



IntelliFill® i.v.
Medication Preparation,
Storage and Beyond-Use Dating



COMPOUNDING DOSES WITH INTELLIFILL i.v.

The IntelliFill i.v. is used to compound syringes containing sterile medication doses for use in humans. Compounding is the practice of preparing medications for immediate or near-term use in response to a physician's order or in reasonable anticipation of receiving such an order.

In some cases, the usage is of sufficient magnitude that just-in-time preparation is impractical, and users may prefer to prepare doses well in advance of their anticipated use. Doing so requires the assignment of shelf lives longer than those traditionally given to pharmacy-compounded sterile injectable doses.

BEYOND-USE DATING AND SYRINGES AS STORAGE CONTAINERS

The governing documents regarding shelf life are found in the United States Pharmacopoeia (USP), specifically in the chapter regarding the compounding of sterile preparations (Chapter <797>) and the chapter regarding sterility testing (Chapter <71>). USP <797> refers to the matter of shelf life using the term "beyond-use dating."

Determining a beyond-use date involves assessing three parameters:

- The chemical stability of the drug solution at varying temperatures
- The ability of the filling system to generate a container with sterile contents
- The ability of the container to maintain sterility once it is achieved

Chemical stability is generally a matter of public record; information regarding the stability of drugs in solution under various storage conditions can be found in a variety of reference books and articles (commonly available in hospital pharmacies).

USP <797> provides default beyond-use dating presuming the drugs involved are stable and sterility is the primary consideration. These beyond-use dates presume the products may be contaminated and so attempt to enforce use or destruction before any such contamination could become clinically significant.

Interestingly, USP <797> appears to presume the third item as a given; default beyond-use dates are to be used *in the absence of sterility testing or end-product sterilization*. If end-product testing or terminal sterilization is employed, USP supplies little guidance about assigning beyond-use dates. End-product testing is described in USP <71>. This chapter permits either end-product sterility testing using a statistically derived sampling procedure or process-simulation using a statistically significant number of tests to assert sterility of a batch.

Of specific interest to IntelliFill i.v. customers is the suitability of a syringe originally intended for immediate use as a storage container.

RESPONSIBILITIES

Customers are responsible for developing and enforcing their own beyond-use dating policies based on their knowledge of preparation, storage and distribution of doses prepared on IntelliFill i.v.

The role of Baxa Corporation is limited to providing information to customers regarding the beyond-use dating policies used by other Baxa customers and providing validation data regarding the operating capabilities of IntelliFill i.v.

CHEMICAL STABILITY

Drug manufacturers are required to provide information on the stability of drugs in varying solutions for their intended uses as described in their product literature. While this does not require them to identify the conditions under which the longest stability may occur, it does require them to identify the minimal stability available for their drugs under common use conditions.

A variety of professional journals, such as the *American Journal of Health-System Pharmacy*, publish original articles on the stability of drugs in solution under various conditions.

These two sources of information are well summarized in such reference texts as:

- *American Hospital Formulary Service*
- *Trissel's Handbook on Injectable Drugs*

The vast majority of disposable syringes in the United States are made of polypropylene; the Terumo syringe used in IntelliFill i.v. is a polypropylene syringe. Unless specifically stated otherwise in cited research, results obtained with one polypropylene syringe can generally be transferred to another.

Baxa does not perform drug stability research; nor can it provide direct information about the chemical stability of a drug in a polypropylene syringe. On occasion, Baxa may fund public research into the stability of specific drugs in polypropylene syringes to advance the state of public knowledge. Such research is expected to be published in peer-reviewed literature to become part of the community of practice for the profession.

Baxa can provide an annotated summary of drug stabilities of interest to its customers, based on this public literature.

STERILITY

Baxa asserts that the IntelliFill i.v. device, maintained and operated as described in the user manual and training materials, produces syringes with sterile contents.

During validation, this sterility was asserted based on more than 800 media challenge syringes being produced under a variety of use cases without contamination. Only those syringes prepared on an uncleaned device as a control were contaminated. Laboratory analysis confirmed that syringes that appeared contaminated were, in fact, contaminated and that syringes that appeared uncontaminated did contain uncontaminated media.

Every IntelliFill i.v. customer performs weekly media challenges to assess their own performance. By our estimates, more than 50,000 such media challenge syringes are produced each year without evidence of contamination on production devices.

Use of HEPA-filtered air (maintaining an ISO Class 5 environment), appropriate cleaning and sanitizing techniques and careful monitoring of bioburden with media challenges, contact paddles and air paddles provides the kind of process controls necessary to reliably deliver syringes with sterile contents.

In 2007, ForHealth Technologies (now Baxa Corporation) performed data analysis of customer production data and determined that in the year between November 2005 and November 2006, customers prepared over 25,000 media challenge syringes with no reported contamination.

That same year ForHealth Technologies contracted with ClinicalIQ to develop and execute an evaluation of IntelliFill i.v. operating in reservoir mode in an uncontrolled environment against USP requirements. That study is pending publication. The study evaluated air flow both inside and outside the automation deck, active environmental monitoring, USP-compliant end-product testing of a run of more than 2,000 0.9% sodium chloride syringes and media challenge testing producing over 10,000 media challenge syringes using three different operators over a three-day period. The results demonstrated that:

- IntelliFill i.v. maintains ISO Class 5 conditions or better during operation and restores those conditions within 45 to 60 seconds of losing them.
- IntelliFill i.v. maintains CFU/1,000 ft³ of air consistent with aseptic manufacturing suites.
- IntelliFill i.v. produces syringes with end-product testing results that support extended beyond-use dates.
- IntelliFill i.v. produced 10,497 media challenge syringes without a single contaminated syringe, indicating a statistical contamination rate considerably better than the minimum required for an aseptic manufacturing suite.

Eric Kastango, of ClinicalIQ, has therefore stated that an IntelliFill i.v. device operated by a properly trained user who has demonstrated the ability to produce sterile syringes can assert sterility of a batch per USP <797>, as long as the procedure at risk (mounting and hanging the reservoir bag) can be demonstrated to not have introduced contamination. This is done by

using the same reservoir tubing used to deliver a batch of drug to prepare a batch of media challenge syringes.

THE SYRINGE AS A STORAGE CONTAINER

ForHealth Technologies (now Baxa) and its customers have assessed the suitability of the Terumo 10 mL syringe (with the cap applied by IntelliFill i.v.) as a long-term storage device.

Ultimately, the assignment of beyond-use dating is the responsibility of the pharmacy preparing doses, based on chemical stability, assessment of the suitability of their operation of IntelliFill i.v. and the conditions under which the resulting doses will be stored. The USP places the responsibility for determining beyond-use dating on the compounding pharmacy, and does not permit the vendor community to stipulate beyond-use dating.

Validation media challenge syringes prepared during initial device validation at ForHealth Technologies were retained for six months at room temperature without evidence of contamination. No formal study or evaluation was documented.

A review of media challenge syringes produced at a customer site in both modes of operation and analyzed after two years of storage at room temperature demonstrated that the syringe contents were sterile and that the media could have promoted growth had they become contaminated.^{1,2}

Customers have performed their own long-term studies, keeping media challenge syringes prepared on IntelliFill i.v. in reservoir mode incubated at 30° C for periods in excess of six months without evidence of contamination. The longest such syringes have been kept is more than two years (prepared April 23, 2003) without visual evidence of contamination.

In a study conducted Septemer 2003, one hundred syringes were filled with 6 mL 0.9% Sodium Chloride for Injection, weighed, stored at room temperature and weighed weekly to assess passive fluid loss. At the conclusion of 12 weeks, the mean syringe weight was unchanged and the greatest syringe weight variance was less than 0.1 g.

ADDITIONAL PACKAGING

Baxa also provides an optional bagger that can be used to enclose each syringe in a sealed plastic bag for additional protection during shipping and storage.

CONCLUSION

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Baxa can describe recommended behavior and actions but cannot control the manner in which IntelliFill i.v. is used at particular sites; nor can it control the methods by which doses are manipulated, packaged, distributed, stored or used once they have been prepared on the IntelliFill i.v. As such, customers must determine their own beyond-use dates based on their best practices.

Chemical stability is determined by a review of public literature. Baxa provides annotated summaries of some of this literature as a convenience to our customers.

Baxa asserts that doses prepared on IntelliFill i.v. maintained and used as described in the device literature will have sterile contents.

ForHealth Technologies (now Baxa) has performed internal experiments showing syringes do not lose weight when stored at room temperature and exposed to ambient air over a period of 12 weeks.

Customers have reported retention of media challenge syringes without growth for periods as long as six months.

Customers have reported producing more than 25,000 media challenge syringes within a one-year period with no contamination across a variety of locations and operators.

ClinicalIQ has performed analysis of IntelliFill i.v. operating in reservoir mode as a primary engineering control, concluding that IntelliFill i.v. supplies conditions similar to those of an aseptic manufacturing suite. That analysis has further resulted in the opinion that syringes produced by IntelliFill i.v. in reservoir mode can be given extended beyond-use dates when operated according to manufacturer instructions and supported by media challenge testing of the tubing after each run.

IntelliFill i.v. is manufactured for Baxa Corporation by FHT, Inc.

1. Dennis A. Tribble **Long-term sterility of syringes filled robotically from vials** *Am. J. Health Syst. Pharm.*, May 2007; 64: 926 - 928.
2. Dennis A. Tribble **Long-term maintenance of sterility in single-use syringes** *Am. J. Health Syst. Pharm.*, April 2006; 63: 702-703.