manufacturing changes since approval).

[20] Section 7002 of the BPCIA notes that the statute requires a single 351(a) reference product for each biosimilar and this section also provides a 12-year exclusivity provision, all of which is evidence of the experience that FDA has with that reference product.

[21] FDCA § 501(j).

[22] Public Health Service Act (PHS Act) 351(j), confirming that all biological products approved under PHS Act are subject to the FDCA.

[23] FDCA § 501(b).

[24] FDCA § 502(e).

[25] FDCA § 502(e)(3).

[26] It should be pointed out that such a change would necessitate a parallel change to the USP name of the originator.

[27] FDCA § 508.

[28] FDA paper submitted to WHO, "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (Sept. 2006) (attached below as Appendix).

[29] As a statutory matter BPCIA defines biosimilar/biosimilarity as meaning that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

[30] FDA paper submitted to WHO, "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (Sept. 2006)(attached below as Appendix).

[31] *See e.g.*, comments to Docket No. FDA-2011-D-0618, letter dated May 25, 2012, from American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA); letter to Commissioner Hamburg, dated April 17, 2013 from the National Association of Boards of Pharmacy ("The use of INNs as a naming convention is unfamiliar to health care providers and patients and could cause confusion, resulting in the incorrect drug being dispensed to patients or therapeutic duplication"); letter to Commissioner Hamburg, dated August 20, 2012 from the National Council for Prescription Drug Programs (NCPDP) ("[Unique individual nonproprietary names for biosimilars] could cause public health concerns due to therapeutic duplication and healthcare professional and patient confusion regarding appropriate use, safety and efficacy of biologic products. Over the years we have observed how small, seemingly

inconsequential, changes in product descriptions and data formatting or structure can have significant consequences within healthcare."); letter to Commissioner Hamburg, dated June 4, 2012 from 22 stakeholders including AARP, Blue Cross Blue Shield Association, California Public Employees Retirement System, National Association of Chain Drug Stores.

[32] Comments to Docket No. FDA-2011-D-0618, letter dated May 25, 2012, from American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA).

[33] Reference to the terminology in the USP submission to the docket on the three biosimilar draft guidances published February 2012.

[34] FDA Guidance for Industry "Contents of a Complete Submission for the Evaluation of Proprietary Names", February 2010, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf (accessed Oct. 18, 2013). See Page 10:

> *4. Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)*
>
> A modifier, such as a prefix of suffix, in the proprietary product name might suggest different meanings to health care professionals and consumers, which could potential lead to product confusions. When an applicant or sposnor submists a product name with amodifier (for example with the prefix Lo- or suffix XR), the submission should include the intended meaning of the modifier, the raionale for the modifer, and any studies that have been conducted to support the use of the modifier.

Appendix

U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars

September 1, 2006

Support of INN's Original Purpose

The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world's public health, especially in facilitating the exchange of scientific data and reports on various products with the same active ingredient(s).

The USA recognizes the INN system as a cataloging system whereby many products worldwide may share the same internationally recognized nonproprietary name based on drug substance. In this manner, the INN system provides a clear mechanism to health care professionals worldwide for identifying medicines and communicating unambiguously about them based on pharmacological class.

The U.S. FDA's concerns in today's discussion are (a) that the INN not be used in ways that could jeopardize the health of patients, and (b) that we not unnecessarily institute changes that could jeopardize the public health benefits of the present INN system.

Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist.

Pharmacologic Interchangeability

"Interchangeability" is a term used for purposes of this discussion to designate the situation where scientific data convincingly demonstrates that two products with very similar molecular compositions or active ingredient(s) can be safely substituted for one another and have the same biologic response and not create adverse health outcomes, e.g., generation of a pathologic immune response.

With small molecular products, there is a long history to support the use of various scientific approaches to establishing "bioequivalence" between products with the same active ingredient(s) produced by different manufacturers. We know now that these "bioequivalent" products can indeed be expected to behave in a pharmacologically interchangeable manner when used in patient care.

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

When scientific data establishing pharmacologic interchangeability do not exist, especially with more complicated protein molecules with potential critical immunologic safety issues, it is important that patients and physicians be aware that protein products with similar molecular composition may indeed not be interchangeable.

U.S. FDA believes that the only way to establish pharmacologic interchangeability is through scientific data, and nomenclature should not be used as a way to imply such when there are not credible supporting data.

Situation in the United States of America

Product Dispensing

To date, the USA does not use non-proprietary names as a vehicle for communicating pharmacologic interchangeability. There are examples in both small molecule products and more complex proteins of products having the same non-proprietary name and there not being scientific data establishing the interchangeability of the products. For example, multiple innovator products containing interferon β-1a, insulin, or somatropin share the same non-proprietary name and there are not scientific data that support the pharmacologic interchangeability of these products.

In the USA there are recognized mechanisms in place other than non-proprietary names for assigning pharmacologic interchangeability: e.g., equivalence ratings in the Orange Book; specific labeling regarding pharmacologic interchangeability.

In addition, in the USA, there are drug dispensing systematic "checks" to help assure appropriate dispensing of products based on whether or not there are scientific data establishing interchangeability. However, this might not be true in other countries.

Because of the many alternative mechanisms in the U.S. for preventing inappropriate substitution, at this time the U.S. FDA does not consider the proposed change to the INN policy for naming biosimilars to be necessary to prevent inappropriate substitution in the United States. Appropriate prescribing and dispensing practices in the U.S. encompass more than just conveyance of a drug name from prescriber to pharmacist. Regulations concerning drug substitution by pharmacists vary from state to state in the United States. However, there is always a mechanism by which the prescriber can authorize that the brand or innovator product be dispensed. As an additional safeguard, many states utilize a state drug formulary that includes listings of drugs with the "same" active ingredient(s) considered to be pharmacologically interchangeable. Even if two biosimilars would have the same nonproprietary name, they would

only be included on a list of interchangeable products, if there were scientific data to justify such. Thus, a common INN in itself does not imply or warrant inclusion on a state's list of interchangeable drugs. The FDA recognizes that the authorized prescribing information represents the most important means of communicating information about an authorized product to prescribers and pharmacists. The authorized prescribing information should distinguish a product from others considered to be biosimilar if indeed there is not data to substantiate pharmacologic interchangeability. In addition, the role of continuing professional education about interchangeability risks with biosimilars should be further emphasized.

The issue of interchangeability is not an issue of nomenclature but a scientific question that needs to be decided on its own merit. The question of nomenclature is more relevant to concerns about pharmacovigilance and the prevention of inappropriate substitution. However the FDA believes that these issues transcend a naming convention. It would be the U.S. FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

Pharmacovigilance:

In the USA, the non-proprietary name may serve as a useful tool in pharmacovigilance as it may be one means of product identification, but it should not be relied upon as the sole means of product identification. Pharmacovigilance is the dual responsibility of the manufacturer and the U.S. FDA. In order to practice the most robust pharmacovigilance, all involved should employ all the various tools available for product identification, including lot numbers, NDC codes or other such national coding systems, etc.

As such, the USA does not see any reason to change present INN practices for pharmacovigilance purposes when there are other identification systems in place to allow product identification beyond the level of the non-proprietary name.

U.S. FDA Concerns Regarding INNs and Complex Proteins

If the outcome of assigning the same INN to two products with highly similar ingredient(s) created the implication that the two products were pharmacologically interchangeable AND there were NO scientific data to support that finding, then the U.S. FDA would have serious concerns

about such an outcome, especially with more complicated proteins. As of today, FDA has not determined how interchangeability can be established for complex proteins.

If the outcome of assigning different names or names with unique identifiers to two products with highly similar active ingredient(s) created the implication that two products were not interchangeable when indeed there were scientific data establishing such, the U.S. FDA would have serious concerns.

It is beyond the role of the INN Expert Committee to make product interchangeability determinations. This would place an unrealistic burden of responsibility with accompanying liability on the INN Expert Committee. The INN should not be used as a determinant of interchangeability. It would be bad public health policy to allow, just because they share the same INN, the substitution of products with a shared INN in patient care when there are no scientific data to demonstrate pharmacologic interchangeability.

Likewise, it would be bad public health policy to disallow, solely because they have different INNs, the substitution of products with different INNs which indeed have scientific data that demonstrate pharmacologic interchangeability.

Each national regulatory authority should oversee the evaluation of interchangeability based on bioequivalence and/or other validated scientific data and not link such decisions to INNs.

Conclusions

This discussion among national regulatory authorities and the WHO should be a first discussion on this issue to fact find and to determine how changes to the INN system would impact both positively and adversely, the regulatory systems and public health of WHO member states.

- The FDA is concerned that some countries may be using the INN as an indicator of interchangeability. Although this is not the case in the U.S., the U.S. FDA considers this apparent inappropriate use of the INN to be a public health concern.
- The U.S. FDA encourages the WHO to further investigate the worldwide prevalence of using the INN as a determinant of interchangeability (note: the BCG study sponsored by Amgen investigated 6 EU countries and use of the INN in prescribing was encouraged in most of these 6 countries, but not required).
- The U.S. FDA suggests that the WHO/INN Expert Committee clarify and re-iterate the intent of the INN with participating countries.

It would be the U.S. FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at

a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

At this time, the U.S. FDA acknowledges that biosimilars have not been demonstrated to be interchangeable through any scientific process. The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small molecule drugs. A different naming scheme for these products might involve utilizing a different level of granularity, which may be more detailed or less detailed depending upon the utility in the INN system. Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.

Date created: September 5, 2006

http://www.fda.gov/cder/news/biosimilars.htm (accessed16Apr08, no longer available)