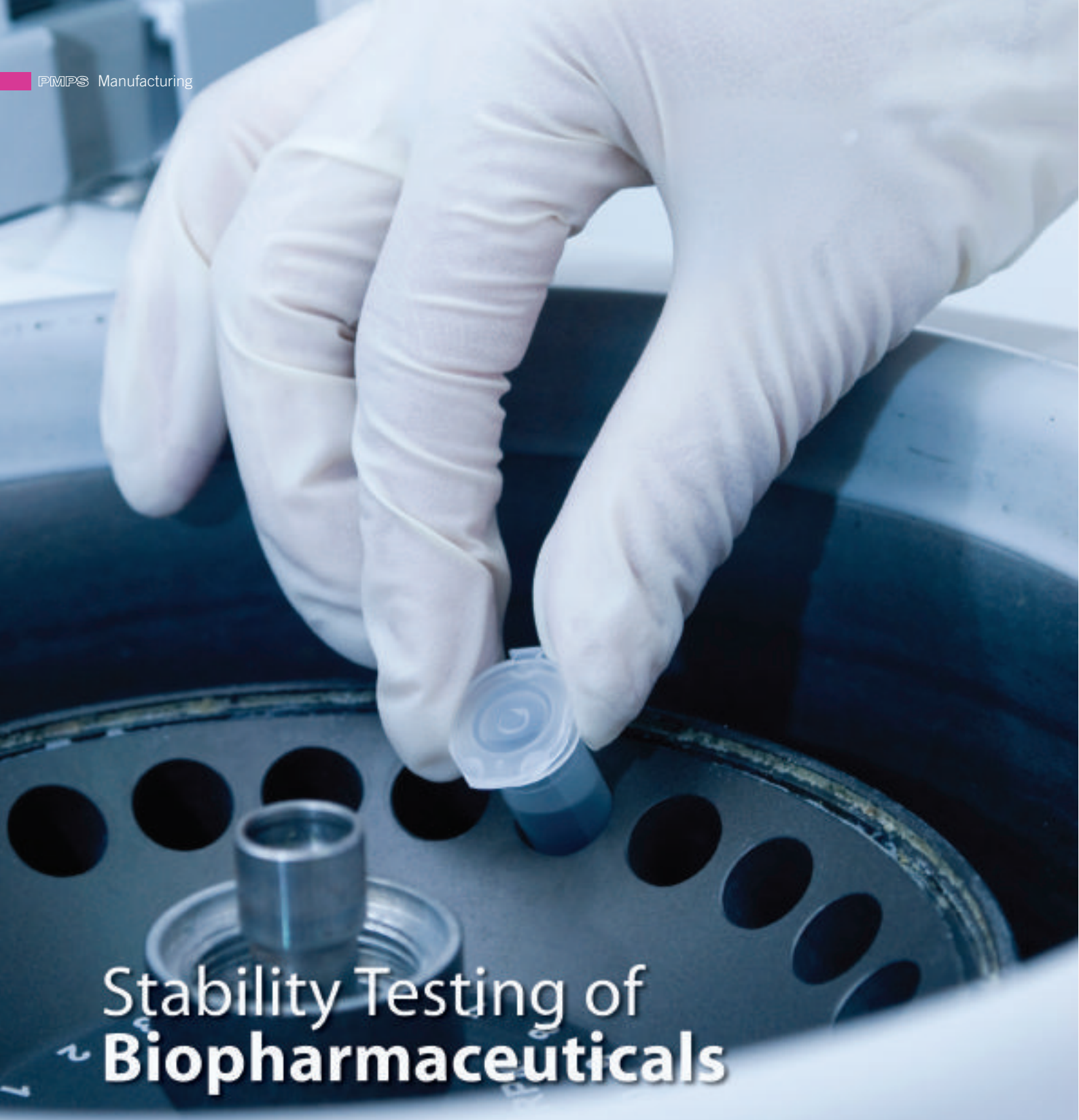


Stability Testing of Biopharmaceuticals

Since 2005, the approval rate of biopharmaceuticals has slowed down. Dave Scott of Tepnel Research Products & Services investigates some of the considerations which must be taken into account when stability testing biologically-derived drugs

Stability testing of a drug substance or a finished product is a vital part of the data package submitted in support of new drug applications or marketing authorisations. The principle ethos of stability testing is to provide evidence to a regulatory body that the quality of the product or raw material does not vary with time or under the influence of a range of other factors including temperature, humidity and light.

With the evolution of drug development to include whole new classes of molecules, the application of the International Conference on Harmonisation (ICH) guidelines remains the same, but the level of technical complexity in designing stability programmes that are fit for purpose has increased dramatically. Therapeutic agents that include proteins and peptides or monoclonal antibodies pose a different set of practical challenges in providing data that meets the needs

of both the regulatory authorities and the developers of these drug products.

This article will consider the regulatory requirements for both drug substances and finished products, whilst comparing the scientific considerations that come into play when stability testing biologically-derived drugs compared with conventional small molecule products and substances.

STABILITY TESTING AND HARMONISATION

The stability programme and subsequent testing of both the active pharmaceutical ingredient (API) and the finished product plays a pivotal part in the drug development pipeline. It is crucial that any programme undertaken is sustainable, and also compliant with current regulations of the Medicines and Health Regulatory Authority (MHRA), US Food and Drug Administration (FDA) or other relevant regulatory organisations.

Stability testing provides the scientific evaluation of both the API and finished product to determine shelf-life for the label, and also governs the suitability of any formulations for clinical trial to be active for the duration of any intended dosing regime. The intention is to establish that, under certain pre-prescribed conditions, the item under investigation will retain its original properties and thus its efficacy, whilst not undergoing any significant changes in either its composition or structure which could cause deleterious harm to the eventual recipient.

Stability testing also plays a significant role in the development of a product down the drug development pipeline, by providing information which is useful in facilitating decisions and understanding the product or formulation in greater detail. This can include information on the purity, strength and quality of both the drug substance and finished product; expiration dating and compliance with CGMP requirements; information on product characteristics when exposed to stress conditions; degradation pathways; facilitation of analytical methods development; facilitation of the design of the formulation and the manufacturing process; information on the compatibility of the container closure and/or delivery systems; finalisation of the release and stability specifications, and any in-use conditions which may be vital to the successful efficacy of the product; and a comparability assessment after any manufacturing changes have been made.

"The history of medicinal product registration in much of the industrialised world, has followed a similar pattern which could be described as: Initiation, Acceleration, Rationalisation and Harmonisation" (1).

This statement is taken directly from the ICH website and summarises the steps that have taken place since the early 1990s to arrive at a situation today whereby, the mechanism for the assessment of the stability of a drug substance or API, finished product or investigational medicinal product (IMP) is uniform and universally accepted in principle by regulatory authorities across the globe. The ICH in itself is a joint initiative that has involved both regulators and industry, crucially as equal partners, in the scientific and technical discussions that have centred on the testing procedures required to ensure and to assess the safety, quality and efficacy of medicines. It is composed of six member bodies with three observers who represent the regulatory bodies and the research-based industry in the EU, Japan and the US.

A review of the current ICH guidelines establishes that there are six documents which are specific in their application to the stability testing of pharmaceutical products and components, both small molecule and biopharmaceutical. These six guidance documents are summarised in Table 1.

ICH Q1 F defined storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid). In the course of the discussions which led to the development of the guideline, a survey among member states to find consensus on 30°C or 65 per cent RH as the long-term storage conditions for hot and humid regions was reached on the basis of no significant objections being raised during the survey. However, based on new calculations and discussions, some countries in Climatic Zone IV expressed their wish to include a larger safety margin for medicinal products to be marketed in their region. As a consequence, several countries and regions have revised their own stability testing guidelines, defining up to 30°C or 75 per cent RH as the long-term storage conditions; therefore, due to this divergence in global stability testing requirements, the ICH decided to withdraw ICH Q1F. It is recognised that the quality guidance documents are by definition interlinked; however, Table 1 notes those documents which give specific guidance on the conduct of stability studies. The regulatory requirements of Q1A(R2) versus Q5C are in principle the same: to assess the stability characteristics of either the drug substance or the finished product; to determine storage conditions and expiration dates; and to check that the application of the remaining Q1 guidance does not vary for either class of molecule.

The scientific principles in stability testing have not changed significantly in recent years, but there is now a far greater understanding of the complexities that biopharmaceuticals intrinsically carry. There are a number of subtle differences which come into play and mean that a blanket approach to stability testing of both types of molecules cannot be applied.

Table 1: Stability-specific ICH guidance

Guidance	Title	Status
Q1A (R2)	Stability testing of new drug substances and products (second revision)	Status: step 5, February 2003
Q1B	Photostability testing of new drug substances and products	Status: step 5, November 1996
Q1C	Stability testing for new dosage forms	Status: step 5, November 1996
Q1D	Bracketing and matrixing designs for stability testing of drug substances and drug products	Status: step 5, February 2002
Q1E	Evaluation of stability data	Status: step 5, February 2003
Q1F	Stability data package for registration applications in Climatic Zones III and IV	Status: withdrawal June 2006
Q5C	Quality of biotechnological products: stability testing of biotechnological/ biological products	Status: step 5, November 1995
Q7	Good manufacturing practice guide for active pharmaceutical ingredients	Status: step 5, November 2000

NCES VERSUS NBEs

There are a multitude of definitions as to what constitutes a biopharmaceutical. A recent survey of those involved in biopharmaceutical development and production agree that biopharmaceuticals are pharmaceuticals which are inherently biological in nature due to their method of manufacture. Specifically, they involve the use of a biotechnology process which involves the use of live organisms. In such cases the API is referred to as a new biopharmaceutical entity (NBE).

The predominance of pharmaceutical products currently licensed to the marketplace are new chemical entities (NCEs) or more generally referred to as small molecule APIs. While stability testing for small molecule drugs is well-established, its counterpart for NBE-derived products is still evolving, and the complexity of both the NBE and the process by which it is manufactured dictates that a very different view must be taken when considering stability testing.

If we consider NCEs versus NBEs at four basic levels, we can start to understand the complexities which are inherent in the NBE and consequently play a major role in the design required in a biopharmaceutical stability testing regime.

MANUFACTURING

The first area of interest and impact is the process of manufacturing. Small molecule APIs and products are the end result of a chemical synthetic process that is generally well characterised, understood and controlled, and therefore the end product demonstrates a high degree of homogeneity from batch-to-batch production runs. In contrast to this, NBEs are usually the end product of either a single or series of steps within a biological system. Biological systems are often poorly understood or characterised and as a consequence there is a large amount of heterogeneity that can exist within both the process and the end product. It is therefore very difficult to design the component parts of a stability study when the endpoint of the manufacturing process can vary from batch-to-batch. Consideration must therefore be given to establishing that inter-batch variation, as a consequence of the inherent variability of the process, are not mistaken as losses in the stability of either the API or the finished product.

STRUCTURE

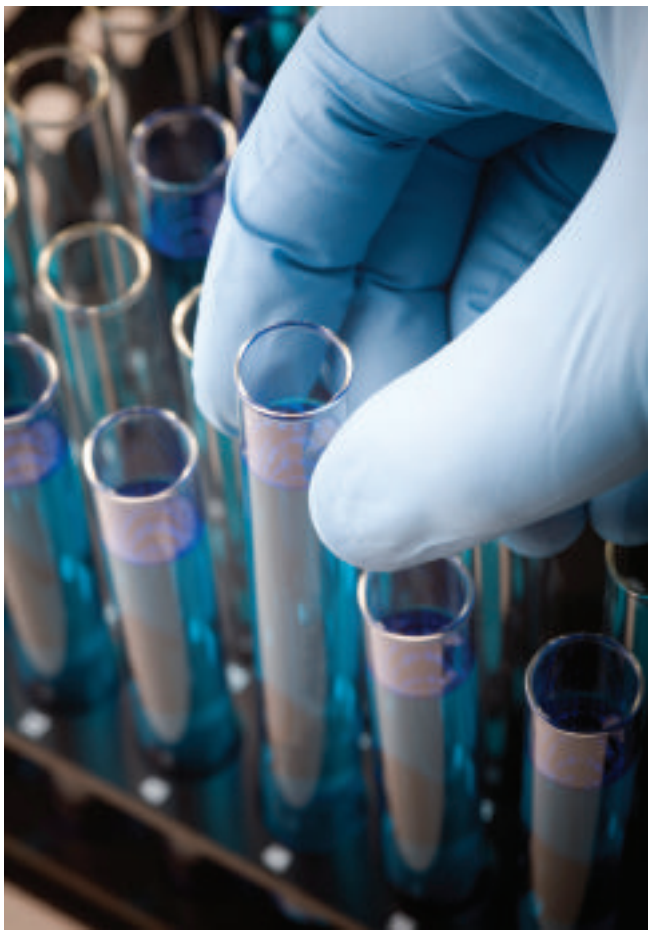
We must consider the entity itself and any impurities that arise as a part of the manufacturing process. In relative terms, small molecule APIs and products are simple – the API is structurally well-defined and the presence of any impurities are easily qualified and quantified in either manufacturing standards or specifications. In contrast, NBEs are complex molecules, many orders of size larger than NCEs, whose activity depends on their complicated structure that can be based on secondary, tertiary and sometimes even quaternary folding structures. The end result of the manufacturing process should lead to a homogeneous product batch, but as these are biological systems slight variations in the environmental conditions can have a major impact on the system, which can result in both intra- and inter-batch heterogeneity. It is therefore extremely difficult to define both what impurities can exist and which should be quantified.

METHODS OF ANALYSIS

There is a plethora of well-developed NCE platforms, analytical methods and techniques that will allow for the characterisation of the drug substance both in bulk and in formulation, which are sensitive, provide good analytical standards to aid accurate quantification and which discriminate the analyte of interest from impurities of constituents of the final product. NBEs often have structures that cannot be fully defined with the present set of analytical techniques or approaches for potency testing. There are therefore a set of limitations on the available methods for quantification of activity, potency and impurity profiles, which are present before any assessment of stability can commence. It is not always inevitable but it is often required that a number of different methods be applied to provide the same endpoint data. This is especially true when we consider the measurement of potency. Where small molecule potency and purity is predominately measured using high performance liquid chromatography (HPLC), the potency of an NBE can be quantified using HPLC, electrophoretic techniques and biological assays. Within these methods the levels of accuracy and precision vary; therefore, consideration must be given to finding not necessarily the most efficient method of analysis, but rather those methods which are most effective in demonstrating what is required to meet the regulators' expectations.

BIOLOGICAL CONTAMINATION

In general, extraneous or intrinsic biological contamination of NCE drug substances or finished products is minimal. The chemical synthetic process is often very restrictive towards opportunities for microbial growth and contamination. This is not to say that there are circumstances whereby biological contamination can occur; certainly, products which are classified as parenteral will always be checked for both sterility and endotoxin content at the end of the process. NBEs are derived from biotechnological processes, all of which will contain various sources for contamination from adventitious agents. These can include elements of the cell substrate such as endogenous viruses, exogenous microbial contamination, cell culture reagents both animal and non-animal derived and environmental agents. With such a large number of possible biological contaminants, the concern from a stability-indicating point of view would not just be the presence of these from a contamination perspective, but the consideration that the moiety of these contaminants could lead to results which were wrong due to the relative specificity of some of the analytical methods employed.



About the author

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CONCLUSION

Stability testing of small molecule APIs and finished products is at a mature level of development. The requirements of the regulatory authorities, the scientific principles and techniques for accumulating, analysing and presenting the data are well understood and documented in the ICH guidelines. With every advancement in the production and manufacture of biopharmaceuticals, additional knowledge and understanding is gained; however, the goalposts are also changing and the requirements of the regulators and the mechanisms of meeting these needs are under constant review. As we have noted, the basic principle behind stability testing has not changed; however, the inherent variability and difficulties in manufacturing biopharmaceuticals are making effective stability testing an increasingly difficult art.

Approvals of biopharmaceuticals reached a peak in 2005 within the FDA, with 21 products receiving official approval. However, in subsequent years, there has been a slow down in approvals. There are a number of reasons behind this and the inference is not linked to stability testing failure, but is indicative that the regulatory requirements for a biopharmaceutical are evolving and that success of a biopharmaceutical can be enhanced through constant and continued dialogue coupled with a full understanding of the process, the product and the variability that lies within.

Reference

1. http://www.ich.org/