



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Media Fills

The Microbiology Way

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TGA Health Safety
Regulation



Australian Government

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What I'll be Talking About

- Standards and Guidelines applied
- Update on ISO
- Ideal World
- Problem areas
- Incubation of integral units



Documents Applied

- **ISO 13408-1:2008 Aseptic processing of health care products – Part 1: General requirements (parts 2-8 also deal with aseptic processing)**
- **PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 1 Manufacture of Sterile Medicinal Products**
- **PIC/S Recommendation on the Validation of Aseptic Processes January 2011**
- **PDA Technical Report No. 28 Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals**



ISO

- **OLSS Chief Microbiologist is the Australian representative on the ISO Technical Committee 198 (which deals with sterilisation standards) through Standards Australia – she represents Australia, not the TGA.**
- **OLSS Microbiology is heavily involved in the ISO standards writing and review process. Review process is open to everyone.**
- **We are currently involved in the drafting of ISO 13408-7 Aseptic processing of healthcare products – Part 7 Alternative processes for atypical medical devices and combination products and ISO 13408-8 Aseptic processing of health care products – Part 8 Cell-based health care products**
- **ISO 13408-7 draws heavily on detail already included in ISO 13408-1, but includes an excessive amount of information concerning application of risk assessment – is likely to undergo modification before entering final draft stage**



**Listed documents are applied during evaluation of pre-market submissions,
during audit and during assessment of post-market problems**

What do we expect to see??

In an ideal world:

- Every sterile bulk hold period would be simulated for the maximum hold period**
- This would immediately be followed by simulation of the maximum permitted filling time**
- Every possible intervention, stoppage, process, procedure or worst case situation would be simulated**
- Every possible container/closure combination would be tested**



- Zero contamination would be detected**
- Results of environmental monitoring would be zero**
- All would be repeated every 6 months thereafter**

Reality is somewhat different – can be considerable variation in performance of media fills – but this is not always bad!



Aspects that are usually acceptable

- **Simulation of procedures, interventions, maximum number of personnel**
- **Frequency of simulations**
- **Simulation of container/closure combinations (bracketing is accepted provided worst case combinations are tested)**
- **Incubation period and conditions for filled units**



Problem areas

- Simulation of prolonged holding periods directly followed by filling
- Simulation of the maximum permitted filling time
- Use of alternative media that may not be appropriate
- Attitudes to media fills as a whole
- Investigation of failures
- Campaign filling



Sterile Hold times

- **ISO 13408-1:2008 states “*Process simulation shall cover all parts of the aseptic process and include all aseptic manipulations. It is possible to divide the process into unit operations but all parts of the process shall be simulated (Clause 10.1.1)***
- **“*Simulations shall include ..maximum permitted holding times... “***
- **If bulk holding periods short, this is not usually a challenge but some sterile bulk holds can be three months or even longer (ie for some vaccines) – bulk holds such as these are therefore not always simulated during the 6 monthly revalidation.**
- **There can also be problems with the shelf life of the culture media used for such a simulation – if bulk hold period is up to 12 months, there are difficulties simulating this even if growth promotion test passes**



Sterile Hold times

Solutions –

- We have accepted long hold times being simulated separately from media fills, provided that the entire process is simulated regularly
- No defined time complete simulation, but yearly seems to be a popular choice
- For really extended holding periods when quality of media is an issue, other measures such as stability of product, whether product is frozen and thawed before filling, tank integrity and monitoring are looked at



Filling times

- **Maximum permitted filling time is not simulated, or is simulated infrequently**
- **ISO 13408-1:2008 states that “*Process simulation runs shall be conducted over the maximum permitted filling time. Where this is not possible, simulation runs shall be of sufficient duration to cover representative manipulations, interventions and shift changes performed in actual processing*” (Clause 10.3.8)**
- **PIC/S Recommendation on the Validation of Aseptic Processes states that “*where filling takes place over extended periods ie longer than 24 hours, the process simulation test should extend over the whole of the standard filling period*” (Clause 4.1.2)**



Filling times

- The premise is that media fills will follow manufacturing conditions as closely as possible
- Several manufacturers do perform media fill simulations to cover the maximum permitted filling time – this is easier when the fill time is less than 24 hours
- However, significant proportion do not, particularly if they are US based manufacturers
- Some never do it, some do it once every year or two years
- OLSS Microbiology first line is that the maximum permitted filling time should be simulated, and we evaluate submissions with this in mind



Use of alternative media

- **Use of alternatives is allowed under ISO 13408-1, but the choice must be reasonable and appropriate for the type of product and process**
- **Anaerobic media use obviously acceptable if a media fill needs to be performed to detect anaerobes**
- **Sterile bulk APIs can be a challenge to validate – usually a “wet” phase and a “dry phase” - can use media to validate, but more often see combinations of media and dried substances like lactose or mannitol**
- **Have seen saline washed through the system with the whole lot filtered and filter placed on agar – not ideal**



Problems with Interpretation

- **Problems seen with this are more to do with attitudes to media fills as a whole**
- **Assessment of the success of media fills should include conduct and results of both filled units and environmental monitoring**
- **Have seen interpretations of the results of media fills which show compliance with requirements for filled units but out of spec results for environmental monitoring with interpretation of “all OK” as filled units showed no growth.**
- **ITS NOT OK!!!**



Failures

- **Typical scenario is that a submission for a new company will contain media fill data, but it may be several years old – not uncommon for us to received data generated in 2004 or sometimes earlier.**
- **Always will ask for more recent data**
- **Sometimes comes out at this point that there has been a major or catastrophic failure in media fill validation**
- **What happens then??**
- **Failure investigation is examined – checking to see what has been done to rectify the problem, - does not mean that regulatory disaster will follow!**



Campaign Filling

- Usually several batches of sterile API or product manufactured and filled over several days, sometimes weeks
- Can be problematic to validate
- Have accepted “piggy back” media fills where a fill is performed after a campaign, before CIP and SIP
- If CIP/SIP occurs during campaign, have accepted simulation of period between these events
- - if no CIP/SIP occur during campaign, expectation is that the duration of the campaign will be simulated



Incubation of Integral units

- Non intact units are not expected to be incubated
- What about units that are intact but would normally be rejected??
- Views on this vary – below is a compilation of views from OLSS Microbiology
- All intact units should be incubated and counted in media fill
- If units would be routinely discarded during normal production process, then should be discarded and not incubated
- Units discarded should be set aside and incubated separately, and “considered” in terms of results



Incubation of integral units

- We currently have no agreed position in Microbiology – doesn't mean that you will be getting grief from us about this

The issue is currently under consideration by the Sterile Medicines-
Technical Working Group