Supporting Safe and Effective Biosimilars: the role of NIBSC

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Meenu Wadhwa
An introduction to NIBSC  
(a division of the MHRA)

A UK government funded laboratory with a statutory function in the control and standardization of Biological Medicines, effected by:

- Establishment of biological standards and reference materials
- Batch release of vaccines and blood products
- Underpinning R & D
- Strategic alliances with major stakeholders (eg, WHO, Pharmacopoeias, other regulators)
How do these core activities translate into a work program in the specific area of Bio-similars?
Biosimilarity

1 The concept

-A regulatory concept which seeks to extend the “generics” paradigm into biological medicines

-Recognises complexity of biological medicines and production processes with enhanced requirements

-Based on demonstration of similarity to an existing (comparator) licensed product

-Additional clinical testing specified in guidelines
Biosimilarity

2 Global significance

- A European concept, but adopted (with minor differences) in most global regions

- Applicable at patent expiry

- Early authorizations for traditional products (EPO, GH), but increasingly extended to next generation products (pegylated cytokines, MAbs, fusion proteins)

- Widely recognised as being essential to public health by promoting affordable access to essential medicines
Biosimilarity: Essential supporting activities

- Providing essential standards (reference materials)

- Understanding similarity as an analytical concept (identical vs similar vs different)

- Understanding bio-similars in clinical application
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Standards for biosimilars

NIBSC WHO International standards are usually Bio-potency standards, established to support the performance of regulatory bioassays, and to define units.

Determination of biological activity remains an essential component of the regulatory approach to biologicals.

Drug development
Setting quality specifications (e.g., IU/mg)
Dosing and labelling (increasingly less common)
Batch release/control criteria

Regulatory bioassays in these contexts would be expected to be traceable to WHO international standards. High level guidelines and requirements usually reflect this.

Logically, bioassays for Bio-similar products might be expected to be supported in the same way.

The current Bio-similar environment has challenged this expectation.
- The first generation of bio-therapeutic products were recombinant DNA versions of existing bio-molecules (insulin, growth hormone, interferons, erythropoietin etc)

- International Standards and units of bioactivity had already been established for these molecules

- Usually, separate International standards for the recombinant DNA versions were established, with the unit in some way traced or related to the previous “natural” IS

- Recombinant therapeutic products were traced to the new recombinant IS’s

- The well recognised hierarchy was established
“Next generation” products include:

- Biosynthetic structural variants (eg darbopoietin)
- Chemically derivatized natural molecules (eg pegylated interferons, filgrastim)
- “Natural” molecules with no natural equivalent (monoclonal antibodies)
- Artificial constructs which don’t exist in nature (receptor-Fc fusion (proteins))

In most cases, licensed products are brought first time to the market without reference to International Standards, as they don’t exist.
Reference standards for “New Biologicals” and changes in the drug development timeline

1. A traditional Biotech drug; erythropoietin

- **1967** – first IS for EPO (natural) defines unit of biological activity
- **Mid-1980’s** – EPO cloned and first recombinant products developed. Activity traced to original IS
- **1990’s** – 1st IS for recDNA EPO, replacement IS’s and regional and Pharmacopoeial reference standards, all with traceability to original IS
- **Currently** – development of bio-similar EPO products. Unit of activity remains continuous with original unit, and internationally harmonised
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2. A “new biological” eg a monoclonal antibody

   No natural material, and hence no pre-existing activity unit
   
   ▶
   
   Drug discovery and development take place without international bioassay standards. Standardization is internal, and meets requirements of regulators
   
   ▶
   
   Product life during patent protection. Single manufacturer situation. No IS’s or other public bioassay standards needed.
   
   ▶

   Bio-similar or other copy products developed and licensed.

   Requirement to demonstrate bio-similarity with respect to Reference Medicinal Product

   ▶

   If an IS is needed at all, it is needed here. Is it needed?
Standards for biosimilars

As new biologicals, eg Monoclonal Antibodies, approach or pass patent expiry, and become the subject of Bio-similar interest

As Biologicals, there would an expectation that the biological activity is measured in units, and is traceable to WHO International Standards

The requirement to compare the activity of a candidate bio- similar with a reference medicinal product has lead commentators to express the opinion that reference standards are not necessary as the Reference product serves as the *de facto* reference standard

This position is further supported by the fact that current medicines of interest were successfully licensed without IS’s
Invoking this argument, innovator manufacturers have been reluctant to donate candidate materials for the purpose of establishing International standards for Bioassay of MAbs.

On the other hand, other stakeholders (eg pharmacopoeias, regulators) are keen to see the development of International Standards for new Bio-similars, and expect this to be part of the WHO program going forward.
NIBSC and WHO are currently working to establish in the public domain the principles that:

The reference product and the reference standard are different things.

- the reference product serves to define the quality criteria that the candidate must meet, a function that the reference standard does not serve

- The Reference standard serves to define and calibrate the performance of the test measurement system, a function that the reference product cannot serve
We are confident that for Biosimilars such MAbs (eg Rituximab) we will be able to establish a program of WHO Bioassay standards, to define the IU in potency assays.

Establishment of reference standards for physico-chemical assays, which can be used to define quality criteria such as purity or identity, will be more difficult, and is likely to be resisted by some stakeholders.

Similarly, there have been many calls, particularly from developing Biotech industries, for the public availability of *reference medicinal products*. This has been, and will probably continue to be, resisted.
Biosimilarity: Essential supporting activities

- Providing essential standards (reference materials)
- Understanding similarity as an analytical concept (identical vs similar vs different)
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Pegylated G-CSF: a test case for standardizing the biological activity of a derivatized molecule

-Pegylated filgrastim (GCSF) is a successful (extended half-life) licensed product approaching patent expiry

-Subject of intense biosimilar activity

-As a biological, there will continue to be an absolute requirement to demonstrate biological activity in a validated bioassay

-An international Standard is necessary
The pegylated molecule has qualitatively identical activity to the un-pegylated form.

In principle, the activity of PEG GCSF could be standardized in terms of GCSF, and early product did so.

These products are intended to have different biological activities in man and such an approach is both illogical and risks clinical misunderstanding.

A problem of both practice and general principle requiring investigation and solution.
An extensive International Collaborative Study was conducted to investigate three possible approaches:

- Expressing the activity in terms of GCSF (ie no new standard needed)

- Establishing an independent standard for PEG GCSF without reference to the GCSF standard

- Establishing an independent standard for PEG GCSF, but with a statement allowing traceability (but not conversion) to the GCSF unit
Is Filgrastim a suitable Bioassay standard for pegylated filgrastim? (Meenu Wadhwa, WHO 2013)

Comparison by cell proliferation bioassay of the International Standard for Filgrastim with four preparations of pegylated filgrastim (N-term linkage, 20K PEG)

Assays are valid in terms of parallelism and linearity
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Assays are valid in terms of parallelism and linearity

Assay of two pegylated preparations against a candidate pegylated filgrastim reference standard

Assay of three pegylated preparations against a non-pegylated filgrastim reference standard

Even though all assays are valid, between-assay agreement is significantly improved when a “like” reference standard is used.

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In this case there are two options:

Define units in terms of the parent molecule using only one specified assay method

Or

Have a method-independent unit, in which case you need a specific standard for Peg-Filgrastim

Assay of two pegylated preparations against a candidate pegylated filgrastim reference standard

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The study was innovative and essential because it:

- Established the International Standard for an essential Biosimilar medicinal product

- Equally important, established at WHO the principle, for the first time, of how to go about this kind of standardization exercise which will be increasingly important as such products are extended in scope
Specific standards for pegylated forms unlikely to be a generic solution, even within a single class of medicines.

Pegylation may vary between site of derivatization, coupling chemistry and PEG structure. Different Pegylated Interferon-alpha 2a for example may be as different from each other as they are from non-derivatized Interferon-alpha 2a.

Different stakeholders have produced guidelines which are not entirely consistent in their recommendations.

It is likely that most simple, first generation molecules will be progressively replaced by derivatized versions. The derivatized units issue will become major and needs to be incorporated into the WHO biological standardization strategy, decision-making paradigm, and technical guidance documents.
Biosimilarity: Essential supporting activities

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Example: Interferon-β

IFN-β –Two innovator IFN-β-1a products are approved for treatment of multiple sclerosis

We compared the in vitro potency and molecular properties of innovator IFN-β-1a products with four non-innovator products:
Potencies of IFN-β products

Different IFN-β products

**Immunoblot**

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**HPLC Profile**

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- Avo
- Cla
- Cin
-Similarity as an analytical concept (identical vs similar vs different) is by no means well understood,

-Nor is there a common understanding of the significance biological and physico-chemical differences between preparations such as those shown for IFN-beta

-Continued studies of this type will be essential in further development of the concept of biosimilarity
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Biosimilarity: Essential supporting activities

Clinical evaluation will focus on both efficacy and safety.

For biologicals, one of the most consistently observed adverse reactions is immunogenicity in the patient.

For biosimilars, licensed with restricted clinical studies, immunogenicity is a highly significant concern.

NIBC role is both to seek to understand the underlying causes of immunogenicity, and also to support its accurate and reproducible measurement.
Immunogenicity (1):
Erythropoietin and antibody induced pure red cell aplasia

Binocrit approved - 2007
Rigorous physico-chemical, biological characterization & clinical trial data

Safety Study for Binocrit Suspended
- No increased immunogenicity from IV use in patients with renal anaemia or SC use in cancer patients (both licensed)
- Postmarketing SC trial in previously untreated renal anaemia patients: two cases of neutralizing Ab

>60 PRCA cases identified in Thailand. 14 EPO products marketed. Link to product (s)?
Proposed 1\textsuperscript{st} WHO Erythropoietin (EPO) antibody Reference Panel

Meenu Wadhwa
Rationale

• Clinical success of EPO – several products available for anemia in renal failure and other clinical settings incl. cancers
• Small proportion of renal patients treated with EPO develop antibodies
  – neutralize all EPO products and endogenous protein causing pure red cell aplasia (PRCA) - life threatening and requires intervention.
  – rare with products in the western world but of significant concern as many EPO products with disparate quality on the market worldwide.
  – PRCA problem noted in Korea, Thailand
• Important to assess immunogenicity & test patients for EPO antibodies
• Several methods in use - these differ in sensitivity and the types of antibodies detected. Currently, no universally accepted method or reference reagents
• Reference panel would standardize the testing for EPO antibodies across different assays and provide consistency in detecting/measuring EPO antibodies.
• ECBS : 2010
<table>
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Adapted from Mytych et al 2012
Panel for testing of human antibodies against EPO

**Strategy —**
- All MAbs (incl –ve control) lyophilised & suitability assessed.
- 4 serum samples (3 from PRCA, 1 –ve)
- Multi-centre international collaborative study
  - 18 labs – manufacturers, CROs, control and academics
  - 8 countries – Korea, Thailand, USA, UK, Switzerland, Japan, China, India

**Aims —**
- To compare a panel of EPO antibodies across available methods and assess their suitability for use as performance indicators
- To define the minimum acceptable potency/dilution if possible for the different antibodies
<table>
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<td>Flow cytometric bead array</td>
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<th>NAb Assay</th>
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<td>EpoR SPR+</td>
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All cell-based proliferation assays except for SPR+ which is non cell-based
Results

• Antibody Panel –
  Control MAb mostly negative (except direct/indirect ELISAs - 1:2 dil). For others, recognition varied on the assay and the affinity/isotype. Where recognised, titres varied between assays/labs. Generally, low affinity & IgM antibodies missed in most assays except SPR/RIPAs
  Binding assays –
  – Direct ELISAs - spurious results and very low titres; **OLD assay**
  – Bridging ELISAs did not detect B & C (low affinity); J, E & H (high affinity) not detected in 2 labs
  – Bridging ECL – slightly better than bridging ELISA; did not detect B
  – SPR - All abs recognised in all labs; similar titles seen.
  – RIPA – data varied among the 3 labs; all abs recognised in 1 lab; IgM variably recognised in 2 labs, B, C & G not recognised in 1 lab

• Serum Samples –
  – All 3 PRCA sera detected as +ve in all assays; -ve control sera as -ve
Results and Proposal

Neutralization data - generally less variable than binding assays

- **Panel** - Low affinity and IgM Abs – non-neutralizing/weakly neutralizing
- Other Abs – moderate/strong neutralizers.
- **Sera** - 3 PRCA sera: +ve in all assays; Control: -ve

Conclusion: Selection of an assay capable of detecting all antibodies (those representing early onset and mature responses) important. The panel will facilitate decision-making on assay selection and be useful for validation.

Proposal - Establish the antibody panel as the 1st WHO EPO antibody reference panel for selection and evaluation of the performance of EPO antibody assays, for assay validation and for standardization.
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Summary and Conclusions:

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Essential NIBS supporting activities

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