Planting a "non-biological" seed – will this meme persist?

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Abstract
Some word uses persist and some do not. Part of what makes use of a word stick is how catchy it is. This word is already used on our supermarket shelves. This proposed new use illuminates a small way in which language evolves. And it helps to compartmentalise differences between chemical and biological manufacture of pharmaceuticals. The question is, will this word use persist enough to enter common vocabulary? The word is *non-biological*.

Survival of the fittest was coined in 1864 by Herbert Spencer in *Principles of Biology*. He did this after he read *On the Origin of the Species* by Charles Darwin.[1,2] *Survival of the fittest* describes biological evolution through natural selection. *Meme* was coined by Richard Dawkins in 1976 in his book *The Selfish Gene*.[3] A meme transmits by natural selection analogous to that of biological evolution. Yet, a meme is an element of a culture or system of behaviour passed from one individual to another by imitation or other non-genetic means. It is a play on the word *gene*. New words and meanings enter the language as memes. They persist if they are catchy enough to enter common vocabulary.[4] In 1993, Mike Godwin proposed *internet meme*.[5] Richard Dawkins characterised *internet meme* as something deliberately altered by human creativity that goes viral on the internet.[5]

I have met scientists who coined phrases that stayed in their laboratories. For example, my PhD supervisor, Chris French, coined the phrase *bactin*.[6] It means any bacterial actin-like protein. To us *bactin* is an efficient word that conveys a great volume of meaning. Today, Bactin® is a registered trademark of an antibiotic.[7] This is similar to convergent evolution. Convergent evolution is the independent evolution of similar characteristics in a separate line. Like flight evolving independently in birds, bats, flying fish, and flying frogs. The word *bactin* originated in two places independently.

The motivation for coining *bactin* was to avoid saying the "bacterial actin-like protein" mouthful. At the time coining *bactin* was fun and witty. It was also a relief to have a shorter more practical word to describe the topic of my research. *Bactin* was catchy to us and I suppose the antibiotic marketers thought it was catchy too. They registered Bactin® as a trademark.

More practical word usage appears in the pharmaceutical industry. A common trait among these words and phrases is that they are less of a mouthful to say – *pharma* being one. Some of these words and phrases convey a great volume of meaning. They include *big data* to describe the extremely large data sets generated during drug development; *KOL* short for key opinion leader; *vax* for vaccine or vaccination; and *mAb* for monoclonal antibody. Enter *pharma buzzword bingo* into your favourite search engine and see what you come up with.

A case for using the term *non-biological drug*

This article presents a case for wider pharmaceutical industry use of *non-biological*. *Non-*

biological is self-explanatory. Something that is non-biological does not involve a biological system.

In the pharmaceutical industry, a biological is any drug manufactured from a biological source, e.g., vaccines, blood products, cells, allergens, genes, tissues and recombinant proteins (Table 1). Generally, *biological, biologic,* and *biopharmaceutical* are collective interchangeable terms meaning the same thing.[8] A biopharmaceutical is not any drug (chemical or biological) with an intended use in humans or animals.

The larger proportion of drugs manufactured use chemical means (Table 1). At times chemically manufactured drugs are referred to as *small molecule* drugs. This term is arbitrary. It refers to molecules below a range of 500 to 1000 Daltons depending on the reference.[9,10] Plus, some biological drugs are below this cutoff. For example, cerliponase alfa is a biological drug that is 59 Daltons.[11] Chemically manufactured drugs are also referred to as *more traditionally manufactured chemical* drugs. *Non-biological* is more practical to say.

I imagine some are saying "poppycock!"

Using *non-biological* is not being irreverent towards the scientific discipline of chemistry. Chemistry is in a less stable and more unpredictable higher order within biology. Various scientific disciplines mould molecular biology into a fascinating study to improve lives.

It is important to acquaint industry with the use of *non-biological*. The US FDA has a Non-Biological Complex Drugs (NBCDs) Working Group.[12,13] Non-biological complex drugs are nanotechnologies unable to receive comprehensive characterisation through physicochemical analysis (Table 1). Most traditionally manufactured chemical drugs (*non-biological drugs*) can receive comprehensive characterisation through physicochemical analysis. Yet, *non-biological* is not widely used to refer to the more traditional manufacture of chemical drugs.

Biological and non-biological drugs differ at molecular level

Biological drugs contain chemicals from the table of elements. Everything around us contains chemical elements. In routine life, we see chemistry in the animate that reproduce and in inanimate objects. (Figure 1).

Biological drugs consist of many more atoms compared to non-biological pharmaceuticals (Figure 2). They contain thousands of carbon atoms and have a higher molecular weight compared to a few carbon atoms and a lower molecular weight in non-biologicals. Biological molecules are generally larger than non-biological molecules and this alone makes them less rigid. Lower molecular rigidity has stability profile consequences to consider.[14]

Often, non-biological drug names contain a reference to chemical elements and functional groups. For example, acetylsalicylic acid (aspirin).

Where do biological drugs come from?

Recombinant biologicals are the highest proportion of biological drugs approved worldwide.[8] This classification includes monoclonal antibodies, hormones, clotting factors, enzymes, vaccines, nucleic acid-based products, and engineered cell-based products.[8] Indications are for cancer, inflammation-related diseases, haemophilia, diabetes, asthma, migraine, HIV, and inhalational anthrax.[8] Of 71 genuinely new biological active ingredients that came to market between January 2014 and July 2018, 62 were recombinant proteins.

The trend is to identify the genetic code of a natural source biological drug, whatever it is, and to create a recombinant form in the laboratory.[15] This is a more sustainable approach to using the natural source. The natural source is not depleted and controls are engineered in the clone. Product purification is easier using a model organism and higher product yields are gained.

Recombinant protein example

A wild-type molecule is deemed beneficial as a therapeutic protein

Therapeutic proteins represent biological drugs. The therapeutic protein is concentrated and purified from a biological source. The biological source occurs in nature. One example includes human chorionic gonadotrophin (hCG) which represents a natural source.

hCG was first purified from human urine. Pregnant women produce hCG as their placenta grows. They excrete hCG in their urine. It causes the positive pregnancy line to appear on a home pregnancy test. Concentrated hCG is used to treat women who have less success in getting pregnant.

Or, the gene coding the protein might be recombined by a manufacturer. Genetic recombination bypasses the natural source to produce concentrated and purified protein.

Table 1. Lists representing biological and non-biological medicines[13]

Non-biological[a]	**Non-biological complex drugs (NBCD)**	**Biological**
Functional group names • Acetyl • Alcohol • Aldehyde • Alkane • Alkene • Alkyl halide • Alkyne • Amide • Amine • Benzene ring (phenyl) • Carboxylic acid • Ester • Ether • Ketone • Thiol	• Swelling cross-linked polymers • Liposomes, dendrimers and polymeric micelles • Iron carbohydrate complexes • Glatiramoids • Ocular emulsions **Worldwide classification varies**[b] • Albumin-bound nano-particles • Low molecular weight heparins	Recombinant • Bone morphogenetic proteins • Enzymes • Growth factors • Hormones • Interferons, interleukins, and tumour necrosis factor • Monoclonal antibodies • Recombinant vaccines • Toxin and anti-toxin Blood, blood component or derivative Allergenics for immunotherapy Vaccines Advanced therapeutic medicinal products • Gene therapies • Somatic cells • Tissues engineered therapy

Non-biological chemically manufactured drugs are represented by examples of functional groups often specified in drug names. The allowable word count of this article does not do justice to the number of classifications.

[a] In this instance '*non-biological*' is an informal term.

Non-biological complex drugs (NBCD) are nanotechnologies unable to receive comprehensive characterisation through physicochemical analysis.

[b] Worldwide classification varies where some NBCDs are considered biological.[13,18]

Biological medicines listed based on USA and EU definitions.[13]

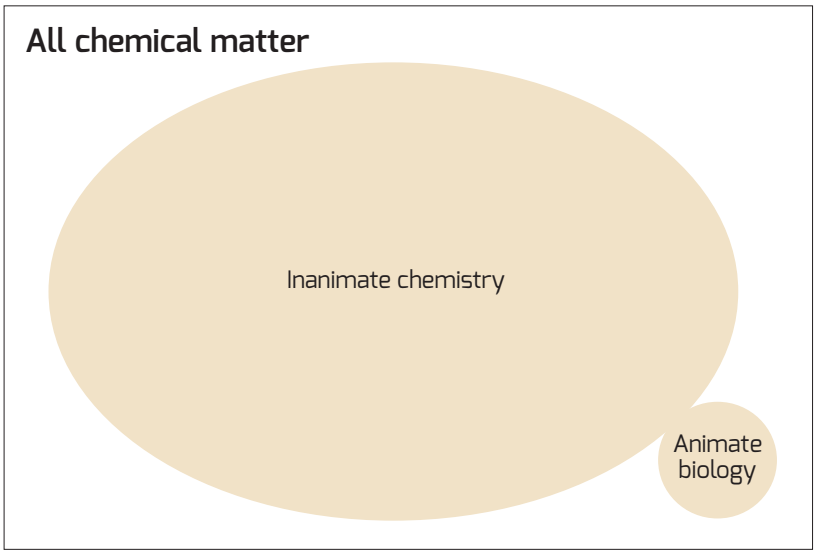


Figure 1. A Venn diagram representing how biology is animated and chemistry is not
The chemical composition of all things in the universe is represented. Out of all chemical things a small proportion is considered under the scientific discipline of biology. Biology is self-animated and chemistry is not. The inanimate and the animate complement each other (A^c).

Recombinant forms are manufactured using biological source genetic code.
Understanding the genetic code for hCG has allowed the development of recombinant hCG. This means hCG does not always come from the urine of pregnant women these days. Molecular biology techniques allow high concentrated volumes of hCG manufacture without urine. Today women receive the recombinant form.

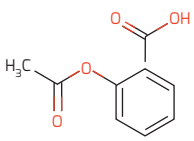
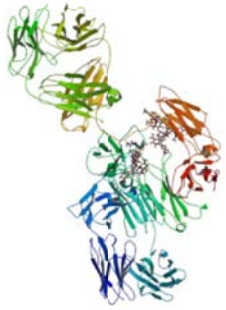
Other biological drugs may utilise transplant or transfusion technology like stem cells, tissue, and blood products. Examples of biological allergenics are pollens that cause hay fever and bee stings that cause anaphylaxis. Allergenics might be used by your doctor to identify sensitivities that you might suffer from.

Their differences determine their regulatory pathways

The term *reference originator biological* is used for the first drug of its kind licensed by a regulatory agency – a *biosimilar* follows on.[16]

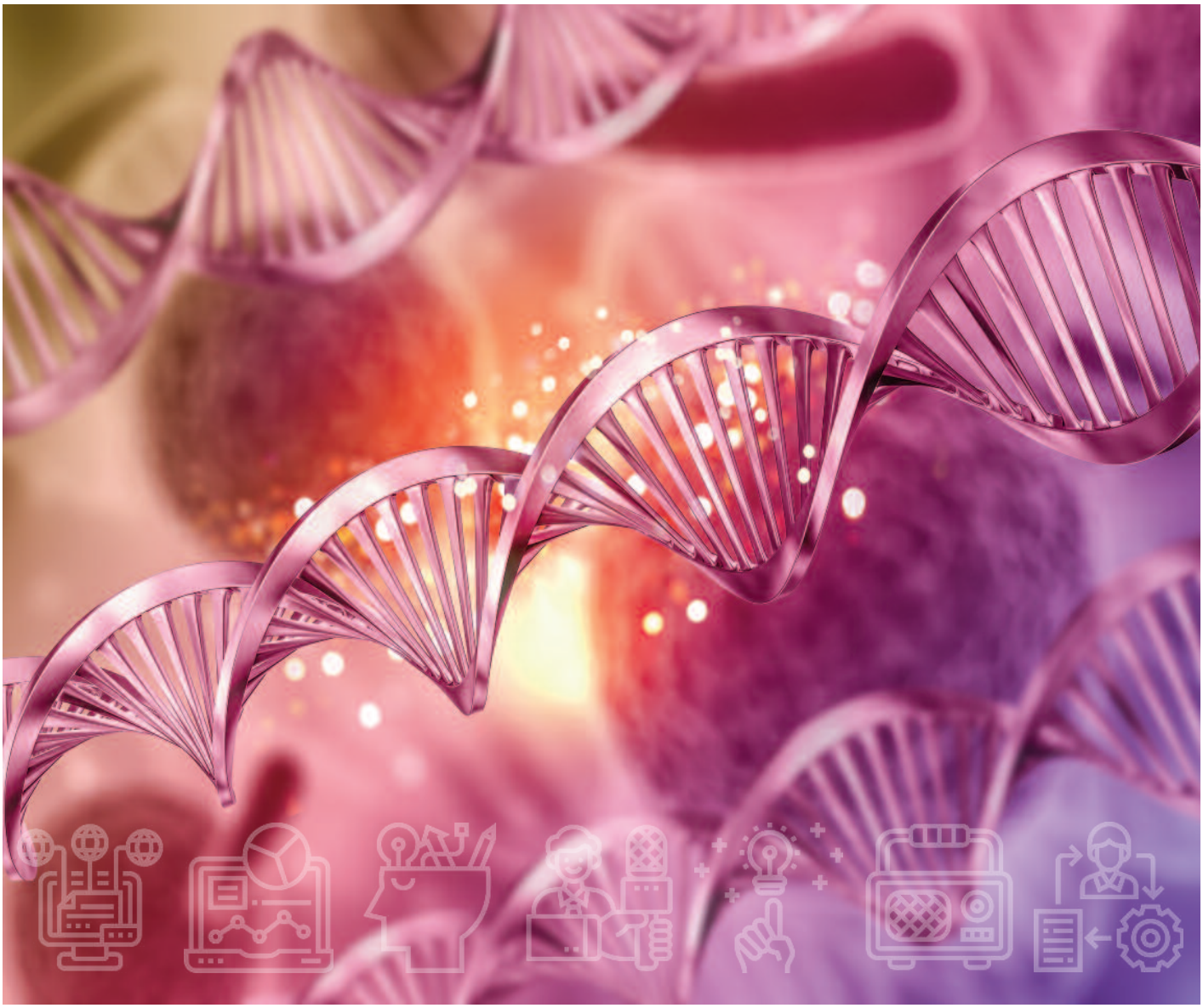
Reference originator biological and *biosimilar* compare to *originator* and *generic* of *non-biological drugs*. The terms are comparable and not interchangeable, i.e., biosimilars are not generics. Biosimilar drugs are often in different suspensions compared to the reference originator biological. Generics could have variation in functional group placement compared to the originator product.

Biologicals and non-biologicals follow different regulatory pathways to the marketplace. The US FDA regulates biologicals through the Center for Biologics Evaluation and Research. It regulates non-biologicals through the Center for Drug Evaluation and Research. In the EU, biologicals market authorisation follows the EMA Centralised Procedure. Non-biologicals

Name	Aspirin (Acetylsalycylic acid)	Abciximab
Synthesis	Non-biological	Biological
Chemical formula	$C_9H_8O_4$	$C_{6462}H_{9964}N_{1690}O_{2049}S_{48}$
Molecular weight	180.157 Daltons	145651.1 Daltons
Chemical structure		

https://www.drugbank.ca/

Figure 2. An illustrative comparison between a non-biological and a biological drug
Generally, chemically manufactured non-biological drug molecules are smaller and less complex compared to biologically manufactured drug molecules. The molecular weight cut off for a chemically manufactured drug is from 500 to 1,000 Daltons. Aspirin and abciximab are blood thinners. Aspirin is a chemically manufactured drug with nine carbon atoms and a total molecular weight of 180.157 Daltons. Abciximab has 6,462 carbon atoms and a total molecular weight of 145,651.1 Daltons. Information in this figure is from Drugbank.[11]



follow the Centralised Procedure, Decentralised Procedure, Mutual Recognition Procedure, or National Procedure. Regulatory pathways reflect differences in the molecules, their manufacture, their administration, and their risk-benefit profiles. Yet for many, it is difficult to imagine differences in things that are invisible to the eye. So, the importance of their differences is not always appreciated.

The June 2019 issue of *Medical Writing* has articles cover-to-cover on generics and biosimilars. It highlights clinical and regulatory considerations for drug development of these types of medicinal products.[17] It is a very interesting and insightful read and partly inspired this article.

An outlier at first glance

Regional dossiers have a section for BCS data. BCS is an acronym for Biopharmaceutics Classification System which can be applied to non-biological drugs.[18] The Biopharmaceutics Drug Disposition Classification System (BDDCS) is also important in drug development.[19] Biopharmaceutics is the study of physical and chemical properties of drugs, their bioavailability, and therapeutic effects. The Biopharmaceutics Classification System (BCS) developed from bioavailability work by Gregory Amidon.[20,21] All drugs whether biological or non-biological have various levels of bioavailability as they are metabolised by their patients.

Amidon published his work in 1995.[20,21] BCS and BDDCS developed after that.[20,21] In these systems *biopharmaceutics* refers to any drug with an intended use in humans or animals. This is an understandable cause of confusion among laypeople and uninitiated industry personnel when differentiating between biological and non-biological drugs.

Will *non-biological* persist?

The use of biological drugs is becoming more accepted and commonplace. Non-biological drugs are sometimes referred to as *normal* drugs. Once biological drugs are thought of as normal, this differentiation will be obsolete.

Year on year, the number of biological drugs sold on the market is increasing. Terms to make a clear distinction between biological drugs and non-biological drugs are increasingly necessary.

Drug definitions become rigid by necessity as they are used in regulatory frameworks.[21] *Non-biological, non-biologic,* and *non-biopharmaceutical* are descriptively agreeable and contain more intuitive meaning when compared to *biological, biologic,* and *biopharmaceutical*. Also, *non-biological, non-biologic,* and *non-biopharmaceutical* do not have formal designations, and they are appropriate in describing all drug products that have not been manufactured biologically.

To me, *biological* and *non-biological* as drug descriptors are synonymous with biological and non-biological washing powder found on supermarket shelves. Biological drugs are not traditional chemical drugs – and they should not be treated as such.[22]

In fact, Hussaarts *et al* 2017 does refer to *biological* medicines compared to *non-biological* medicines.[13]

Will this meme gain popularity? Time will tell if this meaning persists and is used more widely in industry.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

Conflicts of interest

The author declares no conflicts of interest.

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