



Nomenclature for Biological and Biotechnological Substances, including Biosimilars/Generic Biopharmaceuticals

**Gordon Johnston, RPh., M.S.
VP Regulatory Affairs
Generic Pharmaceutical Association**

WHO Headquarters

Geneva

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Outline

- Background
- Scientific Considerations
- The Role of WHO & the INN Process
- Interchangeability
- Pharmacovigilance
- Summary

Background

- Biologics have been included in the WHO INN system from the beginning in 1953
- Purpose of INN
 - Cataloging system
 - Allows international use of a common name for the active ingredient
 - Provides for a clear mechanism for worldwide exchange of information
- “...the system has provided many positive elements to the world’s public health...”*

* U.S. FDA statement September 6, 2006

Background

- Biotechnology products were first approved in 1982 – nearly 25 years ago
- Multiple biologics have received the same INNs and there have been no safety problems shown to result from these products being confused



Overview

GPhA Position

- Support the original purposes of INN program
 - Represents a clear system for nomenclature for the global healthcare community
 - Clearly identifies active ingredient by name
 - Communicates pharmacological class
- Concurs with U.S. FDA position that changes to INN program are unwarranted and jeopardize public health benefits



Scientific Considerations

Scientific Considerations

- Neither brand nor generic biopharmaceuticals are 'identical' from batch to batch, or after changes to cell lines, source materials, process, etc.
- “Similarity” or “comparability” determinations are made by regulators only when credible scientific data demonstrates no pharmacologically relevant differences
- “Similar = The product attributes are similar enough to establish the same safety and efficacy as the comparator drug”*

* S. Kozlowski, M.D., Acting Director, Office of Biotechnology Products, FDA
FDA/DIA Workshop, February 2005

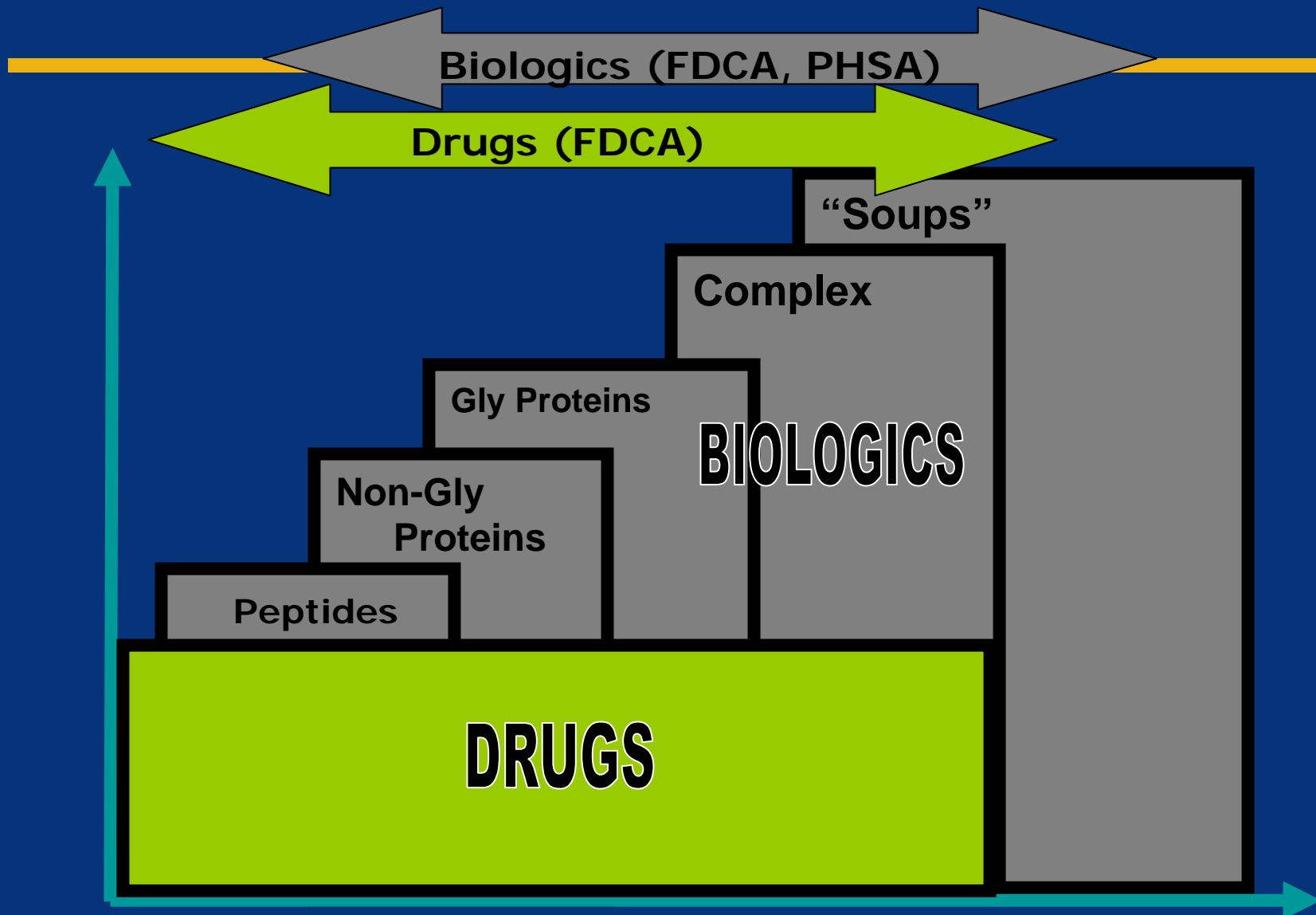
Scientific Considerations: FDA Comments

- “Analytical tools are becoming increasingly sensitive ...This may allow for certain biotech products to be shown to be interchangeable and pharmaceutically equivalent...”¹
- “When people say the science isn’t there...that flies in the face of experience...”²
- “Specific, precise, predictable.” Those are the words that best describe today’s biotechnology.”³

1 June 20, 2003 FDA Week, Anthony Mire-Sluis, FDA, Office of Pharmaceutical Science

2 October 20, 2003, The Scientist, Bill Hubbard, FDA Associate Commissioner for Policy Coordination

3 Biotechnology Industry Organization



Biologics (FDCA, PHSA)

Drugs (FDCA)

"Soups"

Complex

Gly Proteins

BIOLOGICS

Non-Gly
Proteins

Peptides

DRUGS

Scientific Considerations: Comparability Testing

- Cornerstone for demonstrating 'sameness'
- Changes to manufacturing process, source material or cell line are permitted based on demonstration of comparability (identity, strength, quality, purity or potency)
- Manufacturers use the most sophisticated technology available to ensure consistent safety and efficacy between the pre-change and post-change product
- Generic manufacturers use exactly the same sophisticated technology to characterize biopharmaceutical products



Scientific Considerations: Comparability Testing

- **Comparative Characterization**
 - Physicochemical tests
 - Bioactivity/Potency assays
 - Stability
- **Non-clinical Studies**
 - PK/PD
 - Toxicology
- **Clinical Studies**
 - Immunogenicity
 - Efficacy, if necessary

Characterization
for
pharmaceutical
equivalence

Confirmatory
or
Complementary





Scientific Considerations: Manufacturing Process

The New Era

- Quality by Design
 - Manufacturing process is scientifically designed to achieve a product equivalent to the reference product (quality, safety & efficacy)
 - Extensive characterization of reference product (multiple batches)
 - Broad set of orthogonal state-of-the-art analytical tools
 - Accounting for formulation, packaging materials, etc.
- Process Analytical Technologies
- FDA has clearly stated process \neq product

Scientific Considerations

Example of multiple changes (cell lines, processes, specifications, etc.)

- All human growth hormone products approved in U.S. use INN of Somatropin
 - No applicant has sought an interchangeability determination to date
- Approved labeling states:

“In vitro, preclinical, and clinical tests have demonstrated that somatropins are therapeutically equivalent to human growth hormone of pituitary origin and achieve similar pharmacokinetic profiles in normal adults” (emphasis added)

Examples of Abbreviated Approvals for Biopharmaceuticals with Same INN

FFDC Act	
Octreotide	ANDA
Desmopressin	ANDA
Glucagon	505b2 NDA
Calcitonin Calcium	ANDA
Somatotropin	505b2 NDA
Menotropins	505b2 NDA
Menotropins	ANDA
Hyaluronidase	505b2 NDA
PHS Act	
Albumins	Limited clinical data
Immunoglobulins	Limited clinical data

Yellow = Interchangeable



Role of WHO - INN Process

Role of WHO – INN Process

- WHO INN Expert Committee has served the original and current purpose of INN very well
 - Assigns globally recognized nomenclature based in collaboration with national groups
 - Single INN allows for universal identification of active ingredients that applies worldwide
 - Facilitates medical and scientific discussions



Role of WHO – INN Process

- WHO Expert Committee not designed to assess comparability
 - Lacks sufficient technical infrastructure
 - Does not have access to regulatory files
 - Excessively burdened by proposed changes
- Scientific determinations of comparability should be conducted by National regulatory authorities
- National Regulatory authorities can continue to recommend distinct INN when products differ



INN Process: U.S. Perspective

Is there a problem?

- No. Hypothetical issue by raised special interests
- Different INNs for same active ingredient will likely lead to more confusion, not less



INN Process : U.S. Perspective

- What are the consequences of this proposal?
 - Change INNs for marketed products? (e.g. Multiple HGHs, Erythropoietins, Interferons)
 - New INN when comparability study performed to support post-approval change by brand product?
 - If INNs grandfathered for existing products, one can assume no actual safety problem with same INNs; so existing system can continue safely

INN Process: U.S. Perspective

- Pharmacovigilance can only be effectively addressed by identifying manufacturer and lot number (already available) when product is dispensed.
 - Concern that a single INN may not distinguish adverse events
 - 7 approved HGH in U.S. using same INN; no reported problems in tracking/tracing
 - Generics approved for some biological products; no reported problems with tracking/tracing
 - No evidence to support hypothetical scenario

INN Process: U.S. Perspective

- Scientific data should drive decisions as to the appropriateness of the same INN
 - A product deemed by regulators to have the same active ingredient should have the same INN
 - A different active ingredient would have a different INN





Interchangeability



Interchangeability in the U.S.

- U.S. laws limit interchangeability to those products deemed therapeutically equivalent by FDA when products have:
 - Same active ingredient (same INN), PLUS same dosage form, strength, route of administration and bioequivalent
- The same INN does NOT indicate interchangeability unless FDA has determined the products to be interchangeable
- Physician always has final authority on interchangeability

Orange Book

DILTIAZEM HYDROCHLORIDE

CAPSULE, EXTENDED RELEASE; ORAL
CARDIZEM CD

AB3	BIOVAIL	120MG
AB3		180MG
AB3		240MG
AB3		300MG
BC +		360MG

CARTIA XT

AB3	ANDRX PHARMS	120MG
AB3		180MG
AB3		240MG
AB3		300MG

DILACOR XR

AB2	WATSON LABS	120MG
AB2		180MG
AB2 +		240MG

DILT-CD

AB3	TORPHARM	120MG
AB3		180MG
AB3		240MG
AB3		300MG

DILTIAZEM HYDROCHLORIDE

AB2	ANDRX	120MG
AB2		180MG
AB2		240MG
AB3	BIOVAIL	120MG
AB3		120MG
AB3		180MG
AB3		180MG
AB3		240MG
AB3		240MG
AB3		300MG

Drugs are same strength, dosage form and route of administration

Some are rated therapeutically equivalent, some are not

All bear the same INN

The Orange Book is routinely used by pharmacists and physicians to dispense proper medication

DILTIAZEM HYDROCHLORIDE

CAPSULE, EXTENDED RELEASE; ORAL
DILTIAZEM HYDROCHLORIDE

	+ MYLAN	120MG
AB3	PUREPAC PHARM	120MG
AB3		180MG
AB3		240MG
AB3		300MG
AB2	TORPHARM	120MG
AB2		180MG
AB2		240MG

TAZTIA XT

AB4	ANDRX PHARMS	120MG
AB4		180MG
AB4		240MG
AB4		300MG
AB4		360MG

TIAZAC

AB4	BIOVAIL	120MG
AB4		180MG
AB4		240MG
AB4		300MG
AB4		360MG
	+	420MG

INJECTABLE, INJECTION

Interchangeability Recap

- **Different** INN = Substitution never permitted
- **Same** INN
 - Not deemed interchangeable = No substitution
 - Deemed interchangeable = Substitution

The same INN is necessary, but by itself, does not determine interchangeability



Pharmacovigilance

Pharmacovigilance

- Both brand and generic manufacturers must comply with the **same** pharmacovigilance requirements
- Track & Trace is critical
 - Requires an effective system that records upon dispensing the name of drug, manufacturer, strength and lot number
 - For rare events, and to enable earlier detection, pooling of data by the active ingredient (enabled by a common INN) will raise a flag if there is a safety problem related to pharmacological class
 - If the problem is product specific, track and trace provide product identity by use of manufacturer, lot number and/or NDC number

MEDWATCH

U.S. Reporting System for Adverse Events

- Safety Information and Adverse Event Reporting Program: FDA's "Medwatch" forms used for reporting adverse events ask that reporters specifically provide "**Name, Strength, Manufacturer, Lot Number and NDC** (from product label)" for the suspect product.

MedWatch Home Page - Microsoft Internet Explorer

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Address http://www.fda.gov/medwatch/

FDA U.S. Food and Drug Administration Department of Health and Human Services

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Join the E-list
Get safety alerts by e-mail

What's New

[Nortrel 7/7/7 Oral Contraceptive \(norethindrone and ethinyl estradiol tablets, USP\)](#) - Recall of 3 lots due to improper sequence of tablets, increasing risk of pregnancy. (Posted 7/11/2003)

[Topamax \(topiramate\) Tablets/ Sprinkle Capsules](#) -

Safety Information Medical Product Reporting

Done Internet

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

FDA USE ONLY

Triage unit sequence #

Page 1 of 1

A. PATIENT INFORMATION

1. Patient Identifier 2. Age at Time of Event, or Date of Birth: 3. Sex Female Male 4. Weight lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

In confidence
Check all that apply:
1. Adverse Event Product Problem (e.g., defects/malfunctions)
 Product Use Error Problem with Different Manufacturer of Same Medicine
2. Outcomes Attributed to Adverse Event (Check all that apply)
 Death (mm/dd/yyyy) Disability or Permanent Damage
 Life-threatening Congenital Anomaly/Birth Defect
 Hospitalization - initial or prolonged Other Serious (Important Medical Events)
 Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (mm/dd/yyyy) 4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, including Dates

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
 Yes No Returned to Manufacturer on: (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 #2
2. Dose or Amount Frequency Route
#1 #2
3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 #2
4. Diagnosis or Reason for Use (Indication)
#1 #2
5. Event Abated After Use Stopped or Dose Reduced?
#1 Yes No Doesn't Apply
#2 Yes No Doesn't Apply
6. Lot # Expiration Date
#1 #2
7. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # Lot #
Catalog # Expiration Date (mm/dd/yyyy)
Serial # Other #
5. Operator of Device
 Health Professional
 Lay User/Patient
 Other
6. If Implanted, Give Date (mm/dd/yyyy) 7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
 Yes No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (evolve treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address
Phone # E-mail
2. Health Professional? Yes No 3. Occupation
4. Also Reported to:
 Manufacturer
 User Facility
 Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:

Name, Strength, Manufacturer

Lot #

Expiration Date

NDC # or Unique Identifier

Pharmacovigilance



- Label must Contain:
 - Manufacturer
 - INN and brand name (if applicable)
 - Strength
 - Lot number
 - Expiration date
 - NDC Code*

*NDC – identifies manufacturer, product, and packaging



Pharmacovigilance: Program Attributes

- Track and trace dependent upon multiple factors
 - INN
 - Manufacturer
 - Lot number
 - NDC number
 - Well-defined pharmacovigilance system
 - Post-approval adverse event reporting requirements same for brand and generic
- Unique brand name or INN alone is not adequate to assure robust pharmacovigilance reporting or assessment

U.S. does not depend on INN for tracking/traceability



Summary

Summary

- Access to affordable medicines is critical to global healthcare system
 - INN should not be changed in order to create unnecessary barriers to access
- The purpose of INN is to identify the active ingredient - pharmacovigilance and interchangeability issues must be addressed elsewhere

Summary

- Patient safety is helped, not hurt, by common INNs for products with the same active ingredient
- National regulatory authorities are in the best position to determine interchangeability of brand and generic biopharmaceuticals
- GPhA continues to support the original purpose of INN and its implementation for generic biopharmaceuticals

