Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

In vitro fertilisation (IVF) solutions

How to demonstrate that IVF solutions comply with the Essential Principles for safety and performance.

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The following table summarises requirements for IVF solutions to demonstrate compliance with the Essential Principles for safety and performance of medical devices (see the Australian Regulatory Guidelines for Medical Devices (ARGMD) (https://www.tga.gov.au/node/289305)), or the Australian Medical Device Requirements (DR4, for devices containing material of human origin) (https://www.tga.gov.au/node/285112).

Type of data components	Requirements
Device name and predicate device name	• Device name(s) • Classification
Administrative information	• Contact person and title • Telephone number and fax number
Device description, intended use and direction for use	• Device description - schematic diagrams, photographs, and drawing in addition to a written description • Device specification - identification of components and materials used as well as rationale for use • Patient-contacting status including whether contact is with donor during oocyte removal, gamete, embryo or recipient • Intended use - clear and device specific statement • Indication(s) for use - including safety requirements
Status of overseas approval	• Required
Commercial history	• Required

Type of data components	Requirements
Incidence reports	• Required
Risk analysis	• Should identify each potential hazard to the patient (or the gamete/embryo), the cause of the hazard, the level of concern, and the steps taken to address the hazard • Include risks of individual components, particularly in relation to chemicals and ingredients of biological origin
Materials	

All components and materials (raw materials including drugs / diluents / all packaging	• Should be clearly identified. In detail, their sources and specifications / characteristics should be clearly identified
	• Medicinal component:
	  ○ ARTG number, if it has been approved in Australia;
	  ○ Drug Master File (DMF);
	  ○ assessment reports prepared by the approved agency, if it has been approved in overseas; or
	  ○ a Certificate of Suitability with supporting information described in Appendix 11 of the Australian regulatory guidelines for prescription medicines (ARGPM) (https://www.tga.gov.au/node/285079)

Animal/human origin	• Justification (e.g. donor screening and testing) is needed to minimise risks for transmission of pathogens.
	• Animal origin - following information is required:
	  ○ Sources (e.g. derivations if applicable, country of origin)
	  ○ Specification / characterisation (compliance with Conformity Assessment Standards Order No. 2 (http://www.comlaw.gov.au/Details/F2007B00587) if applicable)
	  ○ TSE / Viral safety evidence
	• Human materials - TGA inspection of the manufacturing facility may be required. For HSA, reference to a Plasma Master File (PMF) and/or Drug Master File (DMF) held by TGA.
	  ○ human materials/tissues (except blood) - audit of facility according to cGMP Human blood and tissues (https://www.tga.gov.au/node/285122) may be required
	  ○ human blood/derivatives - requires:

Type of data components	Requirements
	1. third party audit (for overseas manufacturers), and 2. Master File (MF) (PMF and/or DMF as relevant) to be evaluated according to the appropriate drug evaluation guideline
Water	BP Water for Injections or USP Water for Injection BP Water, highly purified
Manufacturing	
Manufacturing process	• Required
In-process testing	• Required
Performance testing / special controls of each solution	
Mouse embryo assay (one-cell or two-cell MEA) information	• MEA is used for toxicity (embryotoxicity) and functionality of reproductive media. The MEA should correspond, as closely as possible, to the procedures used for human IVF, such as the acquisition, maintenance, culture, transfer and cryopreservation of embryos
	• Manufacturer should provide clear information about how the assay was performed (one-cell or two-cell MEA) and the assay results in the labelling (see labelling (#labelling) below)
Stability (e.g. shelf life, storage condition, preservative efficacy)	• Required • For IVF solutions that are not introduced into sterile sites in the body and are intended for multiple use, evidence of adequate preservative efficacy is required to support the shelf life, to satisfy the requirements of 8.1 (1) (b). • Expectation is that IVF solutions introduced into sterile sites in the body (e.g. used to flush the follicle during oocyte removal) should be for use in one patient only during a single procedure.
Sterilisation validation	• Expectation is that solutions are intended to be sterile. • Where possible, solutions should be sterilized in their final sealed container (terminal sterilization) and a sterility assurance level (SAL) of 10^{-6} is expected. Validation of these processes can be performed in accordance with Medical Device Standards Order No. 3 (http://w

Type of data components	Requirements

	ww.comlaw.gov.au/Details/F2008L04336), Schedule 1, 1tem 1 and other items as applicable.
	• When the solution cannot be terminally sterilized, the solution may be aseptically processed. When aseptic processing is used:
	  ○ an appropriate sterility assurance level (SAL) is expected as demonstrated by media fill validations. The aim of any process simulation shall be to achieve zero contaminated units. Validation of aseptic processes can be performed in accordance with Medical Device Standards Order No. 3 (http://www.comlaw.gov.au/Details/F2008L04336), Schedule 1, Items 2 and 9.
	  ○ presterilization of solution container/closure, product parts and/or components and all equipment coming into direct contact with the aseptically processed solution is required. Validation of the processes used to sterilise containers etc can be performed in accordance with Medical Device Standards Order No. 3 (http://www.comlaw.gov.au/Details/F2008L04336), Schedule 1 Item 1 and other items as applicable.
	• Sterility testing of the finished product is required as a batch release test for all aseptically prepared products. Sterility testing of terminally sterilised products is also required unless approval for parametric release has been granted.

Product validation (e.g. pH, osmolarity and assays)	• Required
Physical / chemical (if applicable, e.g. impurities) testing	• Required
Endotoxin test	• Tests for bacterial endotoxins and material-associated pyrogens are both required, and test methods are not limited to USP.
	• Manufacturer should provide clear information about how the assay was performed and qualified, provide a justification for the specification, and the assay results (should be included) in the labelling.
Biological safety testing	• Results of biocompatibility testing including the raw data and reports as well as summaries performed on the finished device (for testing, refer ISO 10993-1[1]), or certification that identical materials

Type of data components	Requirements

	are used in a legally marketed device with a similar intended use, are needed
	• For maternal safety, the following test is needed:
	  ○ cytotoxicity test
	• For the safety concerns with gamete/embryos including their development, the following tests need to be considered[2]:
	  ○ genotoxicity test -
	  1. bacterial gene reverse mutation assay, if this test is not successful then the following two tests to be considered:
	  2. in vitro mammalian cell chromosomal aberration assay (or In vitro mouse lymphoma tk assay), and
	  3. in vivo rodent bone marrow micronucleus assay
	• embryotoxicity/sperm toxicity assay, to include
	  ○ mouse embryo assay (if applicable) or
	  ○ sperm mortality assay (if applicable)

Non-clinical efficacy study	Pregnancy rate testing including MEA - this can be observed during the biological safety testing (#bio) above.

Clinical testing	• Clinical data are needed to satisfy the requirements in DR4 (https://www.tga.gov.au/node/285112) or Australian Regulatory Guidelines for Medical Devices (ARGMD) (https://www.tga.gov.au/node/289305) as applicable, such as:
	  ○ Efficacy
	  ○ Safety of the product

Labelling	• Labelling should meet requirements in the Australian Regulatory Guidelines for Medical Devices (ARGMD) (https://www.tga.gov.au/node/289305).
	• Specifically:
	  ○ labelling is to clearly identify the intended use, indication(s) for use, contraindications, precautions, warnings and instructions for use
	  ○ labelling is to include the word 'sterile' and information on the method that was used to sterilise the device (for symbols, refer to ISO 15223-1[3])

Type of data components	Requirements
	• Labelling should indicate whether the product has been tested for reproductive or developmental toxicity

1. ISO 10993-1 *Biological evaluation of medical devices* - Part 1: *Evaluation and testing*
2. If these tests are not conducted, a scientifically justified rational in the form of a report including any relevant published data, must be supplied
3. ISO 15223-1: *2007 Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied* Part 1: *General requirements*

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Topics:

In Vitro Diagnostic medical devices (IVDs) (https://www.tga.gov.au/vitro-diagnostic-medical-devices-ivds)