Designing Bespoke Stability Studies for Veterinary Drug Products

The National Office of Animal Health, which represents over 97 per cent of the UK's animal medicine market, states that approximately £745 million is made each year in sales of authorised veterinary medicines. As with pharmaceutical products used for humans, animal medical products are also subject to rigorous regulatory standards, with stability studies forming a crucial part of the testing process. Here, Beccy Bell, Operations Manager at analytical testing specialist Broughton explains how manufacturers can develop bespoke stability studies for veterinary medicines.

Stability testing can help determine a product's shelf life and recommended storage conditions. These studies provide evidence of how the quality of a drug substance or medicinal product varies over time under the influence of different environmental factors, such as temperature, humidity, and light.

Stability studies are also used to establish a re-test period for a drug substance that is then applicable to future batches of that substance manufactured under similar circumstances. Usually, manufacturers will determine this by testing a minimum of three batches of the drug substance and evaluating the stability information generated (including, as appropriate, results of the physical, chemical, biological, and microbiological tests).

The degree of variability of individual batches impacts the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through a formal statistical analysis. If so, justifying the omission should be sufficient.

Designing a Bespoke Stability Study

Several design factors must be considered before initiating a stability study. Sometimes, stability study designs may be straightforward with a single formulation and strength, but this is rarely the case.

Firstly, for formal registration stability studies required to support the regulatory submission for a veterinary product, these studies must be performed on no fewer than three representative batches of the manufactured product. This will allow manufacturers to assess the potential batch-to-batch variability in the product's shelf life. Those tests include biological and physiochemical stability studies carried out at regular intervals, for the finished product until three months beyond the claimed end of shelf life.

In addition, stability studies for veterinary drug products may consist of multiple strengths, packaging types, storage orientations, and container closure systems, resulting in numerous stock-keeping units (SKUs). For studies of multiple strengths and packaging types, the requirement of the study may be reduced if bracketing is applied.

When designing a stability study consideration should be given to the impact of the product's packaging. Generally, the impact will depend on the study, and packaging assessments may not be required for all stability studies. Manufacturers may also want to consider the impact of the surface area contact ratio of the substance to the container. For veterinary drug products, shelf-life stability studies should be performed in the primary container closure system proposed for marketing. However, suppose the secondary packaging has protective properties, and the labelling states that the product is to be stored in the primary and secondary packaging. In this event, manufacturers must also assess the secondary packaging as part of the stability study.

As part of the study design, you may also want to consider an in-use stability study. In-use stability tests assess product quality after any packaging has been opened, simulating the expected use of the product.

Finally, when designing a stability study, the sample quantities set down at the start of the study are critical. Insufficient quantities can have a huge impact on cost and timelines, as stability studies may need to be repeated. It is crucial to have adequate sample quantities to cover all testing specified in the stability study protocol and account for potential repeat testing, investigation of atypical results, and subsequent confirmation of data. Additionally, we recommend a sample quantity overage is applied for flexibility, to allow for additional ad-hoc testing that may be required at unspecified stability time points.

Challenges Facing Veterinary Products

A significant difference between veterinary drug products and those specified for human consumption is the dosage forms and the product matrices as those required for many veterinary medicines are highly complex. This is particularly true of products with active ingredients administered via animal feed. Often, feeds and premixes are based on natural products such as grains, which can be variable by their nature. This can present challenges in developing sufficiently specific test methods. Grains sourced from different locations may have taken on different levels of components from various soil compositions. Therefore, new interferences can appear during product analysis.

Additionally, premixes often contain high levels of vitamins and minerals, potentially interfering with the separation and detection of analytes of interest. During method development, scientists must use sample extraction and clean-up techniques such as Solid Phase Extraction (SPE) to maximise the specificity of the method, which can help address these issues. Additionally, many medicines for companion animals (such as cats and dogs) may require complex flavourings to ensure the product is enticing enough to consume. Complex flavourings can introduce significant challenges when developing methods employing chromatographic separation.

The variety of dosage forms required for veterinary products is vast. Some products are delivered as pastes, which can make accurate and precise measurement difficult given their highly dense and sticky nature. The right choice of solvent becomes essential to disperse the paste, and dissolve the active

ingredient and any impurities to allow accurate quantitation. Granular and feed products may be prone to settling and segregation during transport and handling, so developing robust procedures for homogenisation and sampling are also critical to establishing a reliable testing method.

Manufacturers must consider all possible dosage forms in which the drug may be delivered during method development. There may be a requirement to analyse the active as a raw material even where the final delivery may be in the form of feed in an intermediate premix product.

An additional challenge relates to sourcing reference materials. Although this is rare, when a product is not medically relevant to humans, suitable reference materials can be challenging to source. Appropriate reference materials are critical to ensuring accurate quantitation of the analytes of interest in the product.

Evaluation of Stability Data

How stability data is evaluated depends on the type of study and its objective. Therefore, data evaluation should be considered on a case-by-case basis and defined upfront in the stability study protocol. Similarly, the point in time when the data is assessed is also important. Short-term stability tests, such as excipient compatibility, may be assessed at the end of the study when all the data can be reviewed as a single data package. However, for longer-term stability studies where stability time points are months apart, it is critical to evaluate the data at each time point to determine any changes in the product and assess the potential risk of that change on the subsequent time points.

When manufacturers perform stability studies early in product development, such as when assessing excipient compatibility, there is usually no specification for comparison against stability study data. These tests are usually performed as exclusionary studies to rule out certain excipients based on the degradation profile. As such, the data evaluation can be relatively simple and limited to comparing assay value and degradation profile across excipients.

Stability data generated at the long-term storage conditions can help when proposing a retest period or shelf life longer than the period of stability data generated through extrapolation. In other words, 12 months of real-time data may substantiate 24 months of real-time storage on the pre-requisite that no change is observed in the data sets at accelerated and long-term stability storage. Additionally, stability data generated at accelerated storage conditions may be used to substantiate the long-term stability of the product not yet generated through extrapolation, *i.e.*, six months of accelerated data may substantiate 12 months of real-time storage. Manufacturers can use this approach if no change has been observed under accelerated conditions. They can also perform statistical data analyses to contribute to shelf-life justifications where notable changes have been observed.

To perform more detailed testing of veterinary animal health products, businesses have started using more advanced analytical equipment, and it is becoming common to commission independent testing, rather than conduct it in-house. Often, manufacturers will turn to third-party partners for both technical and regulatory support, to streamline the process of bringing animal health veterinary products to market and obtain data that demonstrates safety.

Stability testing is vital for characterising and understanding drug substances and products. Working with an experienced analytical testing partner, like Broughton, from the project's outset can help manufacturers design stability studies tailored to their veterinary health product and the intended application. For more information, visit Broughton's analytical and testing services page.

REFERENCES

1. https://www.gov.uk/guidance/veterinary-medicines-regulations-annex-ii-requirements/section-iiib

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Operations Manager Beccy oversees all laboratory activities and works with her team to deliver excellent customer satisfaction whilst continuously striving to improve current processes and laboratory efficiencies. Beccy studied a BSc (Hons) in Chemistry with Pharmaceutical and Forensic Science from the University of Bradford and joined Broughton in 2009 as a Scientist. During her career, Beccy has gained experience testing a wide variety of products for both the human and veterinary pharmaceutical markets, gaining product knowledge and troubleshooting experience. Beccy works closely with customers to understand their testing requirements and individual business needs to help these be achieved.