COMPLEX GENERIC APIS: A PRIMER

The US Food and Drug Administration (US FDA) defines complex generics as products having intricacy associated with an active pharmaceutical ingredient(s) (API), formulation process, route of delivery, or drug-device combination. This very definition entails that the commercial versions of these products are challenging to replicate, which means limited competition and potentially great economic rewards.

Even though the US FDA is approving more and more of these applications, the truth is that they require multiple cycles of revisions, leading to potential delays in the realization of these economic promises and, more often than not, additional costs. For some of these complex generics, the difficulty lies with the demonstration of the analytical and biological sameness of the API. Defining the best analytical approach and navigating the many hurdles linked to these complex generics is not a trivial task and needs careful and strategic planning.

EXECUTIVE SUMMARY

The potential for economic reward associated with the development of complex generic medicines means there has been dramatic growth in the sector in recent years.

However, opportunity is not without complexity. Unlike other medicinal products, manufacturers of complex generics cannot rely on textbook characterization or QC testing to prove compliance with regulations. Instead, they are advised to carefully adapt their analytical testing strategy at the start of each product's development cycle and refine it, based on the product's specifics as the process continues. Companies that reject this approach risk seeing their application go through multiple revisions, resulting in delays and increased development costs.

In this technical bulletin we will look at some of the analytical issues surrounding bringing complex generics to the marketplace. In addition, we will see how working with SGS at an early stage may help addressing these ahead of time, lowering development costs and the amount of material required for analytical testing. All of this in view of reducing the number and extent of revision cycle

GENERICS VS. COMPLEX GENERICS

The US FDA defines a generic drug as one that is identical – or bioequivalent to – a brand name drug. This definition means both products must have the same dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

A standard small molecule generic is a copy of a reference drug, and the active ingredient is chemically identical to its branded counterpart. This full equivalency is relatively routine to establish using well-recognized analytical techniques. A biologically-derived molecule, in contrast, can only ever be similar to the originator because of the nature of its production, hence the fact that the term 'biosimilar' is used instead of the word 'generic'.

The complex generic product falls somewhere in between these two drug classes. A complex generic product might have a particularly complex active ingredient, a complex formulation, a complex route of delivery, or even be a complex combination of a drug with a device.

The European Medicines Agency (EMA) refers to complex generics as "hybrid medicines," whose "authorisation depends partly on the results of tests on the reference medicine and partly on new data from clinical trials."

Source: EMA

The US FDA has laid down a set of criteria to determine whether a pharmaceutical drug could be classified as a complex or non-complex entity. Non-complex products include tablets, capsules, and solutions or suspensions designed for oral administration or systemic delivery, including solid oral modified-release dosage forms. Solutions for topical or parenteral administration also fall into the non-complex category.

In contrast, if a product has a complex active ingredient, such as a peptide, then the final product will also be deemed complex; and there are also complex dosage forms, such as long-acting injectables and transdermal systems. Equally, all locally-acting drugs will be considered complex, as will drug–device combinations that have user interface considerations, and formulations that have been designed to offer abuse-deterrent properties.

MARKET INFORMATION

Complex generics are an important part of the biopharmaceutical sector, as demonstrated by the increasing interest in complex active ingredients such as peptides. In 2011, the global peptide market was estimated to be worth USD 14.1 billion, but by 2018 this had grown to USD 25.4 billion.

Currently, 60 peptides have been approved for medicinal use by the FDA. Beyond this, it is estimated around 140 peptide drugs are now in clinical trials, with a further 500 therapeutic peptides in preclinical development.

Of the 7,000 natural peptides that have been identified, it is safe to assume the most obvious have already been targeted for medicinal use. There are, however, considerable opportunities left for exploring new medical avenues for peptides, beyond the traditional. It is this complex generic sector which is expected to continue to see considerable growth.

PEPTIDES – ANALYTICAL SAMENESS

In the absence of clear guidance or mandated methods, a systematic approach must be taken. For peptides, for example, demonstrating saxmeness means demonstrating that the two molecules have comparable physicochemical characteristics, primary sequence, secondary and quaternary structures. They must also have comparable biological activities, both in vivo and in vitro.

This poses a challenge, because these complex APIs are not small molecules, but they are not proteins either. The available analytical toolboxes are well-defined for small molecules and for proteins, but there are very few off-the-shelf methods available for complex APIs. Therefore, the analytical approach cannot rely on textbook characterization or QC testing.

Those methods that do exist are largely focused towards peptides. For structural characterization and confirmation, amino acid sequences can be confirmed using mass spectrometry (MS) and tandem MS (MS/MS) analysis, and amino acid composition can generally be obtained. Sulfydryl groups and disulfide bridges could also be located or confirmed.

Product-related impurities also need to be studied. For peptides and some polyamino acid products several qualitative and semi-quantitative techniques can be applied to the determination of product-related impurities. For most peptides, this could be done by chromatography, either Reverse-Phase, mixed-mode, or HILIC. Their characterization would however require most complex methodologies such as HUPLC-MS.

CHALLENGES IN ANALYTICAL SAMENESS

With so many attributes to analyze, and in the absence of any clear guidance of what is required, it is important that each molecule is considered individually. Applying the same comprehensive set of techniques to every single complex generic is never going to be cost-effective. An appropriate subset of methods is to be selected. This choice of techniques will need to provide all the information necessary on the various quality attributes and, if possible, give a sufficient degree of orthogonality.

Specificity, sensitivity and precision are key to providing the appropriate methods to probe sameness and it should be recognized that these may not be the same as those required from studies. When working with formulated drugs, other issues arise – not least that complex products are often formulated at low concentrations and are likely to contain bacteriostatic compounds that will interfere with analytical methods.

Various difficulties recur. One common one is that all the parties may be very familiar with the requirements for biologics but may not grasp the differences with complex generics such as peptides. For example, one might want to see secondary and quaternary structure comparisons between the reference drug and the generic, yet these products' concentrations are commonly very low, and there is currently no quaternary structure method that is able to reliably detect soluble aggregates at concentrations below 20 µg/mL.

HIGHER-ORDER STRUCTURE ORTHOGONALITY

The canonical methods for determining secondary structure are Circular Dichroism (CD) and Fourier-Transform Infrared Spectroscopy (FTIR). However, the presence of a bacteriostatic component in the buffer used to formulate the product interferes strongly with ultraviolet detection at most of the wavelengths that are used in CD analysis. While this does not affect FTIR in the same way, it leaves only one applicable technique available, and therefore the orthogonality that regulators often demand is not possible for the formulated product. Additionally, the higher order structure orthogonality package cannot be performed on neat material.

To overcome this problem, the obvious solution would be to remove those components of the buffer that are problematic. While this allows both techniques to be run on the same sample, it will not give the necessary insight into how the presence of the buffer in the formulated product affects the higher-order structure.

Alternatively, one could carry out only a set of biophysical techniques, and compromise on the orthogonality, meaning samples of the drug products could be used directly, but at the expense of giving poor control of the quality attributes. Errors and mis-estimation would become far more likely in this case, particularly with a small peptide.

It might be possible to remove the problematic components of the buffer, and back up the qualifications of sameness with a set of techniques that are not buffer sensitive. Techniques that are buffer sensitive are mainly used to demonstrate sameness between non-buffer sensitive methods, but it may be that the results prove that the native and buffer-exchanged samples are highly different. This means only a subset of the conventional techniques can be used.

A final option would be to introduce novel, less conventional higher order techniques. This would allow unaltered samples to be used, but at the expense of timelines extension while agreement was sought with the regulators, who may not be aware of these techniques. The data would have to be carefully explained if they are to prove acceptable.

SOLUTION

The pharmaceutical industry is particularly price-sensitive and drug development can take several years. Manufacturers may, therefore, be tempted to leave contemplation of the analytical testing and approval process until later in the development of the drug. This approach can work with non-complex medicines where textbook characterizations or QC testing is available. Many drug product developers will know the requirements of the regulatory authority and work towards them. In these instances, the developer may only need to work with a Contract Testing Organization (CTO) to ensure the correct testing is carried out for approval.

Complex generics are different. Without clearly mandated guidance from authorities on the analytical path to approval, and very few off-the-shelf analytical methods available, manufacturers need to have a deep understanding of their product at every stage of a drug's development. Analytical methods therefore need to be defined at the start of the process and then evaluated, refined and adapted as development progresses. In these instances, the developer would definitely need to identify an experienced Contract Research Organization (CRO) able to support their product development and take on these analytical challenges.

It is a false economy for manufacturers to save on analytical testing costs during the early stages of a drug's development, as this can result in considerable delays at the approval stage if the drug is forced to go through several cycles of revision. By planning and defining the analytical testing process alongside the drug development program, the manufacturer can ensure they will have the deep understanding of their product that will be necessary.

SGS SOLUTION

Manufacturers need to consider the analytical testing process associated with complex generics to be closer to research than just testing. Without mandated testing solutions, the deep understanding required to gain approval demands will demand a combination of canonical techniques and bespoke solutions. These will all require adaption and evaluation during the process to prove they are fit-for-purpose.

As a highly experienced Contract Research Organization (CRO), SGS has considerable experience in working with manufacturers at every stage of the development process to ensure the correct testing methods are developed, evaluated and utilized. SGS's comprehensive approach to helping manufacturers gain the deep understanding they need for their products to be approved, is matched to our considerable experience of working with authorities, such as the US FDA.

By streamlining the analytical testing process, SGS also reduces the amount of costly materials required, while expediting the testing process.

WHY WORK WITH SGS

- Reduced development costs
- Lower amounts of material required for analytical testing
- Faster turnaround times
- Experienced in working on a wide variety of complex generics
- Work with regulatory authorities
- Global network of experts

CONCLUSION

With so many options for analytical techniques, and limited time and materials, the strategy with complex APIs should be carefully planned, to alleviate the issues with a traditional characterization and comparability approach. Questions that analysts will need to find solutions for include: How can structural changes for some of the quality attributes be detected when the changes are subtle and there is only a small amount of material available? Can orthogonality and/or fit-for-purpose demonstration be used to compensate for uncertainties in the specificity of methods? And should the methods quoted in documentation from the regulators be abided by, despite their technical limitations or limited applicability to the task in hand?

This leaves the option of a more streamlined strategy, where all methods that need to be used will be "qualified" relative to each individual quality attribute to give a method cluster, which will compete on specificity, precision and robustness. The most specific, sensitive, and precise methods will then be selected as the core comparability methods, therefore reducing the need for orthogonality. Degraded conditions will be designed considering each quality attribute. The result will be reduced costs for qualification, faster turnaround times, and lower material requirements.

Overall, it is important to remember that when considering sameness for complex APIs, they are neither small molecules nor proteins. The methods used in a sameness analysis will have to combine both canonical techniques and more out-of-the-box alternatives, and in either case will need to be adapted and then proved to be fit-for-purpose. In addition, the methods will require specific degraded forms or substitute standards in order for analysis be proven specific and/or sensitive enough.

Taking a linear approach to the method evaluation is likely to be both impractical and cost prohibitive. The strategy taken will always have to be adapted to the complexity of the product – either via taking a streamlined approach, and by carrying out fit-for-purpose cross-evaluations for each quality attribute, rather than for each method.

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