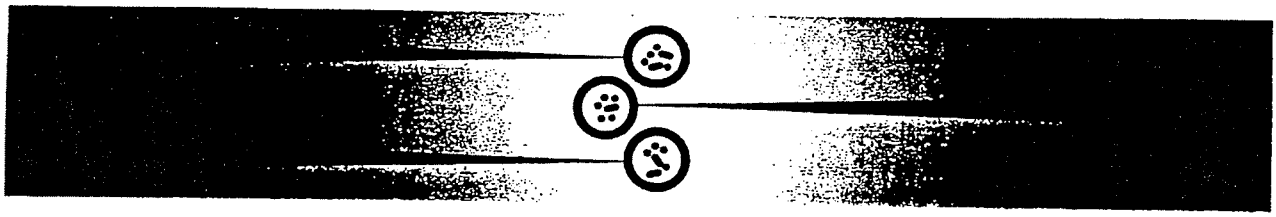

PMF NEWSLETTER

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President's Message

Those of you who were awaiting the much-anticipated harmonized Sterility Test <71> scheduled to become official in USP 24 Supplement 4 (August 1, 2001) will have to continue waiting. The USP decided that some differences still existing between the other pharmacopoeias (mainly the European Pharmacopoeia) and the USP needed to be resolved. There was a possibility that the harmonized version will be published in USP 25 (January 1, 2002) but that will not happen. It may be seen again in the Pharmacopeial Forum (PF) and may be targeted for inclusion in USP 25 Supplement 1 or 2 in 2002.

Also, mark your calendars. The next big USP Microbiology Meeting will be a joint meeting by USP and PDA. This meeting will work as the past USP Open Conferences and it is tentatively scheduled for May of 2002. More details will be given as they become available.

This issue marks the official change of our 483 Corner to the Warning Letter Corner. Warning Letters carry heavier weight than 483's and have become as ubiquitous as 483's previously were. Word has it that FDA now issues Warning Letters more readily as the authority for approval and release of these documents has been pushed down from the Maryland Office (the FDA Main Headquarters) to the Regional offices.

We hope you find the Warning Letter Corner informative and applicable to your line of work.

Laura

IN THIS ISSUE

PURPOSE: To provide a forum for discussion of microbiology issues in the pharmaceutical and related industry.

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About the Author

Lucia Clontz is the Assistant Director for Microbiology at Diosynth in RTP, NC. Lucia is well known for her bestseller book "Microbial Limits and Bioburden Tests". Her newest book "Quality Control Systems for the Microbial Laboratory: The Key to Successful Inspections" is now available.

Failure Investigations, A Key Problem Area During FDA Inspections Still...

The handling of Out-Of-Specification (OOS) test results continues to be a source of FDA 483 observations. As reported in "The Gold Sheet", Vol. 34, No, April 2000, "Out-of-specification result investigations are being cited on almost half of drug and biotech GMP warning letters."

What is the cause for this abundance of observations in an area that has been discussed and over-emphasized for almost 10 years? By now, most companies have extensively studied the US vs. Barr case, to include Judge Wolin's rulings and observations on the case, and reviewed most of the literature on the issue, including the 1998 FDA Draft Guidance on "Investigating Out-Of-Specification (OOS) Test Results for Pharmaceutical Production." The term OOS has become a "house name", and new terms such as OOA (out-of-alert) and OOT (out-of-trend) are now being used during data evaluation. So, what could be the reasons for this continued lack of compliance in an area that we believe, we should have mastered by now?

Well, I think there are two main reasons that could explain this trend:
The first one is that OOS investigations have become the focal point of inspections. According to Marsha Major, an FDA national biologics expert investigator, the quickest way in and out of a firm is to start at the bottom and work your way up. Therefore, FDA inspectors start with the investigations. The focus on failure investigations allows the inspectors to get a handle on the attitude of company managers. It also allows them to evaluate how the higher levels of management deal with internal problems. This gives the FDA a sense for the overall quality system of a company.

In my opinion, the second reason for this continued lack of compliance in the area of OOS investigations, lies within a company's internal systems. Although most firms have at least one SOP on how to deal with OOS results, and in most cases, OOS data do get investigated, companies lack systems to carry out proper investigations. As a matter of fact, according to the FDA, the current top reasons for deficient failure investigations are:

- Lack of retest policy or improper retesting
- Poor documentation
- Use of improper averaging and statistical analysis to report data
- Speed over quality of investigation
- Lack of corrective actions and follow up action plans
- Inadequate level of management involvement
- Lack of training on investigation and troubleshooting
- Issues with accountability and ownership of the investigation process
- Need to clarify when an investigation process should be initiated and concluded
- Systems to prevent recurrence of deviations or aberrant/OOS data not in place
- Resources to conduct a thorough investigation with root cause analysis and corrective action plan not always available.

Companies are being cited for having inadequate procedures, for closing out investigations with undocumented conclusions, and mainly for not implementing corrective actions and follow-up

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plans. So what could be done to reverse this trend? For one, companies must allocate resources, implement systems and have a proactive approach to this crucial area of the business: OOS/aberrant results are inevitable but they must be minimized and managed properly. Companies must invest the resources and time to conduct proper investigations and attempt to find root causes for the problems. Granted, there will be instances where a company will be unable to come up with a conclusive and definitive cause to a failure/excursion. However, true "unexplained results" or "inconclusive investigations" should be rare. If properly evaluated, most investigations, to include microbiological testing, should have an assignable cause or at least a probable cause. When an investigation is performed properly, a company should be able to evaluate the results, consider the "whole picture" and the possible impact on other areas of the company, and implement corrective actions and preventative measures in order to avoid future similar situations.

In summary, a company must realize that OOS investigations are and will continue to be one of the main focus of FDA inspections. Therefore, it is no longer acceptable to push investigations to the "back burner" or quickly complete them for the sake of complying with a timeline established in an SOP, without performing a thorough analysis of the issue's).

To change the current trend, companies must:

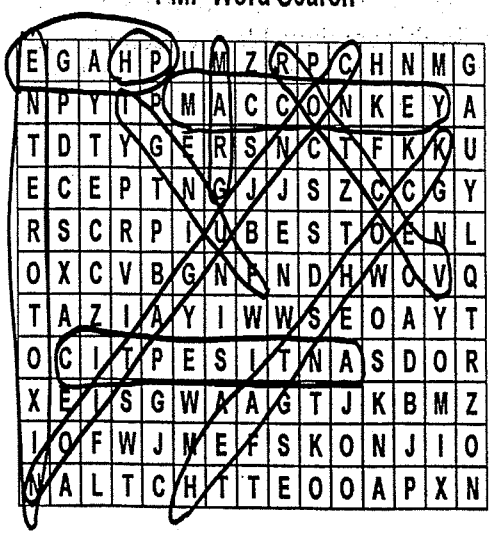
- Follow their own SOPs
- Be aware of potential problems
- Ensure methods being executed have been validated
- Allocate time and resources for personnel training
- Perform routine evaluation of potential sources of error
- Implement corrective action and follow-up plans
- Use alert and action levels to define trends
- Start and complete investigations in a timely manner. If additional testing is needed, which would postpone the completion of an investigation, an interim investigation report must be issued.
- Perform thorough, complete, well documented, and scientifically defendable investigations.

And remember, the FDA will continue to review a company's OOS SOPs, investigation reports (to include the open investigations), process and product specifications, and method validations when evaluating compliance in the OOS area. So it is up to you to make a difference and make your company aware of the importance of conducting proper failure investigations.

"Haste Makes Waste".... The integrity of laboratory and documentation records is of fundamental importance in the pharmaceutical and biotechnology industries.

By Lucia Clontz
Assistant Director, Microbiology
Diosynth RTP, Inc.

PMF Word Search



PMF Thread— Media Fill

Question

Recently, I have heard from several sources that the Agency has been "asking" sterile drug manufacturers to incubate all media fill (process simulation) units, even those units that did not pass a visual inspection due to capping, crimping and other defects. Do the members of this discussion believe it is necessary to incubate obviously defective containers, even grossly defective units, and units that would be removed as part of the normal fill procedure? Do you inspect units prior to incubation? If you incubate defective and rejected units, I assume you incubate all units, segregating those that would fail a visual inspection? Do you use the units that failed the visual inspection in your assessment of the adequacy of the line to fill sterile product (i.e. count any positives found against your media fill acceptance criteria) or is this information kept to better understand your process and show the need for robust inspection methods?

Please comment as to your opinion and the Agency's rationale for this new "request".

Reply 1

If a visual inspection and culling of obvious defective units is part of the normal fill process, which it invariably is, this process is done for media fills, and defectives are culled and rejected without incubation, just as defective product units would be removed and not sold. To incubate obviously defective items which would normally be removed and rejected in the normal process, is absurd.

It makes no sense to incubate rejects that lack container-closure integrity as they would not measuring the aseptic filling operation. I believe the industry practice is to count and inspect the media fill and classify the defects and enter all the filled units including cosmetic defects into incubation. An exemption would be filled units without container-closure integrity would be recorded but not incubated. The level of defects in the media fill would be evaluated against the product inspection reject levels to determine if it was typical. With non-routine interventions the defect rates may be higher for media fills than product. After incubation, all turbid vials after subculture should be examined for container-closure integrity as part of investigation. The sequence of the vials filled should be maintained so the presence of a turbid vial may be related to the level of activity in the filling area and if a non-routine intervention occurred at that time.

Reply 2

While we are on the subject of media fills, we have been informed by FDA that "hand stoppering" of vials is no longer an industry practice. By handstoppering" I mean taking a sterilized stopper and aseptically placing it on a vial with sterilized forceps. This is not a frequent occurrence, as it only happens when the stoppering mechanism misses a vial, and we perform this during every media fill. Do others in the parenteral industry perform manual stoppering? If so, have you received any feedback from FDA on this practice? Any insight on this matter would be appreciated.

Reply 3

That's what one would call a VERY "high-risk" practice, for an aseptic operation--first off, the failure to stopper might have produced more turbulence at the vial opening, and it DID produce a much longer-than-normal exposure time for the open, filled vial; plus there's the additional manipulation in the sterile field; then there's SEATING the manually-placed stopper (unless done automatically at a later stage). I don't think media simulation would justify that, even with a very high-value product. I've seen flat-out told by investigators

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that unstopperred filled units were rejects, period. Anyone else??

Reply 4

Our practice of manual stoppering is consistent with yours. Although it is a somewhat infrequent occurrence we include it as a routine intervention in every media fill. We have also qualified the operation with smoke studies. The FDA and other authorities have not taken issue with it.

Reply 5

I am personally aware of at least three different companies that were forced by the Agency to incubate units that failed visual inspection. The interesting thing is that no one tells them in advance whether a failure of these units which are documented to be non-integral count as a failure of the media fill or whether the unit is like a no test, where it fails but doesn't invalidate the test.

Reply 6

Since inspection agencies want to have vials that would normally be culled during a product fill for defects incubated as part of media challenge, how would the interpretation of those results be handled? Could those of you who incubate these defected units share how they are interpreted in rela-

USP Corner

The PMF recommends that you *write directly to the USP with your comments on all proposals*. You can write representing your company, or as an individual

Any questions concerning USP documents should be sent to Dr. Roger Dabbah. You can reach Dr. Dabbah at (301) 816-8336, via mail The United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852 or via e-mail at RD @ USP. org. When communicating with Dr. Dabbah, let him know you are a PMF member.

Current Compendia

US Pharmacopeia (USP) 24 Supplement 4, August 1, 2001

European Pharmacopoeia (EP) 1997 / Supplement 2001

Japanese Pharmacopoeia (JP) XIII 1996 / Supplement 1998

Chinese Pharmacopoeia (1995)

* If you use any other compendia, let us know for inclusion in this corner.

Warning Letters

1. Investigations into microbial excursion results for the water for injection (WFI) loops are incomplete in that there is no documentation of the recommendations for further investigations, corrective actions and follow up.

2. Well water and city water used in the manufacture of API's has not been demonstrated to be suitable for its intended use. In addition, the firm lacked a written procedure for the routine monitoring of both sources of water and the actual monitoring of both waters for chemical and microbial attributes is very limited.

3. Laminar flow hood in the micro lab and filters in the class 100,000 production area have not been certified.

4. Firm failed to conduct media fills as required by the validation procedures for powder filling. Validation protocol requires specific media fill challenges yearly. Firm did not conduct any two-hole stopper media fill in calendar rear 1999. This specific media fill is intended to demonstrate the sterility of the filling unit during aseptic filling.

PMF Word Search

E	G	A	H	P	U	M	Z	R	P	C	H	N	M	G
N	P	Y	I	P	M	A	C	C	O	N	K	E	Y	A
T	D	T	Y	G	E	R	S	N	C	T	F	K	K	U
E	C	E	P	T	N	G	J	J	S	Z	C	C	G	Y
R	S	C	R	P	I	U	B	E	S	T	O	E	N	L
O	X	C	V	B	G	N	F	N	D	H	W	O	V	Q
T	A	Z	I	A	Y	I	W	W	S	E	O	A	Y	T
O	C	I	T	P	E	S	I	T	N	A	S	D	O	R
X	E	I	S	G	W	A	A	G	T	J	K	B	M	Z
I	O	F	W	J	M	E	F	S	K	O	N	J	I	O
N	A	L	T	C	H	T	T	E	O	O	A	P	X	N

Antiseptic
Conjugation
Enterotoxin
Fungi
Gram
HeatShock
MacConkey
PH
Phage
Vector

Article Review

Determination Of Moisture In Rubber Stoppers: Effect of Karl Fischer Oven Temperatures
Zeren Wang, Brenda A. Frankel and William J. Lambert

PDA Journal of Pharmaceutical Science and Technology, May/June 2001, Volume 55, No. 3, p. 162

The authors of this article have attempted to evaluate the moisture released from rubber stoppers of pharmaceutical products in order to quantify free moisture in processed stoppers. Using a specific brand of stoppers the two methods evaluated at different temperatures were the Karl Fischer Method and the Gravimetric method. The findings of the study showed that the results of moisture content were reproducible at constant temperature using the Karl Fischer Method. The Karl Fisher Method was validated by showing consistency with the Gravimetric Method for moisture content of stoppers using fixed temperature and relative humidity for both assays.

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or
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C/o Laura Valdes-Mora
3166 Wood Valley Road
Panama City, FL 32405

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PMFLIST (An internet news List) ☐		**Other (Please Describe)** ☐

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