Roundtable 35: Microbial Challenge In-use Studies and Requirements

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Scope:

Microbial challenge in-use studies are performed to evaluate the potential for microbial proliferation in preservative-free single dose biological products after first puncture and potential accidental contamination during dose preparation (e.g. reconstitution, dilution) and storage. These studies, in addition to physicochemical in-use stability assessments, are used as part of product registration to define in-use hold times in Prescribing Information and in the pharmacy manual in the case of clinical products. Microbial challenge in-use studies have been recommended by certain health authorities (e.g. FDA requirement for hold times greater than 4 hours at 2-8°C or room temperature). If microbial challenge data are insufficient or unavailable, the allowed in-use storage time will be reduced, which may limit flexibility for health care providers and patients.

Currently, there are no formal guidance documents describing regulator expectations on how to conduct microbial challenge in-use studies and interpret microbial data to assign in-use hold-times. In the absence of formal guidance, publications and presentations by FDA representatives and Information Requests (IRs) by global health authorities during filings have been used as a reference describing regulator expectations for these studies. Industry practice for designing, executing, and interpreting microbial data is highly variable.

Questions for Discussion:

1) What are the challenges of conducting microbial in-use studies and what are the approaches used by the industry?

2) What are the global regulatory challenges for filing microbial in-use data?

3) How do you support in-use hold times in early phase clinical trials and what are the approaches used by the industry for supporting hold times greater than 4 hours?

4) How do you support long infusion times and what risk mitigation strategies do you implement if microbial data does not support long infusion times at room temperature?

Discussion Notes:

Company experiences in addressing microbial support for in-use hold times during clinical stage are variable:

- For IND responses, in the past the microbial concerns were sometimes a possible FDA hold comment
- In recent IND submissions, multiple attendees stated that the comment was received in the FDA "May Proceed" letter, such as "in the absence of microbial challenge studies to support longer storage, diluted drug product should not be stored for more than 4 hours at 2-8C and/or room temperature prior to administration".

- One company acknowledges the FDAs' concerns at the IND stage and state they will address them later in development
- Another company has successfully negotiated for a longer than 4 hour limit in early stages with the FDA, without providing microbial challenge data
- This concern is specific to the FDA – Health Authorities in other countries/ regions do not require microbial support data for clinical stage products.
- Companies with a pipeline of products are using a platform approach (e.g. similar formulation, and dose preparation, route of administration) to justify longer time limits for new clinical stage product by leveraging microbial studies performed for late stage products.
- There is no consensus among companies if the infusion time should be included as part of in-use storage time (and therefore the need for microbial support) and the practice is variable.
- Information requests (IRs) from FDA product reviewers are not consistent

Design of microbial challenge studies

- ICH documents (*ICHQ8, and ICH Q1A*) are referenced for justification of performing microbial challenge testing.
- Agreement that using the 5 microorganisms in USP <51> is a good approach; some companies go beyond this by adding 1 or 2 typical skin microflora and nosocomial agents to simulate the types of flora that may contaminate a drug product in a hospital pharmacy but the feedback is that additional organisms don't improve the data set
- What organisms might be present in clinical/hospital pharmacies? Published information is incomplete
- Inoculation at 10-100 CFU/mL is typical
- Safety factors are required for studies for US approval, but not in other countries (eg, a 2x safety factor – a 24 hour study with passing results for a 12 hour storage limit)
- It is recommended to perform temperature studies separately as worst case. Because the growth state of the microbes may be impacted when studies are performed cumulatively. even if claiming cumulative exposure in label (the physiochemical studies can be performed sequentially)
- For global distribution, the sponsor should decide if it is worth planning for room temperature storage in ICH Zones 3 and 4, where the definition of room temperature is 30C

Interpretation of results

- Microbial data at 5C usually shows no growth – if growth is observed it should be investigated to ensure data are valid.
- If 25C shows less growth than 5C, it should be investigated
- If using an external vendor and unexpected results are obtained, review the method validation and possibly perform a lab investigation for the execution of the method

IQ consortium working group

- A cross-industry/FDA in-use microbial working group was formed through the Innovation & Quality (IQ) Consortium to gain alignment among industry practice and regulator expectations.

- The working group has developed best practices and has submitted a manuscript to the PDA Journal. The manuscript is under review.