



TECHNICAL TIP

IRRADIATION OF ACTIVE PHARMACEUTICAL INGREDIENTS AND PHARMACEUTICAL FILLERS

Abstract

Historically, Active Pharmaceutical Ingredients (APIs) and filler or inert materials for pharmaceutical preparations were not considered for terminal sterilization with irradiation due to concerns such as stability and acceptability by Customers, among others. In recent years, this area has been opened to consideration and evaluation as the benefits of terminal sterilization processes become known and are looked at more closely with individual products. This TechTip will look at issues that must be considered, the benefits of terminal sterilization for these types of materials, characteristics that lead to successful sterilization, areas that incite concern or special care in designing a sterilization plan and tools to improve success rates.

Introduction

Any company producing a healthcare product with the expectation of sterility is eventually faced with the same questions. Can my product be terminally sterilized? If yes, by what method? Will a traditional, well documented method like gamma irradiation, electron beam, ethylene oxide, heat (dry or moist) or a more non traditional, even novel approach provide the assurance I must have and still provide the product performance and safety needed? Historically, little doubt existed in most minds for active ingredients; they were expected to be prepared aseptically. Today we see more consideration and testing involved in these decisions, specifically with irradiation processes.

Why Irradiation?

1. Effectiveness. Well understood mechanism of providing microbiocidal effects.
2. Documentation. Published, accepted methods for setting an appropriate dose and sterility assurance levels.
3. Costs. Avoids or reduces costs, time, equipment validation

and equipment maintenance to manufacture the product in an appropriate class of clean room. Basically, full sterile manufacture is not needed. Locations for sterilization available world wide and turn times are rapid.

4. Adds no moisture to product which can lead to reduced stability.
5. Adds no excess heat (as with autoclaving or dry heat). Heat may also affect stability.
6. Published options for dose setting have expanded in recent years to give more options, especially on low minimum doses.
7. Adaptable to small volume products with special handling conditions.
8. Industry experience, expanded search capabilities in review of published data and suggestions through web accessibility of even very old articles.
9. Leaves no residuals.
10. Useful for product that cannot be filtered effectively.

Considerations

The best advice in this area is always to start early. This is critical since validation data can be obtained in development studies and clinical trial batch production. Also, if it does not work, other options can be considered early. Decisions made with the sterilization method in mind may limit problems later. Even simple choices on a final format or vehicle of delivery may be given proactive consideration if the sterilization process is also considered. Remember, an irradiated drug is considered potentially a different drug than the un-irradiated version. Testing the effectiveness, stability and impurities of an un-irradiated version means additional testing if you do not test irradiated material. Testing early avoids wasted time getting required data.

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1. Remember that irradiation is not going to be universally acceptable, even with a lot of product testing. Some molecules will not tolerate doses high enough to provide required Sterility Assurance Levels (SALs).
2. Irradiation requires consistent preparation methods for process reproducibility. The question is not really if the end product will be sterile or not, but variations in production methods can lead to different results from batch to batch. This includes controlled conditions that affect microbial population (quantity as well as type of organisms in population).
3. The carrier of active molecules for sterilization matters; it too will be irradiated and must maintain the properties for which it was chosen. What if filler used to give the product a desirable viscosity is changed by chain scission of a long chain polymer like a starch?
4. Identify critical parameters and have tests to accurately measure these parameters. Sometimes these are more than just pharmacologic properties. An example may be color. Is the color critical to assuring full solubility? Does a change evoke concern that the product is different or bad?
5. Set reasonable limits for these critical parameters. Within what range will the product still be safe and effective for its intended use? How much of a known impurity is acceptable? What level of potency change is acceptable? Can the potency be adjusted post irradiation to assure consistency if it is changing (bulk irradiation followed by dispensing as needed)?
6. Set specifications for raw materials such as sources and accepted impurity levels. When will the raw materials be considered out of specification?
7. Set the desired or required SAL early to help you test doses high enough to make the claim possible. This is a common mistake, as passing a sterility test is not synonymous with documenting an SAL. Testing at a low dose may result in a product that passes a sterility test, however the product may not meet the required SAL of, for example, 10^{-6} .
8. Dry formats are known to be more successful than liquids.
9. Be open to modification of format. Can bulk powder be sterilized rather than final dispensed quantities?
10. Select containers that can also tolerate the sterilization process. Be aware of materials effects on these as well.

Where can more information be found?

Information on pharmaceuticals is available, though limited. The conditions under which an experiment was conducted and the exact formulation (manufacture source materials, concentration, etc.) will affect the results. Active molecules are unique as their methods of production and purification can affect their properties dramatically, thus why the details on them are highly proprietary. Small changes can have dramatic results; some positive and some negative.

How can results be improved?

The following chart lists common issues with the sterilization of APIs and pharmaceutical fillers and options for addressing such issues.

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Issue	Options	Notes
Viscosity Changes	Add more of whatever makes the product thick or dilute if too thick	Manufacture at extreme to assure effects of irradiation process give end result needed
pH Changes	Adjust buffers	Appropriate buffer with capacity to handle radiolysis products; especially from water
Color Change	Change carrier or filler materials; limit maximum allowable dose Adjust dose rate	Limiting dose may mean better control of microbial population allowed Faster dose rate can reduce time for oxidative damage
Stability of Active Molecule	Free radical scavengers; antioxidants; freezing; lyophilization Oxygen depletion	Additives must be considered for biocompatibility; concentration must be worked out carefully. Freezing may impact stability if freeze thaw cycles are not acceptable. Lyophilization may be difficult or affect reconstitution Purging oxygen (vacuum, argon or nitrogen atmosphere) removes oxidation potential
Potency	Adjust buffers: solidify by freezing or drying prior to irradiation process even if not needed for long term storage. Adjust initial compound mass to assure percentage active at end is where needed.	Freezing presents issues for transport and storage and may affect selection of containers provided. Cost and availability may limit ability to overfill an active compound.
Liquid Stability	Freezing or drying	Freezing is the most common method to limit free radical damage by limiting active species mobility (forcing recombination to original compound)

Conclusion

Early consideration of the sterilization method allows for changes prior to committing to a final formulation in regulatory filings. Testing early can eliminate options of terminal sterilization as well, but needs to be done with documentation as to why. The benefits of terminal sterilization, frequently only possible with an irradiation process because of lack of added heat and moisture, makes investigating sterilization a worthwhile step in product development.

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