Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Conformity assessment procedures for immunohaematology reagents

Version 1.0, February 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

Version history

Version	Description of change	Author	Effective date
V1.0	First version	IVD team	Feb 2012

Contents

Overview

The TGA has published the following regulatory guidelines for manufacturers and sponsors of in vitro diagnostic (IVD) medical devices on the TGA website:

Classification of IVD medical devices

The use of GMDN codes for IVD medical devices in Australia

Conformity assessment overview (IVDs)

What a sponsor needs to know about conformity assessment and manufacturer's evidence for IVDs

What a manufacturer needs to know about conformity assessment and declarations of conformity for IVDs

Including IVD medical devices in the Australian Register of Therapeutic Goods (ARTG)

Application audit (technical file review) of IVD medical device applications

There are some specific requirements in the regulation of immunohaematology reagents (IHRs) that manufacturers and sponsors need to consider when applying conformity assessment procedures or making applications for inclusion in the Australian Register of Therapeutic Goods (ARTG). These requirements are specifically addressed in this guideline which is designed to be read in conjunction with the other published guidelines referenced above.

Classification of immunohaematology reagents

General guidance on the classification of IVDs can be found in the guideline Classification of IVD medical devices on the TGA website. A limited number of classification rules specified in Schedule 2A of the Therapeutic Goods (Medical Devices) Regulations, 2002 (the Regulations) are applicable to IHRs. Classification rule 1.2 divides blood grouping IVDs into 2 subsets depending on the nature of the blood group antigen or antibody and its importance in a transfusion setting.

Class 4 IHR IVDs

Classification rule 1.2 (2) specifies IVDs that are Class 4 IVDs or Class 4 in-house IVDs. IHRs are Class 4 IVDs if they are intended to be used to detect any of the markers specified for the following blood group systems:

a. ABO system – ABO1 (A), ABO2 (B), ABO3 (AB);
b. Rhesus system – RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e);
c. Kell system – KEL1 (K);
d. Kidd system – JK1 (Jka), JK2 (Jkb); and
e. Duffy system – FY1 (Fya), FY2 (Fyb)

Class 3 IHR IVDs

Classification rule 1.2 (1) specifies that IVDs are Class 3 IVDs or Class 3 in-house IVDs if they are intended to be used for the detection of biological markers in order to assess the immunological compatibility of blood, blood components, blood products, cells, tissues or organs that are intended for transfusion or transplantation, and they are not Class 4 IVDs under rule 1.2 (2). IHRs intended to detect red cell antigens other than those specified in rule 1.2 (2), and HLA antigens, are Class 3 IVDs. Sensitised cells and reagents used in compatibility tests are also Class 3 IVDs. The detection

of biological markers is taken to include any genetic or molecular-based methodologies where the results of testing may be used to establish or confirm suitability for transfusion or transplantation.

Any IVDs, including all associated calibrator and control materials, that are intended to be used for the quantitative determination of maternal allo-antibodies directed towards red cell antigens, in order to detect or monitor haemolytic disease in an unborn child or newborn, are Class 3 IVDs under Rule 1.3 (e).

Class 2 IHR IVDs

Classification rule 1.7 specifies that an IVD not otherwise classified under Schedule 2A is a Class 2 IVD or Class 2 in-house IVD. For example, the Kleihauer test used for the (semi-)quantitative determination of foetal red blood cells in maternal circulation. Note that Rule 1.3 (1) (f) for determining Class 3 IVDs is not considered to be applicable to the Kleihauer test.

Class 1 IHR IVDs

Classification rule 1.6 specifies those IVDs and in-house IVDs that are Class 1. It includes:

a. Instruments to be used for in vitro diagnostic procedures, e.g. automated blood grouping analysers;
b. Instrument-specific reagents that are not also analyte-specific. Analyte-specific reagents are classified as the same class as the parent IVD they are intended to be used with.
c. General laboratory reagents suitable for use across multiple disciplines, e.g. normal saline, provided there is no specific indication that the reagent is intended for use in immunohaematology or tissue typing.
d. Specimen receptacles other than those intended for use in self-testing;
e. IVDs intended only to be exported from Australia.

Laboratory reagents that state in their labelling or in their accompanying information that they are intended for use in immunohaematology or tissue typing are considered to be Class 3 or Class 4 IVDs, not Class 1 general laboratory reagents.

GMDN codes for immunohaematology reagents

The GMDN is an international nomenclature system used by regional or national regulatory bodies to consistently describe medical devices, and selection of an appropriate GMDN code is required when submitting an application to include medical devices in the ARTG.

Regulation 1.7 specifies certain device nomenclature codes that must be used for IVD medical devices, depending on their risk classification:

a. for a Class 4 IVD medical device – the relevant preferred term;
b. for a Class 4 IVD medical device that is an immunohaematology reagent IVD medical device – the relevant Level 2 collective term;
c. for a Class 3 IVD medical device – the relevant Level 3 collective term, or if no Level 3 collective term exists, the relevant Level 2 collective term;
d. for a Class 2 IVD medical device – the relevant Level 2 collective term;
e. for a Class 1 IVD medical device or an export only IVD medical device – the relevant Level 1 collective term.

In practical terms, there are six Level 2 Collective Terms (L2CT) which are applicable to Class 3 or Class 4 IHRs:

- CT887 Immunohaematology blood grouping antisera IVDs
- CT890 Immunohaematology calibrator/control IVDs
- CT1270 Immunohaematology-related IVDs
- CT888 Immunohaematology sensitised cell-typing IVDs
- CT753 Multiple blood grouping and typing IVDs
- CT886 Reagent red blood cell IVDs

Kinds of IVD medical devices

Medical devices must be included in the ARTG as a kind of medical device. Section 41BE (1) of the *Therapeutic Goods, 1989* (the Act) specifies that IVDs are taken to be "of the same kind" as another IVD if they:

a. have the same sponsor; and
b. have the same manufacturer; and
c. have the same device nomenclature system code (i.e. GMDN code); and
d. have the same medical device classification; and
e. are the same in relation to any other characteristics prescribed in the Regulations.

Regulation 1.6 prescribes that, for the purposes of section 41BE (1) (e), a characteristic of Class 4 IVDs **other than IHRs** is the unique product identifier given to the device by the manufacturer to identify the device and any variants.

Therefore, IHRs from any of the risk classes can be grouped for entry in the ARTG if they:

a. have the same sponsor; and
b. have the same legal manufacturer; and
c. nominate the same Level 2 collective term; and
d. are from the same IVD risk class.

Conformity assessment for Class 4 IVDs

A TGA-issued Conformity Assessment (CA) Certificate is required for all Class 4 and Class 4 in-house IVDs before they can be included in the ARTG. As prescribed in Regulation 3.6A, the conformity assessment procedures that must be applied to Class 4 and Class 4 in-house IVDs are either:

a. Full quality assurance procedures as per Schedule 3, Part 1 including clause 1.6 (examination of design); or
b. Type examination procedures (Schedule 3, Part 2) and production quality assurance procedures (Schedule 3, Part 4).

A conformity assessment certificate for full quality assurance procedures (Part 1, excluding clause 1.6) or for production quality assurance procedures (Part 4) can be provided for the full range of IVDs produced by a single manufacturer, regardless of whether they are of the same or different risk class. However, separate conformity assessment certificates are issued under clause 1.6 (examination of design) for each kind of medical device.

IHRs that are Class 4 IVDs, and therefore subject to design examination, will be of the same kind if they are produced by the same manufacturer, have the same Australian sponsor, and reference the same GMDN L2CT code.

Scenario:

A manufacturer produces a range of blood grouping antisera with the following specificities: anti-A, anti-B, anti-A,B, anti–Rh(D), anti-C, anti-c, anti-E, anti-e, anti-K, anti-Jka, anti-Jkb, anti-Fya and anti–Fyb. An Australian sponsor markets the full range of antisera in Australia and New Zealand, and because they are all the same kind of IVD, they can be grouped together for assessment and inclusion in the ARTG as a Class 4 IVD using CT887 – Immunohaematology blood grouping antisera IVDs. The manufacturer is required to apply to the TGA for a conformity assessment certificate under Part 1, including clause 1.6. Following a successful assessment process, the TGA will issue a QMS certificate and a Design Examination certificate that are suitable to use as manufacturer's evidence to support an application for inclusion of the full range of Class 4 blood grouping antisera IVDs in the ARTG.

The manufacturer also produces a range of reagent red blood cells intended for use in pre-transfusion testing. Their products include a kit containing red blood cells for performing ABO reverse groups; a set of three characterised red blood cells for performing antibody screens on potential transfusion recipients, and a kit containing an 11-cell panel of characterised red blood cells for identification of allo-antibodies detected in a patient's specimen. Each of the reagent red blood cells are classified as Class 4 IHRs under Rule 1.2(2), and can be grouped as the same kind IVD using the L2CT CT886 – Reagent red blood cell IVDs.

Before these products can be included in the ARTG and supplied in Australia, the manufacturer must submit to the TGA an application for a conformity assessment certificate under clause 1.6 only (for examination of design) if the original QMS certificate issued by the TGA to the same legal manufacturer continues to remain current. At the pre-assessment stage of an application for examination of design, the TGA will confirm that the scope of the initial QMS certification remains appropriate.

Conformity assessment for Class 2 and Class 3 IVDs

Under Regulation 4.1, a TGA-issued Conformity Assessment (CA) Certificate is required for all IVDs that are manufactured in Australia except for:

- IVD systems and procedure packs;
- Class 1 IVDs
- Class 1, Class 2 and Class 3 in-house IVDs;
- exempt IVDs.

The minimum conformity assessment procedures that must be applied to Class 2 and Class 3 IVDs that are manufactured in Australia are:

For Class 3 IVDs:

a. Full quality assurance procedures (Schedule 3, Part 1 **excluding** clause 1.6); or
b. Type examination procedures (Schedule 3, Part 2) and production quality assurance procedures (Schedule 3, Part 4).

For Class 2 IVDs:

a. Full quality assurance procedures (Schedule 3, Part 1 **excluding** clause 1.6); or
b. The declaration of conformity (not requiring assessment by Secretary) procedures (Schedule 3, Part 6) and production quality assurance procedures (Schedule 3, Part 4).

For Class 2 and Class 3 IVDs that are not manufactured in Australia, see guideline What a sponsor needs to know about conformity assessment and manufacturer's evidence for IVDs for information on manufacturer's evidence that is acceptable.

A conformity assessment certificate is not required for Class 1 IVDs. The minimum conformity assessment procedure for Class 1 IVDs is the declaration of conformity (not requiring assessment by Secretary) procedure (Schedule 3, Part 6).

Documentation to support applications for conformity assessment

Quality management system documentation

Manufacturers who apply for a TGA Conformity Assessment Certificate will be requested to complete a supporting data form and provide documents that detail specific parts of their quality management system. As a guide, documentation that is generally requested to be submitted includes:

- A copy of the latest version of the Quality Manual (as required under ISO 13485:2003, clause 4.2.2)
- Organisational chart (if not part of QM)
- Product requirements (specifications) for the products included in the scope of the certificate
- A list of critical suppliers and a description of how purchasing requirements are fulfilled (ISO 13485:2003, clause 7.4.1)
- Plans of the manufacturing facility or facilities
- List of critical processes and the status of their validation (ISO 13485:2003, clause 7.5.2.1). If the product is supplied sterile, a copy of sterilisation validation reports
- Procedure for a feedback system (ISO 13485:2003, clause 8.2.1; Regulatory requirements for review during the post-production phase)
- Procedure for the issue and implementation of advisory notices and notification of adverse events (ISO 13485:2003, clause 8.5.1, Uniform recall procedure for therapeutic goods).
- Any other information requested by the TGA, as a result of any issues identified during a pre-assessment meeting.
- Documents providing the basis for any abridgement of assessment fees applied for.

Technical documentation

Manufacturers who apply for a TGA Conformity Assessment Certificate are required to have available technical documentation to demonstrate that each device complies with the Essential Principles. For Class 3 IHRs the technical documentation is generally referred to as a STED (Summary Technical Documentation). For Class 4 IHRs, the technical documentation should provide for a more detailed examination including a full review of the design aspects of the product and is often referred to as a Design Dossier.

Where an application for conformity assessment covers a number of IVDs, and particularly a range of Class 3 IHRs that are not subject to examination of the design, the TGA will review the technical documentation for a sample of the IVDs, either as part of a desk audit or on-site audit as required. The technical documentation to be assessed, and the level of detail required, will vary on a case by case basis depending on:

- class of the IVD
- complexity of the IVD
- period that it has been on the market
- whether the IVD has the following characteristics:
  - it incorporates a novel technology
  - it is an already marketed IVD type that is now being offered for an intended purpose different from the original one
  - it incorporates novel or potentially hazardous materials
  - the IVD type raises specific public health concerns

Following is a summary of each of the components of the design dossier or STED that is expected to be held by manufacturers of IHRs. For further information relating to the depth of detail required, please refer to the table shown on Page 16.

Device description

A detailed description of the IVD must be provided, including information addressing each of the following points:

- Intended purpose;
- Intended user;
- Risk class according to Australian regulations;
- Acceptable specimen types;
- Description of principle of the assay(s) and methodologies that are suitable to be used;
- Description of the physical appearance of the reagent; and
- Description of individual components included in the IVD(s), including for monoclonal reagents and blends, the identity of the cell line(s) from which it is derived.

If relevant, the following should also be provided:

- A description of the specimen collection and/or transport materials required or recommended to be used;
- A description of the accessories, other IVDs and other products that are not medical devices which are intended to be used in combination with the IVD(s);
- For assays requiring instrumentation, a description of the relevant instrumentation characteristics or details of dedicated instrumentation to be used;
- A description of any software to be used; and
- A complete list of any configurations or variants of the IVD(s), other than kit size, that will be made available.

Where applicable, a review of all platforms/instrumentation and any other materials, including dedicated specimen receptacles, that are required (or recommended) to be used in combination

with an IVD will occur in conjunction with the technical file review. Relevant information for every aspect of the IVD(s) should be provided to enable this to occur.

Device history

A summary of the product history in both the Australian market and any other jurisdiction(s) in which it is supplied will be requested to allow the TGA to make an assessment of the safety and performance of the IVD in the post-market environment. Details should include a list of countries or regulatory jurisdictions, approximate numbers of IVDs and/or period of time where it is supplied, a summary of any adverse events, recalls, corrective/preventive actions, or refusal to allow supply.

The inclusion of information clearly identifying products either as new to the Australian market, or as previously Registered, Listed or Exempt products transitioning to the requirements of the new IVD regulatory framework will assist the TGA in prioritising the assessment of new products, so as to reduce as much as possible any delay to the market caused by a backlog of IVDs transitioning to the requirements of the new regulations.

Essential principles checklist

A copy of the Essential Principles checklist that summarises conformity to each applicable Essential Principle by reference to appropriately applied standards, or other appropriate means will be requested. Evidence of compliance must refer to documents, reports, internal procedures, etc and should include a cross-reference to the location of the documents listed within the checklist. In order to establish that an IVD complies with the relevant provisions of the Essential Principles, the TGA may request further information in relation to any of the documents referenced or expected to be held as part of the product technical file.

The TGA will accept a European Essential Requirements checklist to IVDD requirements provided it is also accompanied by a short statement to provide assurance from the manufacturer "that the Australian Essential Principles, as described in Schedule 1 of the Therapeutic Goods (Medical Devices) Regulations 2002, have been met".

A template Essential Principles checklist is available from the TGA website at http://www.tga.gov.au/industry/devices-forms-essential-principles-checklist.htm

Risk analysis and control summary

For Class 1-3 IHRs, a summary of the risk management activities performed by the manufacturer of the device must be provided. An example of such a summary is the Risk Management Report required by Clause 8 of ISO14971:2007, and should include as a minimum:

- a list of possible hazards for the IVD arising from false positive or false negative results;
- indirect risks which may result from IVD-associated hazards e.g. instability of test components, integrity of packaging, selection of specimens;
- the user/operator hazards such as any risks arising from reagents and specimens containing infectious agents: and
- the risk mitigation strategies that have been implemented to reduce unacceptable risks.

Taking into account risk mitigating activities, the results of the risk analysis should provide a conclusion that the remaining risks are acceptable when compared to the benefits. The risk analysis and control summary may be submitted either in a summary (text) format or as a reduced table.

For Class 4 IHRs, a full and detailed risk assessment report is required to be submitted for review.

Design and manufacturing information

A summary of the design and manufacturing processes at a level of detail appropriate to the risk class of the device should be provided. The summary should include a review of the design features that make the IVD suitable for its intended purpose, an overview of manufacturing processes and controls, manufacturing sites, a description of critical assay ingredients, a description of the major systems or critical processes, and details of any decision pathways or algorithms used, as appropriate.

Clinical evidence report

Every medical device requires clinical evidence, and for IVDs this represents the information that supports the clinical utility and the performance of the IVD as intended by the manufacturer. A clinical evidence evaluation report that demonstrates conformity with the applicable provisions of the Essential Principles (as specified in EP14) must be available for all IVDs, other than those that are exempt from inclusion in the ARTG. The Clinical Evaluation Procedures described in Clause 8, Schedule 3 of the Regulations set out the requirements, and focus on the manufacturer obtaining clinical investigation data through conducting performance evaluations and/or carrying out a literature review of published and unpublished scientific literature.

If a manufacturer considers that evidence of an IVD's clinical utility or its established usefulness is not required to be compiled and submitted for review due to it being a well developed and extensively utilised IVD, this decision is required to be documented and clearly justified as part of the clinical evidence report.

Evidence to support the clinical competence of the author (e.g. short curriculum vitae) must accompany the submitted clinical evidence report to provide assurance that the clinical evidence has been evaluated by a competent clinical expert.

Performance evaluation studies incorporate both the clinical and analytical performance characteristics of an IVD. Performance evaluation studies for IHRs include evaluation of serological blood grouping reagents, characterisation of reagent red blood cells, red blood cell genotyping assays, and production of calibrators (standards) and control material for use in an immunohaematology setting. Specific consideration should be given to the following aspects of the evaluation process, as appropriate to the type of reagent:

- Use of samples that reflect variants and weak antigen expression eg, neonatal specimens, ABO variants, weak (Rh)D, partial expression of Rh(D);
- Ethnicity of test subjects expressing possible/probable phenotypes;
- Testing for prozone effect;
- Potency testing;
- Nature of red blood cells to be considered (eg, washed/unwashed red blood cells (RBCs), RBC storage times, RBCs collected using different anti-coagulants/storage media)
- Range of methodologies to be considered (eg column, tube, tile)

Clinical performance is a measure of an IHR's ability to correctly group and screen human blood and blood products for compatibility purposes. Clinical performance characteristics include diagnostic sensitivity and diagnostic specificity.

For IHRs, providing data that has been drawn from clinical performance studies is an essential component of the clinical evidence. It is recognised that for some IHRs which have been in routine use for many years (> 10 years) and that have previously undergone the recognised equivalent[1] of a

[1] IVDD 98/79/EC Annex IV.4 or Heath Canada Class IV License

design examination in other jurisdictions, the original validation data may no longer fully demonstrate all aspects now required of a Design Dossier. Where it is available in a suitable form, published literature or a review of experience gained during routine diagnostic testing, which includes post market surveillance data and on-going satisfactory performance in external Quality Assurance Programs should be used as supplementary evidence to support the clinical performance of an IVD. Full details of any investigations into anomalous results or unexpected reactions carried out by, or on behalf of the manufacturer must be provided.

Product validation and verification

Evidence to demonstrate the analytical performance characteristics of the IVD is a requirement under Essential Principle 15 and forms a critical part of the manufacturer's performance evaluation studies, as required for clinical evidence.

The information presented for each study should provide sufficient detail for the assessor to understand how the study was conducted, the characterisation of specimens/samples used, acceptance criteria, explanations for anomalous results, and the outcomes/conclusions drawn. It is acceptable to combine two or more aspects of analytical/clinical performance into fewer separate studies provided each of the studies is well designed and all relevant variables and test characteristics are effectively demonstrated.

In Australia, the minimum acceptable numbers and range of characteristics to be assessed for validation and batch release testing for IHRs is consistent with requirements outlined in the EU Common Technical Specifications for in vitro diagnostic medical devices (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:039:0034:0049:EN:PDF), and the UK Red Book (http://www.transfusionguidelines.org.uk/Index.aspx?Publication=RB&Section=25&pageid=642).

Specimen type

A list of all appropriate specimen type(s) suitable for use with the IVD must be provided, including anticoagulants, matrices or any special instructions or conditions associated with specimen collection. Information should also address specimen stability, appropriate storage conditions and where applicable, transport conditions. Storage includes elements such as different storage media, duration, temperature limits, maximum number of freeze/thaw cycles.

Analytical performance study reports should include information about the nature of the specimen types tested (e.g. spiked, pooled etc) and the source of specimens obtained, as appropriate.

Accuracy

The term accuracy refers to both trueness and precision (reproducibility and repeatability).

Demonstration of trueness requires utilisation of an acceptable reference method or comparison with reference material of a higher order.

Reproducibility should include information about studies to estimate total variability and may include, as appropriate, between-day, between-run, between-sites, between-lots, between-operators and between-instrument variability.

Repeatability should include information about studies to estimate total variability and as appropriate, within-run variability.

Analytical & clinical sensitivity & specificity

Demonstration of analytical sensitivity should provide as part of the study design, the analyte tested, how the levels were established, specimen characterisation and number of replicates tested. Calculations used to determine the assay sensitivity should be included.

Positive specimens used in the performance evaluation for IHR IVDs should be selected to reflect heterozygous and homozygous phenotypes, variant and weak antigen expression. Specimens types tested in these studies should include:

- clinical specimens
- neonatal specimens
- cord blood specimens

Performance evaluation should be consistent with relevant standards and guidelines such as the Requirements for Conventional Blood Typing Reagents, as specified in the UK Red Book. Where relevant, blood grouping reagents should be assessed against international standards such as the WHO International Reference Preparations to ensure minimum potency titres are achieved.

For reagent red blood cell manufacture, a sample from each cell population should be tested using at least 2 antisera prepared from different donors or cell lines, in order to confirm the presence or absence of every antigen specificity claimed.

Information relating to studies conducted to determine the effect caused by potentially interfering or cross-reacting substances or agents on test results should be provided. Consideration should be given to both exogenous and endogenous factors expected to be encountered.

Where relevant, analytical and clinical performance evaluation studies for IHRs should address:

- detection of red blood cell (RBC) phenotypes from different ethnic groups;
- determination of antibody potency;
- determination of haemolytic activity; rouleaux formation; prozone effect;
- RBC sensitisation studies (e.g. IgG sensitised RBCs for testing reagents for use by a direct agglutination method, sensitised RBCs for the assessment of anti-complement activity);
- RBC treatment – e.g. washed versus unwashed RBCs, proteolytic enzyme treated RBCs (for enzyme-treated reagent red blood cells, information should be provided concerning those antigens which are rendered inactive or less active by the enzyme treatment used);
- Specificity of polyvalent antibodies and polyclonal reagents – e.g. testing against a wide range of antigens to confirm specificity and exclude the presence of potentially interfering antibodies.

Traceability of calibrator and controls

Information establishing the traceability of calibrators and trueness control materials should be provided, when applicable. Methods used to determine traceability to reference material of a higher order, acceptance criteria, and the assignment and validation of values should be included.

The phenotype of red blood cells used in the control of blood typing reagents should be confirmed using an established reference standard.

Controls and calibrators that are manufactured for use in immunohaematological testing should be assessed against international reference preparations to ensure minimum potency titres or standards are being achieved.

Determination of assay cut-off

Where applicable, a summary of the process used to establish the assay cut-off should be provided. Information provided should be based on the population studied, method(s) used to establish the true status and any statistical methods used to generate results.

Verification and validation of instrumentation/software

For verification and validation of instrumentation and/or software IVDs, the study report should include a summary of performance testing undertaken conducted in a valid end-user environment.

Stability

Stability studies to support the claimed shelf-life under closed, in-use and transport conditions must be provided.

For closed shelf life studies, data must be generated by testing at appropriate storage time intervals using a minimum of 3 separate production batches of IVDs, with at least one batch of real time data extending beyond the claimed shelf life. Temperature ranges assigned for testing should encompass both the upper and lower storage temperatures claimed. For new products where real-time studies are not yet completed, the initial expiry dating may be determined using accelerated stability studies, and experience gained by the manufacturer with similar reagents that can reasonably expect to be comparable with respect to stability characteristics. Ongoing real time studies for those products where the shelf-life has been assigned on the basis of accelerated data should be monitored closely, and the manufacturer should reduce the shelf-life in line with the real-time data as appropriate.

In-use (open vial) stability and transport simulation studies should be conducted using at least one batch of product, with a study design which includes conditions appropriate to the intended use and expected conditions likely to be encountered for the product.

For further information refer to CLSI standard EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents.

Information to be supplied with the IVD

The sponsor is required to provide clear, legible copies of representative information that is to accompany the kind of IVD medical device when supplied in Australia, including:

- Labelling;
- Instructions For Use; and
- Advertising material (e.g. brochures, web-pages, published advertisements, etc.), where available.

  - Labelling and instructions for use are not necessarily required for every model or variation, unless there are significant differences in content. However, the copies provided are required to be representative of what will be supplied in Australia.
  - The sponsor's name and address must be provided with the IVD in such a way that the user can readily identify the sponsor. Labelling requirements are prescribed in Regulation 10.2 and Essential Principle 13.2 in Schedule 1.
  - All representative information must be provided in English.

Depth of information to be provided

The following table summarises the depth of detail required to be contained in the STED. References to Class 4 IVDs in this table indicate the level of detail expected in the STED for products undergoing a design examination. Class 4 IVDs must be covered by a TGA Conformity Assessment Certificate and are not required to undergo application audit.

Section	Class 1	Class 2	Class 3	Class 4
Device description including variants				
Device description	Address each point – all classes			
Reference to previous device generation – not yet available on any market	SUMMARY	SUMMARY	SUMMARY	SUMMARY
Device history – already available on the market in another jurisdiction	SUMMARY	SUMMARY	SUMMARY	SUMMARY
Risk analysis and control	SUMMARY or REDUCED TABLE			DETAILED
Design and manufacturing information				
Device design	SUMMARY	SUMMARY	SUMMARY	DETAILED
Manufacturing processes	-	-	-	SUMMARY
Design and manufacturing sites	SUMMARY	SUMMARY	SUMMARY	SUMMARY
Product validation and verification				
Specimen type	SUMMARY	SUMMARY	SUMMARY	DETAILED
Accuracy – Trueness	SUMMARY	SUMMARY	DETAILED	DETAILED
Precision – Reproducibility and Repeatability	SUMMARY	SUMMARY	DETAILED	DETAILED
Traceability of control and control materials	SUMMARY	SUMMARY	SUMMARY	DETAILED
Analytical specificity & sensitivity	SUMMARY	SUMMARY	DETAILED	DETAILED
Validation of assay cut-off	SUMMARY	SUMMARY	DETAILED	DETAILED
Stability				
Claimed shelf life	SUMMARY	SUMMARY	DETAILED	DETAILED
In use stability	SUMMARY	SUMMARY	DETAILED	DETAILED
Shipping stability	SUMMARY	SUMMARY	DETAILED	DETAILED
Software	SUMMARY	SUMMARY	SUMMARY	DETAILED
Clinical evidence	SUMMARY	SUMMARY	DETAILED	ELABORATED

The following information provides explanations for the terms used in the table to describe the depth of detail required in the STED:

Summary information

- Brief description of protocol
- Study results
- Study Conclusion

Detailed information

- Study protocol
- Method of data analysis
- Study report (summary of external reports)
- Study Conclusion

Elaborated information

- Study protocol
- Method of data analysis
- Study report (all external reports)
- Study Conclusion
- Raw/line data

Further information may also be found in the GHTF document Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices which can be found at <http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n063-2011-summary-technical-documentation-ivd-safety-conformity-110317.pdf>.

Conformity assessment fees for IHR's

An initial conformity assessment application fee is charged for all applications for a conformity assessment certificate. Relevant fees and charges can be found on the TGA website at http://www.tga.gov.au/about/fees-current.htm.

An itemised (reduced) fee for examination of the design of IHR IVDs "of the same kind" is prescribed in Schedule 5 Item 1.9A (c) of the Regulations. This fee will be applicable to each application for a design examination for IHR IVDs "of the same kind".

References

- UK Red Book
  Guidelines for the Blood Transfusion Services in the UK
- Anti-A minimum potency reference preparation
  WHO International Standard or Reference Reagent 03/188
- Anti-B minimum potency reference preparation
  WHO International Standard or Reference Reagent 03/164
- Anti-Human Globulin
  WHO International Standard or Reference Reagent 96/666
- Anti-D Minimum Potency Standard for blood grouping reagents
  WHO International Standard or Reference Reagent 99/836
- Papain reference preparation 92-658
  ISBT/ICSH Reference Material 92/658
- Common Technical Specifications for in vitro diagnostic medical devices
  Revision of the common technical specifications laid down in Decision 2002/364/EC

Additional background information on the performance evaluation of Immunohaematology reagents (IHRs) may be found at:

- US Food and Drug Administration (FDA) - Recommended methods for Blood Grouping Reagents evaluation (March 1992)
- US Food and Drug Administration (FDA) – Recommended methods for Evaluating Potency, Specificitiy, and Reactivity of Antihuman globulin (March 1992)

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Reference/Publication #