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PRODUCT STABILITY ISSUES

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BACKGROUND

Pharmaceutical products may exhibit thermal degradation. When developing and implementing a sterilization cycle, it is necessary to limit or balance the amount of product degradation while still using sufficient thermal input to achieve the desired sterility assurance level (SAL).

Some product types, e.g., low concentrations (<1%) saline, are extremely heat stable. Overkill-based sterilization cycles may be used to achieve the desired SAL. This is the typical approach used for many products manufactured in Europe. Other products, however, are adversely affected by thermal input. Degradation can lead to the final product not having the required potency, or the creation of degradation products in unacceptable levels. There are several ways to minimize the thermal degradation to the product while still achieving the desired SAL. This chapter discusses some of the requirements for sterilization-related stability studies and methods to reduce the thermal-related product degradation when subjecting the product to a terminal sterilization cycle.

STABILITY TESTING REQUIREMENTS

The Food and Drug Administration's (FDA's) stability guideline (FDA 1987) requires that manufacturers have stability data to support the expiration dating (shelf life) of the product at the recommended storage conditions. The stability of product can be altered based on the stress delivered to the product

during the manufacturing process. FDA's Office of Generic Drugs issued guidance information (1995) that specifically states that stability data must be collected at the worst-case conditions of sterilization. This is defined within the document as the maximum exposure dwell time and the maximum exposure temperature. Additional sterilization stability requirements are provided in another FDA guidance document on sterilization (FDA 1994). These include required stability data at the stresses of sterilization, maintenance of microbial barrier properties following sterilization, and container-closure integrity demonstration at the stresses of sterilization. This document also requires that a maximum F_o for the sterilization process be submitted.

Unfortunately, there is little guidance provided on how the maximum F_o should be utilized in the process, since many companies only calculate F_o in qualification studies. It also does not indicate whether the maximum F_o is for the exposure dwell period or the total cycle. One concern in assigning a maximum F_o is whether the regulatory agencies will ask to see product stability data to support the selected value. Accordingly, it becomes important to understand how to determine the maximum F_o value, and whether the product should yield acceptable stability data if processed at the specified conditions.

Maximum F_o

There are many ways to determine the maximum F_o allowed for a cycle. This section of the chapter describes one example and the concerns associated with the method. A method should be selected by each manufacturer, balancing regulatory risk, business risk, and product.

Example

Company XYZ established the following program for calculating maximum F_o.

It was decided that the maximum F_o value would be defined as being calculated only during the exposure dwell time period (consistent with the firm's requirements with minimum F_o). The firm postulated that the worst-case F_o would be achieved if the product was subjected to the maximum exposure dwell time at the maximum allowable exposure temperature. Numerical calculations were performed to determine what the F_o value would be at these conditions (i.e., assuming that at all of the minutes of exposure, the probes were at the maximum allowable temperature). When the value was calculated, the firm decided to add a bit of tolerance to account for some minor differences in actual product temperature at the time of exposure start. This was achieved by always assigning maximum F_o values to whole integers rounding up to the next number ending in 5 or 0. This rounding provided an extra allowance for F_o accrued during the warm-up period. This yielded an arbitrary number, not based upon scientific research.

An example of this calculation is included in Figure 1. Since the firm executed product stability studies at the maximum exposure dwell time and the maximum exposure temperature, it felt confident that the value could be supported with the available product stability data.

Issues With the Method

In general, this method worked well for the firm. One problem did occur over several years of using this method of calculation, however. For very short sterilization cycles, e.g., less than 10 minutes duration, it was found that the rounding method did not provide enough safety factor to account for the F_o accumulated during the chamber come-up time. An additional safety factor was added for very short cycles.

One other potential issue was noted for cycles that were used to sterilize extremely heat sensitive products. In many of these cycles, tight temperature controls were used during the exposure dwell period, e.g., ± 0.5°C. There was concern that, in this case, there might not be sufficient safety factor to account for the accumulated F_o during the chamber come-up time. The rounding procedure was evaluated on a case-by-case basis, since any additional thermal input had the potential for an extremely adverse product profile.

Methods to Reduce Thermal Degradation of Product

There are several methods that may be used to reduce the negative impact of thermal degradation on the product stability. Some examples are as follows:

- Change in sterilization process
- Presterilize some components or areas of the product that are difficult to sterilize

Figure 1. Example of Maximum F_o Calculations

Where
Maximum Exposure Cycle Time = 10 minutes
Maximum Exposure Temperature = 123.5°C
F_o for one minute at 123.5°C = 1.753

Then
Maximum F_o = 10 min. × 1.733 $F_{o/min.}$
= 17.33
Maximum F_o (after rounding) = 20.0

- Change the sterilization model utilized
- Aseptically fill the product prior to terminal sterilization
- Reduce the allowable presterilization bioburden
- Change in biological indicator (BI) for the process
- Higher temperature–shorter time cycle
- Change a combination of parameters

While this list is not all-inclusive, it provides guidance to some of the methods available, without eliminating the possibility of aseptic filling. This is especially important for large-volume parenterals (>100 mL) manufactured in the United States, as aseptic filling of product is not routinely allowed.

Change in Sterilization Process

This approach may be of limited value to many companies, as they may not have access to numerous sterilization processes. The method of heating, and the effect on the product, may be altered by the sterilization process. An example of this is the sterilization of lipids and emulsions. The product degradation can be reduced by subjecting the product to a rotary sterilization process. By rotating the product, it does not heat/settle in one location, and degradation is minimized. Another example is using a lower temperature cycle for semirigid plastic containers, which are not sterilizable at 121°C, but can be sterilized with air or water overpressure at a lower temperature.

Presterilization of Some Components or Difficult-to-Sterilize Areas of the Product

This approach may be effectively used when there are areas that potentially limit steam penetration, thereby causing dry heat, e.g., container-closure interfaces, syringe interfaces. Presterilization of these components reduces the bioburden present and may allow for a shorter sterilization cycle. This is especially useful for closure, which can be presterilized and assembled to the product, e.g., some parenteral bag closures. In some cases, this may greatly reduce the lethality required in the final terminal sterilization process.

Changes in the Sterilization Model Utilized

An overkill-based sterilization model delivers the most thermal input to the product. A combined BI–bioburden-based model delivers less thermal input to the product, and an absolute bioburden-based model delivers the least thermal input to the product. Accordingly, the thermal input to the product can be reduced by changing the sterilization model used for the product.

Changing the model is usually reflected by a lower minimum F_o required for the cycle. This generally relates to a shorter exposure time at the same exposure temperature.

Aseptically Filling the Product Prior to Terminal Sterilization

Aseptic filling of the product prior to terminal sterilization reduces the initial population of bioburden (potential survivors) in the product at the start of sterilization. When used with the combined BI–bioburden-based model, this can reduce the total log reduction required to achieve the desired SAL. This is reflected by a lower minimum F_o required. This subject is discussed in detail in Appendix 2 of this book.

Reduce the Allowable Presterilization Bioburden

This approach is similar to aseptically filling the product prior to terminal sterilization. In this case, the bioburden level may not be zero, but may be less than specified in the original sterilization model. For example, a product with a very low pH may inherently be bacteriocidal. For this reason, the naturally occurring bioburden may be very low. Many companies develop their sterilization models assuming 10^{-6} survivors, based upon an initial BI challenge of 10^6 changing to 10^2 (i.e., 100). Using a combined BI–bioburden-based model, the total log reduction required to achieve the desired sterility assurance level would be reduced by four logs and reach a corresponding lower minimum F_o.

Initial bioburden limits may also be set to reflect tighter environmental control for certain products. For example, the safety factor above the actual bioburden resistance factor for use in the model may be reduced, becoming closer to the actual resistance.

Change in the BI for the Process

The BI *Bacillus stearothermophilus* (subsequently reclassified by ATCC as *Geobacillus stearothermophilus*) typically has a D-value of approximately 2.0 minutes. The BI *B. coagulans* (ATCC 51232) typically has a D-value approximately 1.5 minutes, and *B. sporogenes* and *B. subtilis* 5230 have D-values of approximately 0.5–0.6 minute. All of these D-values are substantially higher than the environmental flow thermal resistance found in pharmaceutical manufacturing environments. The actual environmental flora heat resistance is well below 0.5 minute. In addition, when the indicators are placed in or on products, the D-value may be increased or decreased.

For example, the *B. stearothermophilus* D-value increases in saline solutions, and may increase 400%–500% in potassium chloride. *B. coagulans* may not increase at all in the presence of saline, but does increase in calcium-based solutions (Moldenhauer et al. 1995).

Since the sterilization model used utilizes the D-value of the BI challenge to determine the required lethality, selecting either a BI with a lower inherent D-value or the BI whose D-value is not increased by the product can reduce the lethality required in the cycle. This is reflected by a lower minimum F_o required.

HIGHER TEMPERATURE—SHORTER TIME CYCLE

When confronted by a product adversely impacted by thermal input, the natural tendency of many individuals is to try to reduce the exposure time and/or the exposure temperature. The degradation kinetics for product, however, show that a lower temperature for a longer time is actually a worst-case condition for product degradation.

One of the most effective methods of sterilization of heat sensitive products is to use a higher exposure temperature for a shorter period of time.

Figure 2 is an example of the difference in the cycle when the exposure temperature is raised 10°C. This type of process may also be called a flash sterilization cycle because of the short exposure dwell time.

CHANGES TO A COMBINATION OF PARAMETERS

In some cases, it may be necessary to change a variety of parameters to achieve the sterilization lethality and product stability parameters desired.

For some oxygen-sensitive products, tighter control of the oxygen level may allow terminal sterilization of the product as it reduces some of the total degradation seen following the sterilization process (Duncan et al. 1998).

Whenever possible, every effort should be made to terminally sterilize product because of its increased safety from contamination to the end user.

CONCLUSION

When evaluating the effects of the sterilization cycle on product stability, it is important to recognize that F_o alone cannot be correlated to product stability. For example, cycles using any of the sterilization models, any BI, and a variety of sterilization times and temperatures can all yield the same total F_o for a cycle. The effect on the product for each variation of the cycle may yield vastly different product degradation profiles. It is useful to perform some stability studies early in the product formulation development process to identify products that may be potentially subjected to a terminal sterilization cycle.

Figure 2. Impact of Change in Exposure Temperatures on the Required Exposure Time

Lethality Calculation
$L = 10^x$

where $x = [T_{actual} - T_{ref}] / z\text{-value}$
For F_o, $T_{ref} = 121.1°C$
z-value = 10°C

Minutes required calculation

Required F_o for Model Selected = 8 minutes

Minutes required = 8 minutes/ (lethality per minute)

Temperature (°C)	Lethality per Minute (F_o)	Minutes Required for $F_o = 8$
121.1	1.0000	8.0000
122.1	1.2589	6.3546
123.1	1.5849	5.0477
124.1	1.9953	4.0095
125.1	2.5119	3.1849
126.1	3.1623	2.5298
127.1	3.9811	2.0095
128.1	5.0119	1.5962
129.1	6.3096	1.2679
130.1	7.9433	1.0071

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