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The Importance of Excipient Testing

An 'Active Pharmaceutical Ingredient' (API) is the term used to refer to the biologically active component of a drug product, while an 'excipient' is often defined as an inactive substance that serves as the vehicle or medium for a drug or other active substance.

This often leads to the misunderstanding that an excipient is an inactive ingredient, a perception reinforced by the fact that they are seen solely as ingredients used to produce a tablet, cream, or solution that allows a patient to receive an API. However, they often perform vital and 'active' roles in medicines, including:

- Helping to control the bioavailability of an API to meet specific requirements.
- Helping with binding and coating in the drug manufacturing process.
- Performing a critical role in stabilising unstable components such as proteins.
- The use of colourings and flavorings to mask unpleasant tastes or odours and allow easy identification of different drugs.

Perhaps some of this misconception or poor terminology comes from the fact that excipients are often not initially developed and manufactured to be used by the pharmaceutical industry and so the origins of an excipient design and intended use of an excipient component of a medicine may have its origins in another industry altogether. For example, a material designed and developed primarily for the automotive industry may have the right characteristics for use as an excipient in a pharmaceutical product. The safety data, specifications and testing requirements for the material may be perfectly sensible for use in the automotive

industry, but it should not be taken for granted that these would be sufficient for its use in a medicinal product. The primary component could be safe, but consideration must also be given to the related impurities that may be the result of the manufacturing process. As such, it is essential that pharmaceutical manufacturers ensure the specifications for excipients and QC testing is handled with the same diligence as for APIs. But this isn't always the case.

Contaminated cough syrup tragedy

Glycerol (or Glycerine) is a popular alcohol used within the food, pharmaceutical, and personal care industry. However, there have been many cases over the years of glycerol adulteration identified by regulatory agencies, usually involving DiethyContalene Glycol (DEG) as the adulterant. In Haiti in 1995-96, 88 children tragically died of diethylene glycol poisoning**,** involving cough syrup. A similar incident occurred in Panama in 2006.

As a result, the FDA stipulated a safety limit of 0.1% w/w DEG in products. Working with the FDA, the USP developed a Gas Chromatography (GC) method capable of separating and quantifying glycerine, ethylene glycol and diethylene glycol and published a revised monograph, which continues as the standard used today and with it came an associated Certified Reference Materials to aid traceability.

It is therefore essential that all components used in the pharmaceutical manufacturing process and not just the active pharmaceutical ingredient (API), must be assessed and tested to full monograph specifications. Limited testing such as a simple ID may not be adequate and may present a risk. A more recent example is the issue with Sartans, where there is evidence that recycled solvents containing NDEA or NDMA are a source of contamination.

As excipients can comprise up to 90% of a pharmaceutical product they are being increasingly identified as important to the performance of drug development. This greater understanding of the critical role and performance of excipients has led manufacturers of both drug products and excipients to develop new 'novel' excipients. The FDA currently does not review the safety of novel excipients outside the context of an investigational new drug (IND), new drug applications (NDA) or biologics license application (BLA). However, in response to requests from various stakeholders, the FDA is now looking at ways of introducing programs to address this issue.

One of the ways that pharmaceutical and biotech companies are ensuring the quality and performance of excipients is by engaging testing laboratories, that specialise in the Quality Control (QC) testing of raw materials and who apply the same level of attention to detail to both APIs and excipients.

See: https://www.butterworth-labs.co.uk/services/quality-control/

Author Biography

John Welch
Associate Director – Business Operations

John joined Butterworth Laboratories in 1987 as an Analytical Chemist and has progressed through positions of Laboratory Manager, QA Manager, and Business Development Manager, to reach his present position. He is a Chartered Chemist and Fellow of the RSC.

business@butterworth-labs.co.uk