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# Shelf-lives of IV products: Are there any limits?

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# Shelf-lives of IV products
## — are there any limits?

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**S**upply of intravenous injections in a ready-to-administer form is an important part of the pharmacy service in hospitals. Unfortunately, NHS hospitals are finding it increasingly difficult to prepare such preparations in-house, particularly in large batches with extended shelf-lives, which require fully licensed facilities.

The introduction of dose-banding (prefilling a stock of syringes with a range of standard doses) and home intravenous administration programmes is increasing the demand for standard doses with longer shelf-lives. Consequently, there is a rapid growth in outsourcing the supply of these products to the commercial sector.

It is becoming evident that the assignment of the longest shelf-lives by particular suppliers is becoming a marketing tool in its own right. However, the temptation is to maximise the shelf-life of such products without fully accounting for all factors which can influence their stability.

It is vital that pharmacists responsible for the purchase and use of centralised intravenous additive (CIVA) products understand the issues which affect the products' quality when their shelf-lives are extended.

## Stability

So what are the factors which influence the stability of a product after transfer to a syringe or other administration system? And is it safe to extrapolate data from one container type, diluent, concentration or supplier to another?

Many injectable drugs are used in their salt form to ensure aqueous solubility, so can be influenced by pH as well as drug concentration and choice of diluent. Thus, even the simplest molecules intended for intravenous injection require some degree of formulation. This, together with product purity and the presence of related substances, will vary between brands of the same drug.

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The safety of extrapolating data between different commercial sources of the same injectable drug is becoming an increasingly important issue with the growth in the numbers of generic alternatives for injections.

How will minor variations in the source and concentration of excipients affect stability after dilution and during storage in a syringe or IV infusion bag? Since drug concentration often effects stability, extrapolation from different concentrations is unacceptable.

Even more important is the chemical form of the drug. For example, etoposide will behave completely differently from the newer phosphate salt now available for injection.

## Containers

The containers used for the preparation of CIVA products are generally restricted to plastic syringes, ambulatory infusion devices and infusion bags — none of which was designed for the extended storage of potent drugs. The possibility of interaction between the injection and the container must be considered as part of the process of assigning shelf-lives, particularly with drugs which are relatively stable in aqueous solution, or contain solvents to maintain drug solubility. In the former case, it is tempting to assign the shelf-life based only on the stability of the drug, but there must be some recognition of the limitations posed by the container. For example, plastic syringes may leach unwanted chemicals into the injection, and PVC will allow losses of water during storage. Since any of these effects is difficult to evaluate, some degree of caution is essential. In the case or poorly soluble drugs, which are usually diluted before administration, there is a danger of phthalate extraction and drug precipitation during storage because the solubilisers and solvents are also diluted in the infusion.

## Evaluating data

There is much published information describing stability studies of injectable drugs in a wide range of containers and storage conditions. However, increasing numbers of studies which have never been published are being used to support shelf-lives, and are often not scrutinised by experts. Those who are not experts in the area of clinical pharmaceutics will find it impossible to evaluate such reports critically.

Acceptance criteria for stability studies are often difficult to define. For example, allowing 5 per cent drug loss in an infusion which is administered on a one-off basis, where the pharmacology and toxicology of the degradation products is known, may be an acceptable practice. If, on the other hand, the infusion is to be administered repeatedly over long periods and little is known about the degradation products, the application of such a limit may compromise both therapeutic effect and patient safety.

The end-user is ultimately responsible for the purchase and employment of CIVA products and it is vital that they feel confident in the safety of such injectables. Asking an aseptic services supplier what shelf-life they apply to a particular infusion may be the wrong question. Prospective purchasers should instead ask: "What is the evidence to support the assigned shelf-life?"

Proper scrutiny of the evidence available is required before the pharmacist can be sufficiently confident that they are not putting the patient at greater risk by employing pre-prepared injectables which have been stored in a ready-to-administer container. Without this careful and critical evaluation by those with sufficient knowledge and experience, patients will be at greater risk and the pharmacist will be responsible for the consequences.

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