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EUROPEAN GENERIC MEDICINES ASSOCIATION



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EGA's Rationale For Continued Application Of WHO's Longstanding INN Naming System To Biosimilars

Geneva, November 13, 2006



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- **Introduction**
- **The WHO INN Naming System**
- **Science and Technology Supports Continuation Of The INN System**
- **Implications for INN Users**
- **Conclusion**



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Introduction

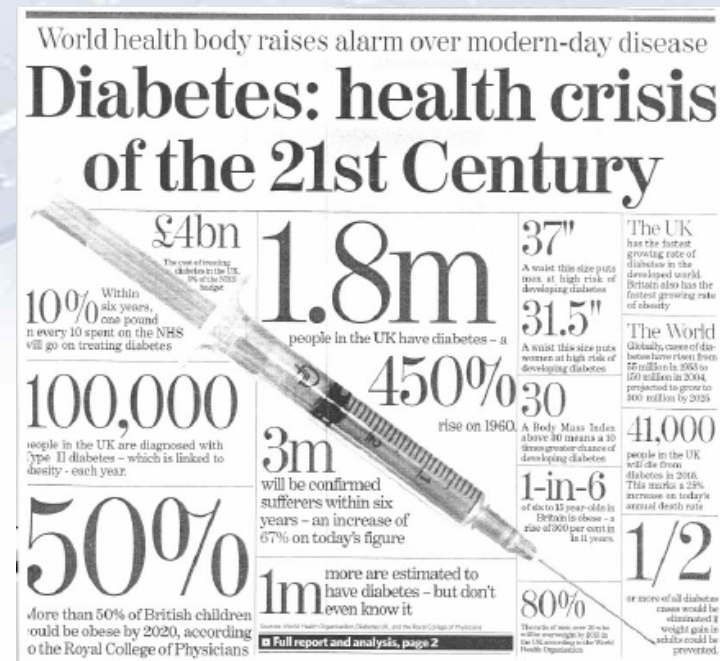


INNs for Biopharmaceuticals are Critical for Public Health

Biopharmaceutical market and pipeline

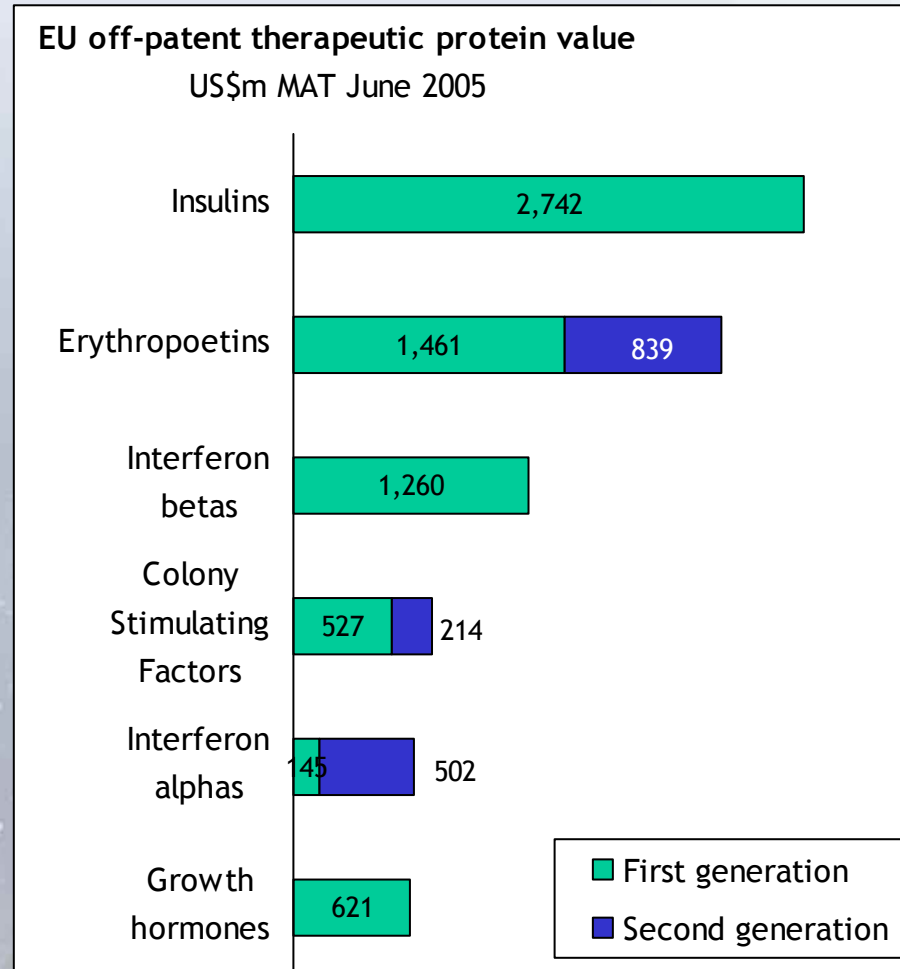
- 6% of marketed products
- 40% of phase 3 pipeline
- Healthcare cost of biopharmaceuticals growing at over 20% each year; US\$40b plus already
- Targeting chronic diseases of aging and lifestyle
- Growing concerns of restricted access to medicines

Source: The Independent, October 2005; Datamonitor; IMS; EGA analysis





Biosimilars can make a Real Difference to Patients



Impact of biosimilars in EU

- Large ...
 - Top 6 off-patent products >US\$6.7b pa (>+20% pa)
 - 30% price reduction >\$2b additional funds pa
74% more diabetics
500,000 chronic kidney patients
- ... and real
 - 2m Polish diabetics
 - Gensulin launched by Biotin 2001 - 28% price decline that year
 - Polish healthcare saved €90m in four years; now saving €65m pa

Source: IMS, Newport, Biotin, EGA analysis



Why are Biopharmaceutical INNs Suddenly an Issue?

- Biotech companies have been developing novel biopharmaceuticals for 25+ years; they've been included in the INN system for over 50 years
- They have changed manufacturing processes and sites many times, claiming INN identity from one process/site to the next each time. In many cases, the same INN has been granted to multiple manufacturers with no comparability exercise
- For the first time, someone other than the originator company is using the same comparative analytical technology and clinical testing to claim INN identity to the originator company product
- This has highlighted some minor inconsistencies in historical application of the INN nomenclature system
- It has also led to attempts to modify the INN nomenclature system to achieve objectives such as drug safety for which it was never intended



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Scientific Overview

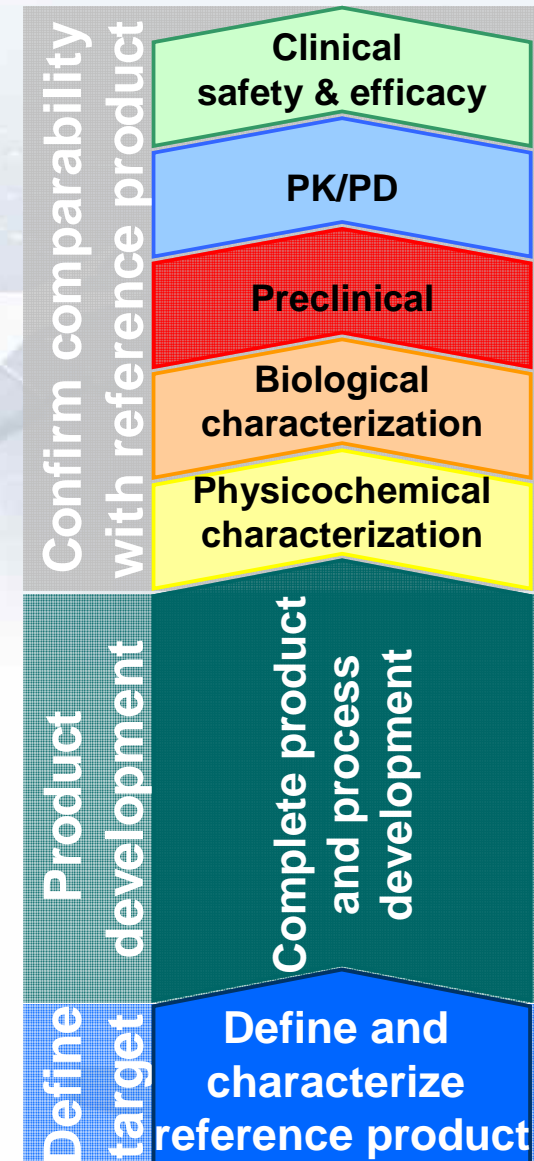
- There is no data or rationale supporting a change in policy, and biosimilars are entirely compatible with WHO's existing INN rules
- There is no basis for expecting a “public health crisis” to emerge from biosimilars carrying the INNs of their reference products
- State-of-the art analytical technologies allow a detailed physicochemical and biological characterization and a sound scientific judgment on comparability based on Design Space
- Regulatory Authorities can decide if comparability has been demonstrated or not, and if a product thus is a biosimilar
 - If product is comparable, the same INN applies
 - If product is not comparable, a new INN should be sought from WHO
- WHO does not evaluate comparability data and thus cannot assign an INN for a biosimilar prior to the regulatory authority's decision
- Assessment and approval of biosimilar medicinal products should proceed independently from WHO's naming process



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Biosimilars are Biologics Too

- The goals of drug development for both originator and biosimilar products are
 - Safety
 - Reproducibility
 - Efficacy
- Biosimilars also require
 - Thorough characterization
 - Comparability to an approved reference product
- Legislation and guidelines are in place in the EU, and in the US for certain reference biologic drug medicinal products
- The concept of comparability and design space is important for all sponsors and enable improved processes, more efficient manufacture, and sites changes





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The WHO INN Naming System



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Scope of WHO INN Program

Within The Scope

■ Naming system for pharmaceutical substances and not drug products

- An internationally-harmonized nomenclature is important for the clear identification, safe prescribing, and proper dispensing of medicines to patients
- INNs enable communication and exchange of information amongst health care professionals and scientists worldwide

Outside Of The Scope

■ Traceability, Pharmacovigilance and Substitution

- Must account for formulation, packaging materials, delivery system, route of administration, etc.
- Must be assured at the dispensing level through recordkeeping oversight by national health authorities
- INN is utilised in, but is not the basis of these systems



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Scope of WHO INN Program

■ Should the WHO INN system be changed? No.

- First, define the problem, and then decide if it is fundamental to the system or due to inappropriate implementation
- Past issues appear to relate to implementation - e.g., inconsistent applications of INNs by companies, regulatory authorities, and other INN users
- Inappropriate use of INNs by health care professionals is an issue that can be addressed at the dispensing level, and this problem would not be solved by creating distinctive INNs for biosimilars
- New INNs for biosimilars would create confusion

■ Can issues be prevented in the future? Yes.

- No issues have been identified for non-glycosylated proteins
 - No inconsistencies in the past
 - Non-glycosylated, homogeneous products can be characterized completely (although many were not at the point of approval originally and it is not required by regulatory authorities)
 - Well accepted practice by all INN users (scientists, health care professionals, regulatory authorities)



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Scope of WHO INN Program

■ Can issues be prevented in the future? Yes.

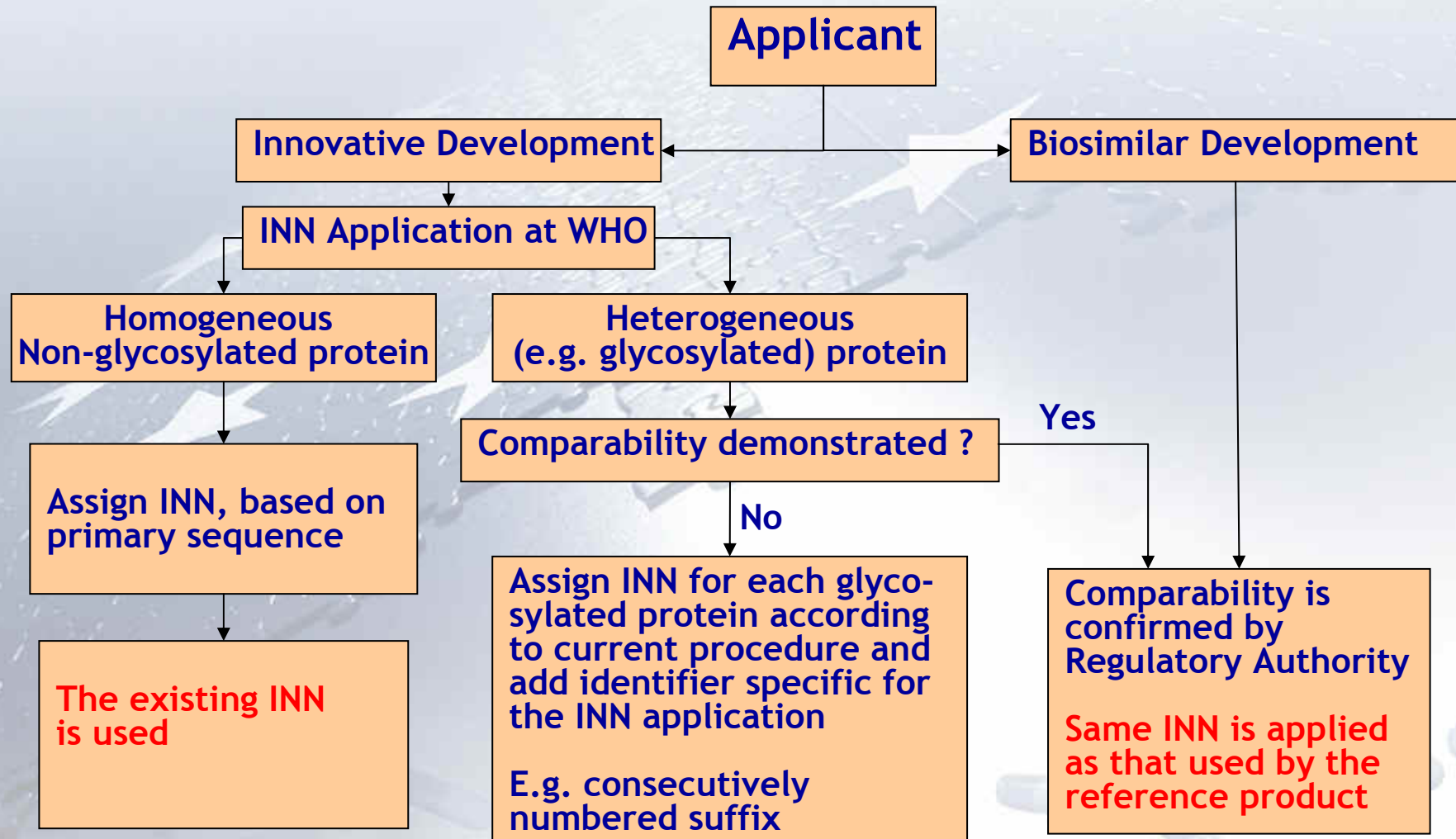
- Greater clarity useful for heterogeneous substances, e.g. glycosylated proteins
- **Biosimilar products (or after manufacturing changes for originator products)**
 - Same INN if comparability is demonstrated
 - Based on sound science and data from head-to-head studies
 - Implements EU biosimilars legislation and matches concepts in current biosimilar guidelines
- **If there is no comparator the product cannot be a biosimilar and would require a new INN from WHO**
 - For related products, especially currently-marketed biologics, possible options include extending the INN with a specific identifier, e.g. specific suffix to same core for each subsequent sponsor



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WHO INN Program - A Way Forward

How to prevent issues in the future?





WHO INN Program - A Way Forward Applying Comparability Concepts

■ Advantages Of Continuation

- Prevents inconsistent use of INNs
- Facilitates implementation of pharmacovigilance (pooled data)
- Enables existing INNs for non-glycosylated proteins
 - Requires new names for complex biologics, such as glycosylated proteins, unless compared to a reference with an established INN
- Addresses naming of biosimilars using comparability criteria
- Enables differences in complexity to be accommodated
- Allows technology to progress with thorough characterization in head-to-head studies critical to establishing comparability
- Defers to regulatory authorities, who have expertise, mandate, and necessary information available, on the comparability assessment
- Avoids conflict with existing scientific nomenclature (e.g. alfa-, beta protein subunits)

■ Disadvantages Of Continuation

- Existing glycosylated proteins with the same INN will have to be compared and/or one given a new INN



WHO INN Program - Same Standards for All Sponsors

- **Advantages of Redesigning WHO's INN Program and Assigning Distinct INNs for ALL Biologics**
 - Appears easy to implement, but would require renaming *all* existing biologics, except perhaps the first in class, as “grandfathering” would not be a legitimate option
- **Disadvantages of Redesigning WHO's INN Program**
 - Undermines the concept of comparability on which changes in innovator processes as well as biosimilars are based today
 - Fosters confusion among health care professionals and regulators
 - Prompts misinterpretation of different INNs assigned to a biosimilar and its reference product creating misperception that a biosimilar is dissimilar instead of similar to its reference product
 - Fails to differentiate between different originators and a biosimilar, the latter of which has established comparability to a specific reference
 - Different originator substances, carrying the same INN, may have very different properties from each other
 - Risks loss of pooled data available for products with common INNs - a patient safety issue
 - Undermines the value of the entire INN naming system globally



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Science and Technology Supports Continuation Of The INN System



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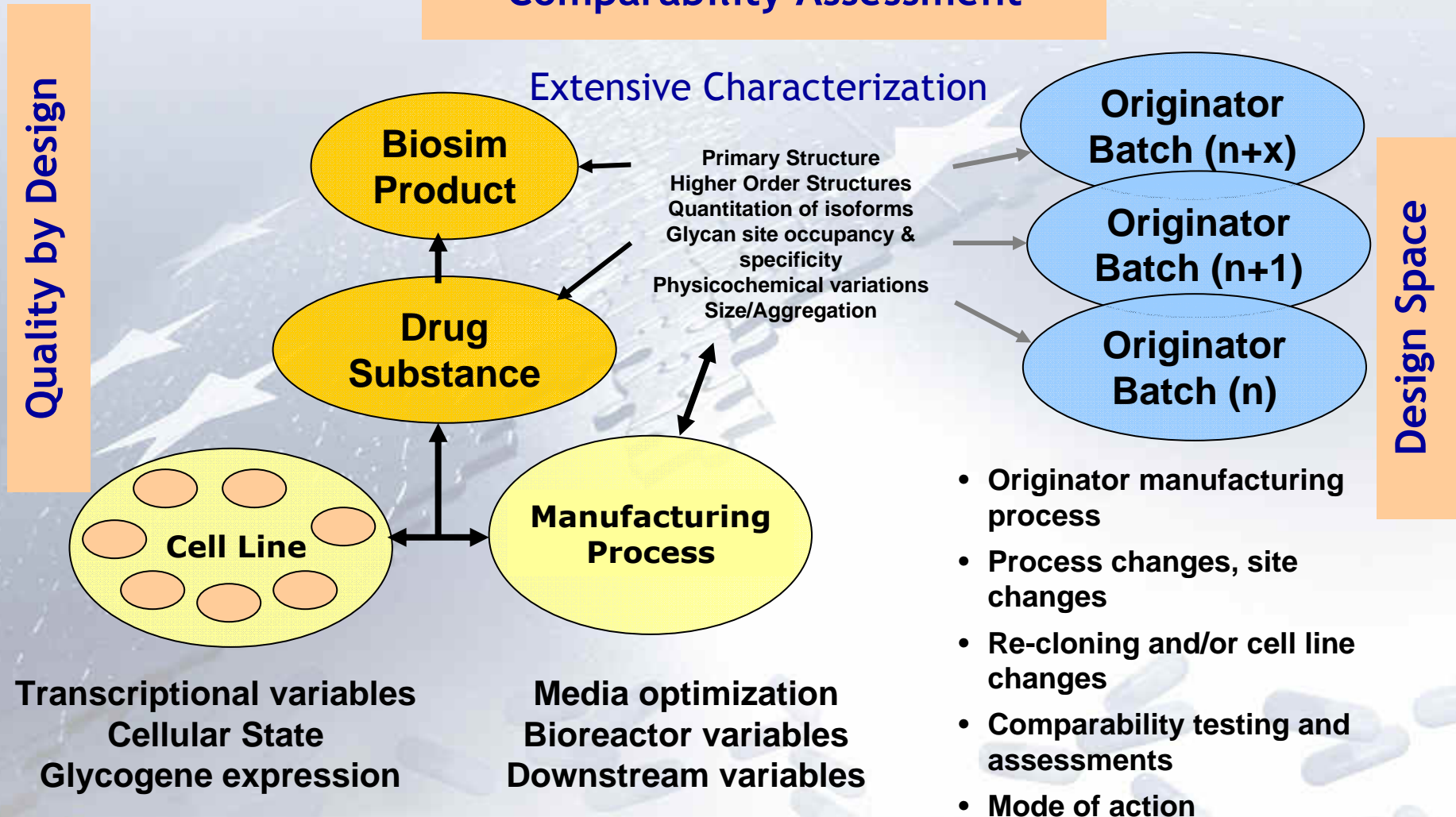
The development of a biosimilar product is targeted to match the reference medicinal product through the application of state-of-the-art science and technology in head-to-head studies



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Quality By Design & Design Space

Comparability Assessment



Defining the Design Space

Example of Product Analysis: single parameter data

Glycan	Method	Batch x1	Batch x2	Batch x3	Batch x4	Batch x5
Man5	MALDI	3.1	3.7	7.4	5.4	2.6
G0-GlcNAc	MALDI	7.1	11.6	9.5	11.6	5.0
G0-Fuc	MALDI	4.0	4.5	4.4	3.9	6.4
G1-GlcNAc	MALDI	1.3	1.7	1.8	1.4	1.0
G0	MALDI	69.9	64.4	61.3	65.2	69.2
G1	MALDI	14.1	13.2	14.7	11.8	15.1
G2	MALDI	0.8	0.9	0.9	0.7	0.7

Qualitative and quantitative analysis and interpretation of relevance regarding quality and mode of action

ICHQ8: „The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.“



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Quality By Design

- **Manufacturing process is pro-actively 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.
 - In vitro biological testing, in vivo PK/PD studies, clinical trial
- **Continuous feedback between process development and high performance analytical techniques result in the required specific selection of**
 - Cell line
 - Raw materials, media
 - Upstream and downstream process parameter
 - Control of critical variables
 - Formulation, primary packaging, delivery system



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Non-Glycosylated Proteins

- **Current methods allow complete characterization of the chemical structure of non-glycosylated proteins**

Parameter	Test	Resolved species
Primary structure incl. disulfide bridging	Orthogonal peptide mapping with UV and MS detection Mass spectrometry: - MS/MS sequencing - LC-ESI-MS - MALDI-TOF-MS N-terminal Edman sequencing	Complete evaluation of primary sequence and post translational modifications possible
Higher order structure	Circular dichroism 1D-NMR Bioassay	Folding

- **The use of the same INN for products of different manufactures has been accepted by competent regulatory authorities (e.g. somatropin)**



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Glycosylated Proteins

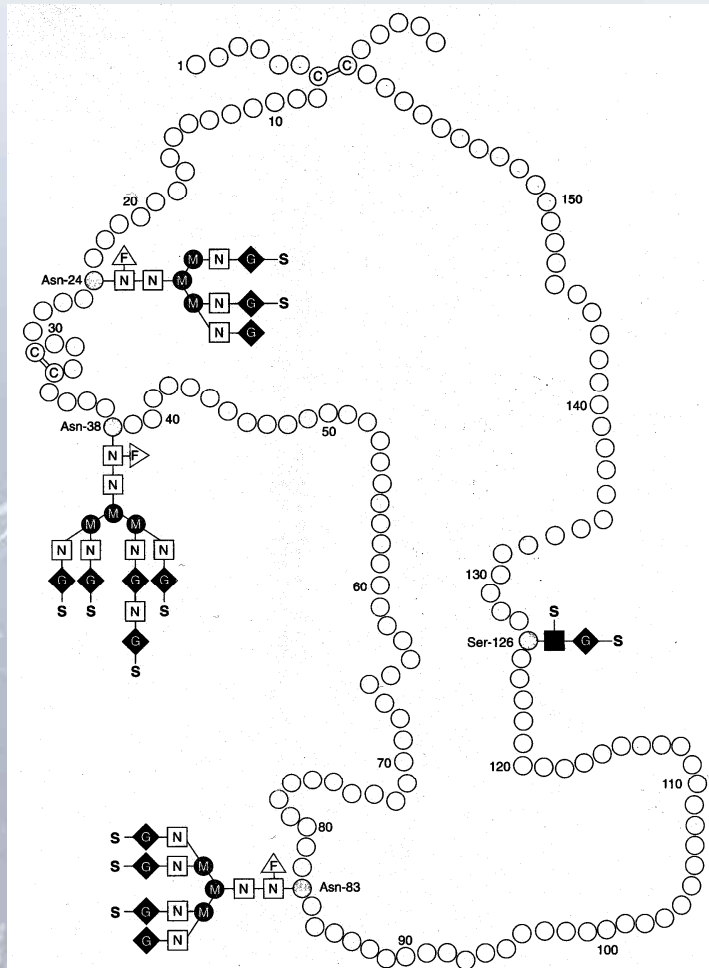
- **Therapeutic glycoproteins consist of mixtures of proteins with the identical amino acid sequence and different glycovariants**

- **Required parameters to define the glycosylation:**
 - Quantitative composition of the individual glycan structures
 - Structural identification of the single glycans
 - Complete chemical structure
 - Site occupancy

- **Glycoproteins can readily be characterized by current state-of-the-art analytical methods**



Glycosylated Proteins



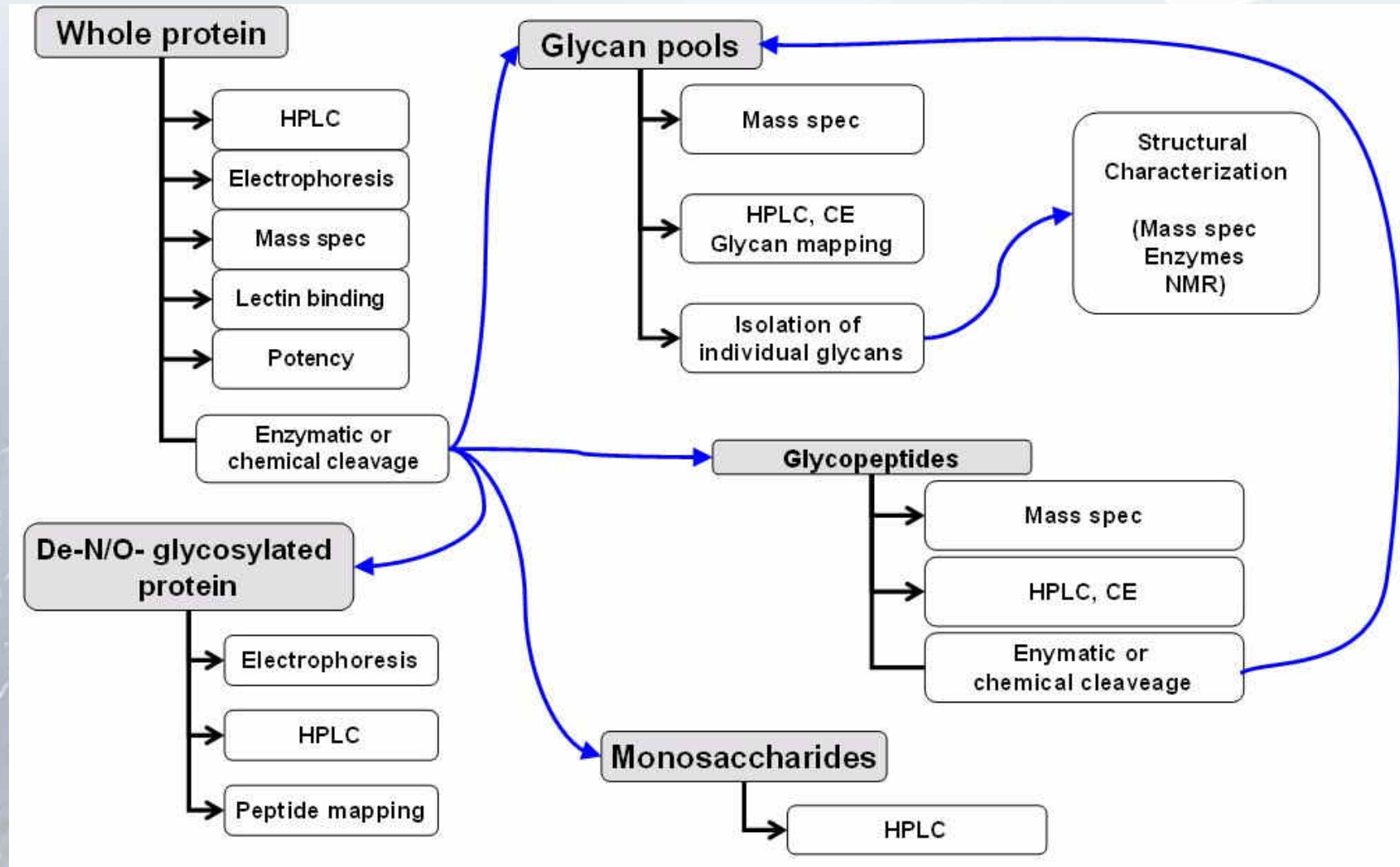
■ Example for typical therapeutic glycoprotein

- Erythropoietin frequently used as a model protein for glycan characterization
- 4 glycosylation sites
- 3 N-glycans (complex type)
- 1 O glycan
- Suitable host: CHO (human-like glycosylation)



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Glycosylated Proteins - Analytical Methods



Advances in Analytical Technologies for Glycan Proteins (Examples)

Technique	Properties	Advances	Added value
HPLC, Capillary electrophoresis	Glycan separation	Stationary phases, instrumentation; miniaturization	Increased resolving power, improved precision; increased sensitivity, hyphenation to MS
ESI-MS MALDI-MS	Glycan structure	Ionization modes, mass analyzers MS/MS and MS ⁿ capabilities, Data evaluation	Increase of mass resolution and sensitivity Structural characterization of main structure and of modifications
Enzymatic sample preparation	Glycan structure	Enzymatic toolbox	Structural characterization

Comparability can be Shown

- Comparability can be demonstrated today applying state-of-the-art technologies
- The decision as to whether a sponsor has demonstrated comparability is a regulatory determination
- If a sponsor fails to demonstrate comparability in the judgment of a regulatory authority, that manufacturer will apply for a new INN from WHO

How Close is Close Enough? Demonstrating Comparability

- The criteria for the comparison of the biosimilar candidate and the reference product are based on
 - Understanding batch-to-batch variability of the reference medicinal product
 - Classification of the product variants into product-related substances or impurities (ICH Q6B)
 - Level of understanding the relevance of subtle differences on safety/efficacy (ICH Q5E)
- **The manufacturing process for the biosimilar is systematically designed to meet the required comparability criteria**
- ⇒ **Design Space Concept**

Scientific Conclusions - Role of the Regulatory Authorities

- Current analytical technology enables physicochemical characterization which along with preclinical and clinical studies provide data to demonstrate comparability
- Manufacturing and characterization of biosimilars, like all other biologics, will comply with established high scientific and regulatory standards
- Regulatory authorities have the expertise and the data to make the judgment of whether comparability has been demonstrated between a biosimilar and its reference product
 - If comparability is achieved, the product is a biosimilar and **will be designated with the same INN**
 - If not, the product is not a biosimilar, and application for a different INN will need to be submitted to WHO



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Scientific Conclusions - Role of WHO

- WHO does not need to repeat the technical review done by the regulatory authorities for a biosimilar
- Assessment and approval of biosimilar medicinal products by the regulatory authority can continue to occur
 - If comparability is demonstrated, the EMEA will indicate this conclusion in its assessment, and the product will be designated with the same INN
 - If comparability is not demonstrated, the sponsor will apply for a new INN from WHO
- EGA does not see any reason to change the INN program due to the advent of biosimilars
- For proper pharmacovigilance and traceability, a combination of INN with the brand name and/or company name must be recorded when a medicine is dispensed



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Implications For INN Users





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Consequences of INN System for WHO

Same INN if comparability demonstrated (EGA)

- No change, beyond any minor corrections to the existing nomenclature system
- Consistency retained between drug and biopharmaceutical nomenclature systems
- Regulatory authorities do not need to compel companies to apply for INN until comparability is disproved; maintains separation of nomenclature and regulatory systems
- Continuity of INN name through successive manufacturing changes

Different INN irrespective of comparability (originator industry)

- Complete review of INN nomenclature decisions in all classes
- Drugs and biopharmaceuticals nomenclature will be different; biopharmaceutical INN naming will cease to be a classification system supporting research and communication within the scientific and medical communities
- Regulators will need to demand an INN before filing, placing WHO in a quasi regulatory position
- Concept of comparability is denied: changes in manufacturing site or process will require application for a new INN



Consequences of INN System for Regulatory Practice

Same INN if comparability demonstrated (EGA)

- Regulatory authorities must determine that product identity, and where asserted, comparability to a reference product, just as they do today for a novel medicinal product, generic drug or biosimilar
- WHO (INN) and regulatory determination of sameness will be aligned
- No need to review past INN naming decisions (unless the very limited errors such as IFN-beta-1a are to be corrected)
- No change to legal basis of approvals

Different INN irrespective of comparability (originator industry)

- Regulatory determination of comparability becomes irrelevant - every product from a different site will be deemed different
- No clear alignment of INN naming and regulatory determination of comparability eg for biosimilars
- Extensive re-naming of existing marketed products will be required (growth hormones, insulins, etc)
- INN will need to change whenever a site change or process change occurs
- Complete review of legal basis of biosimilar approvals required



Consequences of INN System for Drug Safety Practice

Same INN if comparability demonstrated (EGA)

- No compromise - INN + brand name + batch number + MA number + manufacturer still available for full traceability and adverse drug event reporting
- Ensures that class effects are easier to trace and communicate through common INN name

Different INN irrespective of comparability (originator industry)

- Will not correct today's deficiencies in adverse event reporting and traceability since reporting is often not by INN anyway; front line inaccuracies are the cause of poor traceability today
- Class effects will be harder to coordinate, track and communicate

**INN is a nomenclature system for a drug substance
INN never was to, and was never intended to, provide
the sole the basis for pharmacovigilance of drug product
Deficiencies in drug safety systems need to be corrected
at front line/national legislation level**

Consequences of INN System for Clinicians and Patients

Same INN if comparability demonstrated (EGA)

- No change: continued assurance they are using the same medicine from prescription to prescription

Different INN irrespective of comparability (originator industry)

- Significant confusion as a large number of product names are re-aligned with the new practice and as products change INN (and by definition brand) during lifecycle

**INN is a nomenclature system for a drug substance
INN never was, and was never intended to be, the basis for clinical
decisions about drug product use**



Consequences of INN System for Prescribing/Dispensing

Same INN if comparability demonstrated (EGA)

- No change - prescribing/dispensing will remain a matter of national policy, to be determined by clinicians and competent professionals in accordance with clinical practice
- In most cases, biopharmaceuticals are used in specialised care settings, where transparent prescribing/dispensing is critical to public health and patient outcomes

Different INN irrespective of comparability (originator industry)

- Major changes in national legislative frameworks would be required, irrespective of local clinical decisions on public health or individual patient treatment

**INN is a nomenclature system for a drug substance
INN never was, and was never intended to be, more than a single
valuable component of robust track and trace systems for products
dispensed by pharmacists**



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Conclusion





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Purpose of INN

Is ...

- Identification of drug substance
- Nomenclature: means of classifying and cataloguing pharmacological classes

Is Not ...

- Identification of a medicinal product or its impurities
- Statement of therapeutic equivalence or otherwise of a medicinal product
- Means of managing the practice of medicine

INN is a nomenclature system for a drug substance
The INN has never been the primary means for clinical decisions by physicians, nor more than a single valuable component of robust track and trace systems for products dispensed by pharmacists

Demonstrating Comparability is Possible

- Biopharmaceutical INNs refer to a specific profile of micro-variations at the molecular level
- Today's analytical technologies allow a detailed physicochemical and biological characterisation and a sound scientific judgement on comparability between one biopharmaceutical and another reference product
- This has been the basis of comparability allowing manufacturers to retain the same INN designation through multiple site and process changes
- Manufacturing and characterisation of biosimilars comply with the highest modern scientific standards and a more rigorous comparability exercise than original biopharmaceutical products
- Regulators have, and have asserted, the competence to determine comparability - there is no point duplicating this competence at WHO where it does not exist today

Denying Comparability with INNs Creates Issues and Solves None

Problems created

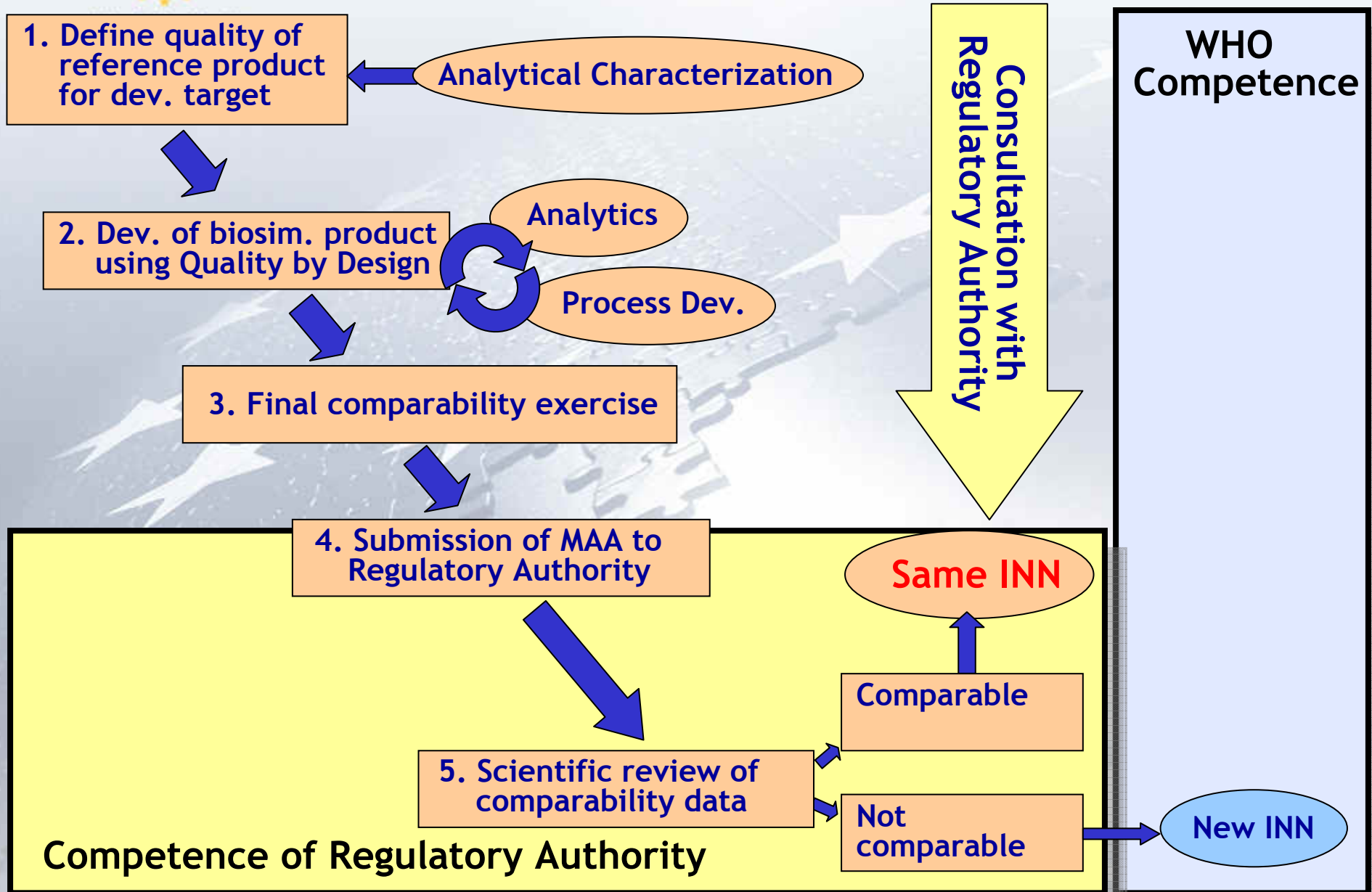
- Large retrospective renaming of existing products: confusion at patient and healthcare professional level
- Change of INN at every change in manufacturing process: confusion again; undermines regulatory basis of process variations
- Reduced visibility of class effects (positive and negatives)
- Inconsistencies between drugs and biopharmaceuticals - no nomenclature system for latter
- Denies local legislatures authority to manage prescribing and dispensing

Problems 'not solved'

- Pharmacovigilance: front line traceability systems limitations not solved
- Non-transparent prescribing/dispensing: already appropriately dealt with at national law level
- No change in risk of 'unknowns' associated with biopharmaceuticals (biosimilar or otherwise)



Conclusion



EGA Position on Biopharmaceutical INNs

- Existing INN nomenclature rules are adequate
- No reason to deny any active biopharmaceutical substance the same INN as another if supported by adequate comparability studies
- Regulatory authorities are already equipped to determine comparability and should be recognised as the competent authority to make definitive comparability rulings
- WHO should assign an INN name in line with existing or evolved nomenclature rules if
 - Comparability to another product IS NOT asserted
 - Comparability to another product IS asserted BUT a competent regulatory authority, after due enquiry, has found to the contrary
- Any alternative that **REQUIRES** a biosimilar biopharmaceutical to have a separate INN name **IRRESPECTIVE** of the comparability exercises that have been conducted will, in addition to being scientifically unsupportable, have negative consequences on users of INNs



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Back Up



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Comparability

Comparability evaluations should follow the principles laid out in ICH guideline Q5E (“Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process”):

“The demonstration of comparability does not necessarily mean that the quality attributes [...] are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy [...].”