Submission on TGA consultation: Proposed standards for human blood and blood components, human tissues and human cellular therapy products

[redacted]

Thank you for providing your comments using the template below.

- Rows may be added or deleted as required. Tables may be left blank or deleted if no comments are to be made on other documents.
- 'Reference' indicates the specific section/ subsection/ paragraph where relevant, e.g. In the infectious disease Order, 8(1)(b) would be used to reference requirements for donor interview timeframe in Part 3, Section 8, Subsection (1), paragraph (b).
- 'Issue' invites a short statement to summarise the comment.
- 'Comments' may include a position including justification or an alternative position.
- Additional general comments are also invited on the impact of these standards, as indicated below each table.

Submission on TGA consultation: Proposed standards for human blood and blood components, human tissues and human cellular therapy products

Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products

SUBMITTING ORGANISATION: [redacted]

Reference	Issue	Comment
DEFINITION	***microbial*** means microorganisms including, but not limited to, bacteria, fungi, Mycoplasma and Rickettsia, but does not include viruses or prions.	By defining Microbial in this way, an unrealistic and unachievable standard is being set, as it is not the aim of bioburden testing to ensure that the product is free of every known microorganism that may exist. Current methodologies do not routinely include mycoplasma and rickettsia. Suggest that this is qualified and covers known pathogenic microorganisms that affect donations encountered within the limits of the standard detection methods for bioburden testing. Can the term specified microorganism of clinical significance be used? SEE 12 (1) where pathogenic bacteria is used
DEFINITION 11(5)B	***specified microorganism*** means a microorganism which, if isolated from the tissue, necessitates discard of the tissue.	How and by whom will 'Specified' be determined? Will this follow the British or European pharmacopeia lists of organisms? Or will it be at the manufacturer's discretion? Suggest Each manufacturing facility must have a list of microorganisms of clinical significance which must be developed using a risk assessment process to specify those microorganisms that, if detected on the sampled tissue specimens when tested for bioburden, will result in discard of the tissue.
9 (6)(a)	The test kits/methodologies used for the mandatory screening and confirmatory microbial and virological tests must: be the most appropriate technology/ methodology for the sample being tested;	How and by whom will "most appropriate technology/ methodology" be determined?. Who will define appropriateness? The manufacturer or the auditor? If the methodology has current approval by the relevant regulatory authority as in point (b) should not an "appropriate" status follow?

9 (8)	Dedicated samples of the serum or plasma from deceased or living donors taken at time of collection, and/or the samples taken from living donors at 180 days post-collection, must be archived at or below minus 25°C (unless the conditions of archive are validated by the manufacturer at a different temperature or as recommended by the test kit manufacturers) to ensure sample availability for retesting or additional testing up to, at minimum, 2 years after the expiry date of products or as set out in product specific Orders for the purposes of section 10 of the Act.	Sentence too long and therefore ambiguous Simplify by using shorter sentences separating the requirements for living and deceased donors Living donors: If there is a 180 day post collection sample is there a need to store the time of collection sample? 180 days post collection samples must be stored. Deceased donor.: the time of collection sample must be stored
9 (9)	Where screening protocols change during the life of a product in storage, the donor's archived sample must be retested with the new screening test protocol prior to release of the product, as determined by the manufacturer based on risk, and in consultation with the regulator.	Screening protocol is a vague term and need clarification. Does this imply a change is test protocol, or does it mean a change in testing platform or test method or kit? Does a "protocol" here cover test algorithms and/or methods? Is it inferring a previous test method constitutes an increase in risk – or does this point only refer to new algorithms which may include additional tests?
11 (1)	A strategy for the minimisation of the intrinsic and extrinsic microbial contamination in a product must be established based on a risk assessment considering the nature and intended use of the product.	Who performs the risk assessment the manufacturer, supplier or laboratory?

12 (1)	Likely to introduce pathogenic bacteria or other infectious agents.	▪ Pathogenic bacteria is not listed in the definitions, but is a much more appropriate term than microbial or specified organism which are used Suggest a general revision of all 3 terms. ▪ Infectious agent is not defined

What is the perceived impact, if any, of implementing these requirements in your organisation?

The definition of microbial would have the greatest impact. Implementing this definition may make our method validations unacceptable as they are not designed to capture every known microorganism that may exist as they only cover the range of most probable potentially pathogenic organisms. As the definition stands, it would imply Rickettsia and Mycoplasma testing needs to be conducted. Currently these are not part of our routine screening protocols as these are not detectable by routine automated systems such as Bactec or BacTalert.

Other general comments:

There are a number of areas which are unclear and a more prescriptive order would resolve ambiguities.

Standards for human cardiovascular tissue

SUBMITTING ORGANISATION:

[redacted]

Reference	Issue	Comment
DEFINITION	***microbial*** means microorganisms including, but not limited to, bacteria, fungi, Mycoplasma and Rickettsia, but does not include viruses or prions.	By defining Microbial in this way, an unrealistic and unachievable standard is being set as it is not the aim of bioburden testing to ensure that the product is free of every known microorganism that may exist. Current methodologies do not routinely include mycoplasma and rickettsia. Suggest that this is qualified and covers known pathogenic microorganisms that affect donations encountered within the limits of the standard detection methods for bioburden testing. Can the term specified microorganism of clinical significance be used?
7(3)	Where antimicrobial agents have been used in the bioburden reduction process on the cardiovascular tissue, validation of bioburden determination must include neutralisation of the antimicrobial agents present in the sample.	*"neutralisation of the antimicrobial agents.* "This is difficult to achieve as there is no agreed pathway of neutralisation. It is highly dependant on which antimicrobial agents are used and in what concentrations, and often this information is not available or known. *Validation of bioburden test:* It is not possible to recover Antimicrobial sensitive organisms that have been killed or inactivated by antimicrobials, even after the antibiotic has been neutralised. - organism do not recover and do not grow once they are already dead The only way to recover antibiotic sensitive organisms from tissue is not to use the antibiotic. This would significantly compromise the product and is NOT the best practice when patient care and safety is a top priority.. Instead of trying to prove a negative a better indication of effectiveness of bioburden reduction (by antimicrobial treatment) is to ensure that methods are able to detect organisms when antibiotic treatment has been omitted or ineffective . ie recovery of organisms indicates a problem. Antimicrobial treated samples for bioburden determination , when tested must demonstrate no microbial growth of antimicrobial susceptible organisms.

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Other general comments:

Standards for human musculoskeletal tissue

SUBMITTING ORGANISATION: [redacted]

Reference	Issue	Comment
DEFINITION	***microbial*** means microorganisms including, but not limited to, bacteria, fungi, Mycoplasma and Rickettsia, but does not include viruses or prions.	By defining Microbial in this way, an unrealistic and unachievable standard is being set as it is not the aim of bioburden testing to ensure that the product is free of every known microorganism that may exist. Current methodologies do not routinely include mycoplasma and rickettsia. Suggest that this is qualified and covers known pathogenic microorganisms that affect donations encountered within the limits of the standard detection methods for bioburden testing Can the term specified microorganism of clinical significance be used?
DEFINITION 7 (4)	***specified microorganism*** means a microorganism which, if isolated from the tissue, necessitates discard of the tissue.	How and by whom will 'Specified' be determined? Will this follow the British or European pharmacopeia lists of organisms? Or will it be at the manufacturers discretion ? Comment : Each manufacturing facility must have a list of microorganisms of clinical significance which must be developed using a risk assessment process to specify those microorganisms that, if detected on the sampled tissue specimens when tested for bioburden, will result in discard of the tissue
7(5)	Where antimicrobial agents have been used in the bioburden reduction process on the musculoskeletal tissue, validation of bioburden test must include neutralisation of the antimicrobial agents present in the	*"neutralisation of the antimicrobial agents.* "This is difficult to achieve as there is no agreed pathway of neutralisation. It is highly dependant on which antimicrobial agents are used and in what concentrations, and often this information is not available or known. *Validation of bioburden test:* It is not possible to recover Antimicrobial sensitive organisms that have been killed or inactivated by antimicrobials, even after the antibiotic has been neutralised. - organism do not recover and do not grow once they are already dead The only way to recover antibiotic sensitive organisms from tissue is not to use the antibiotic. This would significantly compromise the product and is NOT the best

	sample.	practice when patient care and safety is a top priority.. Instead of trying to prove a negative a better indication of effectiveness of bioburden reduction (by antimicrobial treatment) is to ensure that methods are able to detect organisms when antibiotic treatment has been omitted or ineffective . ie recovery of organisms indicates a problem. Antimicrobial treated samples for bioburden determination , when tested must demonstrate no microbial growth of antimicrobial susceptible organisms.
7(6)(a)	written specifications for the tissue must include a list of microorganisms that which, if tested and found to be present in the tissue, will require rejection and discard of the tissue;	"a list of microorganisms" who will determine what organisms will be included on the list is and what will it be based on, British/ European pharmacopeia. How specific and all inclusive will it be?
7 (6)(b)	repeat sampling and testing for bioburden must be performed on the tissue in circumstances where the human musculoskeletal tissue is subjected to further processing; and	If tissue is treated by gamma radiation and this is considered processing by definition, what would be the value of retesting a sample post irradiation be, if the pre irradiated samples showed no presence of specified organisms.?

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Other general comments:

There are a number of areas which are unclear and a more prescriptive order would resolve ambiguities.

Standards for human ocular tissue

SUBMITTING ORGANISATION: [redacted]

Reference	Issue	Comment
DEFINITION	***microbial*** means microorganisms including, but not limited to, bacteria, fungi, Mycoplasma and Rickettsia, but does not include viruses or prions.	By defining Microbial in this way, an unrealistic and unachievable standard is being set as it is not the aim of bioburden testing to ensure that the product is free of every known microorganism that may exist. Current methodologies do not routinely include mycoplasma and rickettsia. Suggest that this is qualified and covers known pathogenic microorganisms that affect donations encountered within the limits of the standard detection methods for bioburden testing. Can the term specified microorganism of clinical significance be used?
7(6)	Evidence of any microbial contamination after testing of the storage medium under subsection 7(5) must result in discard of tissue that has not been released for supply to a recipient.	Vague and unclear as 7(5) refers to transport medium not storage medium.

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Other general comments: There are a number of areas which are unclear and a more prescriptive order would resolve ambiguities.

Standards for human skin

SUBMITTING ORGANISATION:

[redacted]

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DEFINITION	specified microorganism means a microorganism which, if isolated from the tissue, necessitates discard of the tissue.	How and by whom will 'Specified' be determined? Will this follow the British or European pharmacopeia lists of organisms? Or will it be at the manufacturers discretion ?
7(5)	Each manufacturing facility must have a list of microorganisms of clinical significance which must be developed using a risk assessment process to specify those microorganisms that, if detected on the sampled tissue	"a list of microorganisms" who will determine what organisms will be included on the list is and what will it be based on, British/ European pharmacopeia. How specific and all inclusive will it be?

	specimens when tested for bioburden, will result in discard of the skin.	
7(7)	Where antimicrobial agents have been used, validation of bioburden test must include neutralisation of the antimicrobial agents present in the sample.	"neutralisation of the antimicrobial agents. "This is difficult to achieve as there is no agreed pathway of neutralisation. It is highly dependant on which antimicrobial agents are used and in what concentrations, and often this information is not available or known. Validation of bioburden test: It is not possible to recover Antimicrobial sensitive organisms that have been killed or inactivated by antimicrobials, even after the antibiotic has been neutralised. - organism do not recover and do not grow once they are already dead The only way to recover antibiotic sensitive organisms from tissue is not to use the antibiotic. This would significantly compromise the product and is NOT the best practice when patient care and safety is a top priority.. Instead of trying to prove a negative a better indication of effectiveness of bioburden reduction (by antimicrobial treatment) is to ensure that methods are able to detect organisms when antibiotic treatment has been omitted or ineffective . ie recovery of organisms indicates a problem. Antimicrobial treated samples for bioburden determination , when tested must demonstrate no microbial growth of antimicrobial susceptible organisms.

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