PrescQIPP Community Interest Company

An introduction to biosimilars

Introduction

Biological medicines (also called "biopharmaceuticals") are comprised of proteins such as hormones, enzymes, and monoclonal antibodies (mAbs). They work by interacting with the body to produce a therapeutic outcome. The mechanisms by which they do this may vary from product to product and across indications. Biopharmaceuticals can be tailor-made to fit the desired target.[1]

Biotechnology uses living systems and modern technologies to produce biological medicines, typically using genetically-modified cells. Each manufacturer has its own unique cell lines and develops its own manufacturing processes. It is vital that these processes are precisely controlled in order to obtain consistent results and to guarantee the quality of the final product. The production of biological medicines is a complex process which requires a very high level of technical expertise and hundreds of in-process tests will be conducted during product development and manufacture.[2]

What is a biosimilar?

A biosimilar medicine is a biological medicine that is developed to be similar to an existing biologic (originator) in terms of quality, safety and efficacy.[3] Where this is demonstrated then regulatory approval will be granted.

Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to the reference product; however the active substance of a biosimilar and its reference medicine is essentially the same biological substance. The only differences should be minor ones due to their complex nature and production methods. Both the biosimilar and the originator will have a degree of natural variability (heterogeneity).[1]

Biologic manufacture

The complexity of the manufacturing process means that product variation between batches is inevitable. What is also common is that manufacturing processes will evolve and develop throughout a biologic medicine's "lifecycle". Drivers for these process changes include: the need to increase capacity or efficiency, advancements in available technology, regulatory changes, e.g. improved viral safety. Some process changes will be relatively minor, e.g. a new filter supplier or major, e.g. a new manufacturing facility.[4]

The regulatory authorities will oversee the production of these biologic medicines and will seek to ensure that any product produced is of sufficient quality whether this is between different product batches or after a change in the manufacturing process. For pre and post manufacturing changes this regulatory procedure is known as a "comparability exercise".

Comparability exercise

The goal of this exercise is to ascertain that the pre and post change drug product is comparable.[4] The process step(s) most appropriate to detect a change in the quality attributes needs to be evaluated.[5] However, the process is not designed to show they are identical, merely highly similar.[6]

If assurance of comparability is shown via analytics then non-clinical and clinical studies will not be warranted. Where differences are observed then there may be a need for a combination of quality, nonclinical, and/or clinical studies.[5] The nonclinical and clinical studies could include pharmacokinetics, pharmacodynamics, clinical efficacy, specific safety, immunogenicity and pharmacovigilance.

The scientific principles of the comparability exercise are exactly the same for a biosimilar molecule vs. originator.[7] The aim is to show similarity at the drug product level using material produced from the final (commercial), full scale manufacturing process.[8] Should any differences be detected in terms of quality attributes these must be justified in relation to safety and efficacy.

Differences that may confer a safety advantage (e.g. lower levels of impurities) should be explained but are unlikely to preclude biosimilarity. If relevant quality differences are confirmed, a full Marketing Authorisation Application may be more appropriate.[9] "Biosimilarity" is the regulatory term used in the EU to denote comparability between biosimilar and originator products.[1]

Biosimilars vs. generics

The "generic" medicines that we have utilised up until recently have been small molecules with simple and well defined structures. The manufacturing process is predictable and exact copies can be made. Once manufactured these compounds are easily characterisable and typically have good stability with a low potential for immunogenicity. It is safe to say that the opposite is true for the biologics, and now biosimilars, that we are utilising today.

That being said it should also be noted that there are some key similarities between biosimilars and generics.

1. The intention of both manufacturing processes is to produce a copy of the original that satisfies the relevant regulatory requirements.
2. Proving clinical efficacy is not the main driver for product development.
3. Biosimilars are intended to be used in the same way as the reference product; same dose(s), dosing regimen(s), same disease(s).

Therefore, the focus of biosimilar development is not to establish patient benefit per se, this has already been done for the originator product, but to convincingly demonstrate high similarity to the originator. This will then allow the biosimilar to rely on, in part, the existing efficacy and safety experience for the originator. For these reasons, the study design, population, and end points may be different from those used to establish benefit of the reference product.[10]

Licensing of biologics and biosimilars

The European Medicines Agency (EMA) have been overseeing comparability exercises for licensed biologics for several decades and have accumulated extensive experience in the assessment and judgement needed to manage such changes. This has allowed them to ensure that quality, efficacy and safety have not been adversely affected for the pre and post change products assessed.

From a scientific and regulatory point of view, the active substance of the biosimilar is just another version of the active substance of the originator.[7]

The same scientific principles underpinning the comparability exercise apply equally to demonstrating similarity before and after a change in the manufacturing process and the comparability exercise for the purpose of demonstrating biosimilarity.[11] All critical quality attributes, i.e. those which are important for the function of the molecule, must be comparable. The cornerstone of this process is the extensive comparison of the physicochemical and functional characteristics of the molecules using up-to-date analytical tools.[7] It is this extensive use of analytics that paves the way for the abbreviated pre-clinical and clinical testing process required for regulatory approval of biosimilars.[12]

The EMA has been overseeing regulatory approval of biosimilars since 2004 and there were a set of guidelines in place to instruct biosimilar manufacturers on the approval process. Recognising that monoclonal antibodies (mAbs), like infliximab, and soluble receptors, like etanercept, presented unique challenges over and above hormones and growth factors, the EMA issued updated guidelines specific to mAbs in 2012.[13] These guidelines outline the regulatory pathway for defining comparable quality, safety and efficacy between a "biosimilar" and originator product. In addition to this there is the recognition that each product submitted will have unique characteristics in terms of molecular properties, such as glycosylation patterns, unique formulations and unique container closures/ devices. This will necessitate a different evidence package to be constructed and submitted.

There are five key elements to this data package

1. Analytical tests - e.g. primary structure, purity, charge variants, glycosylation.
2. Binding studies - e.g. binding to TNFa.
3. Biological activity - e.g. apoptosis, Antibody Dependent Cellular Cytotoxicity (ADCC).
4. Non-clinical - e.g. pharmacokinetic and toxicity studies in rats.
5. Clinical studies - e.g. Phase 1 and 3 studies in specified indications.

However, the evidence submitted for each element will differ and will also have evolved during the submission process as potential differences were detected and their significance investigated.[14]

Clinical trials

The high specificity of analytical and biological characterisation technologies means originators/ biosimilars can be fully characterised. If critical product attribute differences are detected, the impact on receptor binding and other functional mechanisms must then be assessed. This means that functional integrity and performance can then be assured before clinical studies. However, clinical studies still have a key role and this is to target "residual uncertainty".[15]

Clinical studies are not considered in isolation as the basis for a conclusion of "comparability" and this is true either pre and post manufacturing change or during biosimilar approval. Clinical studies are designed to identify any unusual or unexpected issues and these are predominantly issues of immunogenicity and safety. Clinical end points are far less sensitive than analytics at picking up even moderate differences between products; however sensitive clinical endpoints are still assessed in order to confirm efficacy. The consequence of this is that clinical end points have little value in establishing biosimilarity.[15]

Biosimilar development

The aim of development is not to establish patient benefit per se as this has already been done for the originator product.[1] The aim is to convincingly demonstrate high similarity to the originator product. This will then allow the biosimilar to rely on, in part, the existing efficacy and safety experience.[10]

The process has 3 key steps[16]

Step 1 – Define originator product variability ("otherwise know as goal posts")

Multiple batches of the reference product are assessed to determine the "acceptable" level of product variability. Essentially the goal posts have been set by the originator product which has been judged by these parameters throughout its lifecycle.

Step 2 – Initiate a development process designed towards these "goal posts"

Once the "goal posts" have been established there is an iterative process (characterisation of the biosimilar vs. originator and process development) to produce a product with attributes that fall within the established variability of the originator.

Step 3 – Utilise analytics at each stage to ensure biosimilarity for the final product

Depending on the extent of overlap, preclinical and clinical development can be abbreviated vs. originator, i.e. how well did the biosimilar keep within the "goal posts"?

If product attributes fall outside established "goal posts," various process steps are modified to produce product attributes that fall within the established variability of the originator. The final product will then undergo an extensive comparability exercise to demonstrate "biosimilarity".

The type and extent of clinical data required to demonstrate biosimilarity will vary on a case by case basis and will depend on:

- The complexity of the active substance and how well it can be characterised.
- The availability of an accepted surrogate end point to compare efficacy.
- The type and seriousness of safety concerns that have been encountered (originator product or substance class).
- The possibility to extrapolate efficacy and safety data to other indications of the originator product, (i.e. those which have not been studied for the biosimilar).

However, a repetition of the entire development program of the originator is scientifically not necessary and could even be considered unethical.[10]

Extrapolation

This is the regulatory and scientific process of granting a clinical indication to a medicine without its own or new clinical efficacy and safety data to support that indication. It may be considered if biosimilarity has been shown.

There must be sound scientific justification for the extrapolation and this would include:[17]

a). Clinical experience and available literature data from the originator.

b). Evidence that the lead indication is representative for the other therapeutic indications, both with regard to safety and efficacy.

c). Mechanism of action of the active substance in each indication.

If the relevant mechanism of action for the tested and extrapolated indications is the same, extrapolation is usually unproblematic.[7] Extrapolation is more difficult when the mode of action is complex or involves multiple receptors or binding sites. It can also be problematic if the contribution of these mechanisms differs between indications or is not well known. In such cases, additional data, (such as in vitro functional tests or in vivo pharmacodynamic studies reflecting the respective pharmacological actions), will be necessary to provide further reassurance that the biosimilar and reference product will also behave alike in the extrapolated indications.[7] For all submissions the data is reviewed on a case-by-case basis and depends on the "totality of evidence" presented.[18]

Extrapolation principles apply equally to either originator biologics or biosimilars, and are already widely exercised. For originator biologics they are applied after a significant manufacturing process change or a product reformulation (e.g. trastuzumab IV to sub-cut) and they have also been applied to all the currently UK licensed biosimilars, i.e. epoetin (EPO), granulocyte colony stimulating factor (GCSF) and growth hormone (GH).

Terminology

There are some key terms being used in relation to the biosimilars that warrant clarification.

Interchangeability – This means moving freely between the available products, i.e. like a generic. This is not regulated by the EMA and it is down to each member state to decide. It is not an option within the UK. Also worth noting is that current batches of existing biologics are used interchangeably with each other.[19]

Substitution – This involves changing the products stocked in a pharmacy without informing the prescriber. This is also highly unlikely to occur within the UK.[20]

Switching – This involves switching specific patients to a biosimilar following a mutually agreed local arrangement.

Traceability and naming

Biosimilars so far approved in the EU have typically been granted the same international non-proprietary name (INN). This means that the originator and biosimilar will all be known by the same "generic" name. Therefore the use of brand names in the prescribing, ordering and supply of biosimilar and originator will become essential as and when the biosimilar products become available. This will allow traceability which is vital for accurate post-launch pharmacovigilance and will help assure patient safety, i.e. by reducing the chance of inadvertent switching.

Health Technology Appraisals

Both the All Wales Medicines Strategy Group and Scottish Medicines Consortium have issued positive HTAs in relation to biosimilar infliximab.[21,22] NICE has stated that it does not intend to routinely issue individual technology appraisals for each new biosimilar as it becomes available.[23] Since then the SMC has updated its position and in line with NICE "*will no longer routinely assess biosimilar medicines*".[24]

Primary care commissioners' viewpoint

The majority of biosimilars that are likely to become available in the UK in the coming months/years are for use within rheumatology, gastroenterology and dermatology. This means their funding is primarily of interest to CCGs who commission the use of these drugs, typically (but not exclusively) in accordance with NICE guidance.

Even moderate use of these biosimilar drugs will yield significant savings due to the high cost per patient. Primary care commissioners will be keen to maximise the savings potential associated with these drugs and may consider approaching this issue in one of several ways.

The possibilities are:

1. Agree a commissioning incentive with local trusts and clinicians to encourage early adoption and prescribing in naïve, and, potentially, existing patients depending on local clinician agreement. Incentives could include a gain-share arrangement, or a scheme to re-invest savings in other parts of the relevant clinical pathways.
2. Leave hospital clinicians to adopt the biosimilar at their own rate and continue to fund at the price paid.
3. Only fund future biological medicine usage (new +/- existing patients) at the new biosimilar price regardless of which product is used. This would leave trusts out-of-pocket whilst usage of the biosimilar was implemented. Given the necessity for a phased implementation and uncertainty regarding switching, this would have a negative impact on the introduction of the biosimilars.

Option one is the preferred, and recommended, choice as this encourages a win-win scenario. This option will promote co-operative relations which will be key for the successful implementation of each biosimilar as it comes to market.

Conclusion

It is clear that clinician support is vital in order for the introduction of the impending arrival of biosimilars to be successfully and safely adopted. However, a paradigm shift in thinking is required by prescribers. This is because the regulatory approval for biosimilars centres on analytics and not clinical trials; similarity is the goal and not efficacy in isolation.

Several biosimilars are approaching the UK market and they offer a significant opportunity to free up funds that could benefit both primary and secondary care. A joined up approach is required to maximise this opportunity and ensure that providers, commissioners and patients all benefit.

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Additional PrescQIPP resources

Summaries for commissioners and prescribers

Patient letter

Available here: http://www.prescqipp.info/resources/viewcategory/384-biosimilars

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