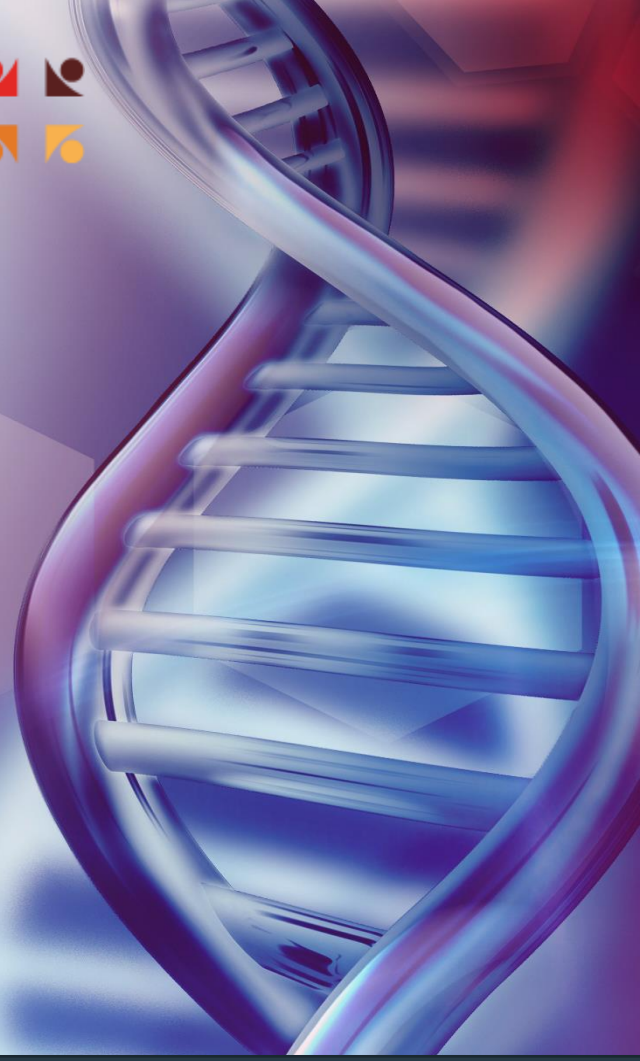
SALDA SOUTHERN AFRICAN LABORATORY DIAGNOSTICS ASSOCIATION

SAMED advancing patient care through MedTech



SAMED/SALDA Regulatory Forum

12 May 2021

IVD Overview & Regulatory requirements

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Overview

- "In Vitro Diagnostic Device or IVD"; a specific type of diagnostic medical device, whether used alone or in combination with other IVDs, intended by the manufacturer for the in-vitro examination of specimens derived from the human body or the environment solely or principally to provide information for diagnostic, monitoring, and compatibility purposes.
- Includes reagents, calibrators, control materials, specimen receptacles, and software relating to a specific IVD.
- Excludes products for general laboratory use which are not IVDs unless, in view of their characteristics, they are used for the purposes outlined in the definition of an IVD.
- Since IVDs do not come into direct contact with the patient, they represent a distinct class of health product, which are different from most medical devices therefore there is a need for separate In Vitro Diagnostic device regulations and guidelines as a harmonized standard.
- IVD’s may also be used in the public health environment for the monitoring of food and water contaminants.

Value of IVDs

- Effectively used, IVDs help to reduce hospital stays, support patients to look after their own health and release resources for use elsewhere in the health care sector resulting in a healthier population and stronger economic growth i.e. cost. Through molecular diagnostics, the industry also contributes to the natural evolution of medicine and more personalised treatment.
- Research and Development (R&D) by our industry has led to the creation of many new and innovative IVDs across a wide range of disease areas.

➢ SAMRC/TIA Medical Device and Diagnostic Innovation Cluster (MeDDIC) Call for Proposals: Localization of Medical Device Manufacture -SAMRC-RFA-GIPD-02-2021

- https://www.samrc.ac.za/request-for-applications/samrctia-medical-device-and-diagnostic-innovation-cluster-meddic-call

➢ Invest SA - http://www.thedtic.gov.za/

The IVD Process

Manufacturer	Laboratory	Doctor	Patient
R&D Manufacturing Marketing Sales Service Training Repairs	Process blood samples -> Report on Result E.g. HIV,Chol	Interpret Blood result -> Clinical Decision Treatment	Treatment Life style Monitoring

Instrument (Capex) / Analyser + Reagent+ Service+ Interpretation = Blood Result

Classification

IVDs should in a practical sense be classified using different risk criteria than that of medical devices and can be divided into sub classifications such as:

- Class A - Low Risk: Individual and Public health risk
- Class B - Low-moderate Risk: Individual and Public health risk
- Class C - Moderate-high Risk: Individual and Public health risk
- Class D - High Risk: Individual and Public health risk
- “RUO - Research use only” for IVDs in development phase.
- “Laboratory Developed Tests (LDT) for in-house testing” where health institutions develop, evaluate and validate tests, and does not place those on the market, but places them into service and uses them in the context of their professional activity and without having been transferred to another legal entity. This is commonly done as an additional tool for a pharmacological clinical trial.

Self-testing

- The issue of near patient testing and self-patient testing, are vulnerable to abuse and exposing the patient to a high risk of misinterpretation which could cause harm.
- This is the only area of IVDs that is not self-regulated and would need the attention of SAPHRA.
- Analysis of specimens in an accredited laboratory pose little or no risk to patients safety since there are currently more checks and balances in place.
- Near patient testing uses ICU blood gases monitors, doctor's room analyzers for urine and blood tests, and rapid tests for sexually transmitted diseases.
- Self-testing (e.g. Pregnancy tests, malaria drugs of abuse, HIV rapid tests).
- For these categories, the risk is increased due to the:
  - Use by lay persons, where risk relates to the competence of the patient or user,
  - inadequate post market surveillance and vigilance, reporting of adverse events, lot traceability, complaints handling, quality control and correct disposal of contaminated material.

CLASSIFICATION RULES FOR IVDS

IVD DEVICE CLASSIFICATION FLOW CHART						
RULE 1	**RULE 2**	**RULE 3**	**RULE 4**	**RULE 5**	**RULE 6**	**RULE 7**
Detection of transmissible agents posing a high public health risk	Setection of red blood cell antigens and antibodies and non red cell typing	Setection of agents posing a moderate public health risk or hogh personal risk	IVD for self-testing for serious condition, ailments or defect	Non assay-specific quality control material	Instruments, reagents, etc	IVDs not covered elsewhere in the classification rules
CLASS D	**CLASS C**	**CLASS C**	**CLASS C**	**Class B**	**Class A**	**Class B**
	Determination of ABO, RH, Kell, Kidd, Duffy systems		IVD for self-testing that is preliminary & follow-up testing is required			
	CLASS D		**CLASS B**			

Guidelines

- 8.02 Medical Devices and IVDs Essential Principles of Safety & Performance_Jul17_v1
- 8.04_Recalls_Vigilance_Medical_Devices_IVDs_Apr17_v2
- 8.05_Classification_Medical_Devices_IVDs_Apr17_v2
- 8.07_Medical_Device_Quality_Manual_Jun17_v2
- 8.10_QA_Licensing_Medical_Devices_Nov17_v1
- 16.03_Licence_Medical_Devices_IVDs_Jul16_v1_1

SAHPRA
South African Health Products Regulatory Authority

SAHPRA Communications

- MD001 – Regulatory Requirements for Medical Devices COVID-19 v2 – 22072020
- MD002 – Regulatory requirements for serological test kits v2 – 22072020
- MD003 – Testing for COVID-19 v1 – 22072020
- MD004 – Extension: Use of acknowledgement letter in lieu of license v1 – 31032020
- MD005 – Expedited Regulatory pathways for medical devices v1 – 22072020
- MD006 – Laboratory testing & use of COVID-19 serological test kits v1 – 22072020
- MD007 – Specification criteria for COVID-19 serological test kits v2 – 22072020
- MD011 – License conditions for COVID-19 serological test kits v1 – 22072020
- MD013 – Process flow: Locally manufactured COVID-19 test kits v1 – 22072020
- MD014 – Regulatory requirements for molecular test kits v1 – 22072020
- MD015 – Process flow: Imported COVID-19 test kits v1 – 22072020
- MD016 – Conditions of use COVID-19 serological test kits v1 – 22072020
- MD017 – Technical review application: COVID-19 molecular test kits v1 – 22072020
- MD018 – Specification criteria for COVID-19 molecular test kits v1 – 22072020
- MD019 – Processing of medical device establishment license applications made to SAHPRA v1 – 22072020
- MD020 – Application for a Certificate of Free Sale for medical devices v2 – 22072020
- MD021 – Regulatory requirements for the use of COVID-19 antibody tests in line with the National Department of Health guidance on the use of COVID-19 antibody test v1 – 20082020
- **MD022 – Application for clinical evaluation of a medical device or IVD v1 – 01092020**
- MD024 – Frequently asked questions: Performance evaluation of point-of-care COVID-19 serology antibody test kits v1 – 08092020

General Regulations

A person referred to in section 22C(1)(ó) of the Act:

must prior to commencing business as such

- apply to the SAHPRA for:
  - a manufacturer license to manufacture, import or export medical devices or IVDs; or
  - a distributor license to import, export and distribute medical devices or IVDs; or
  - a wholesale license to act as wholesaler of medical devices or IVDs;
- appoint, and designate a natural person who resides in the Republic, as such an authorized representative who shall reside in South Africa:
  - be responsible to SAHPRA for compliance with the Act and
  - control the manufacturing, distribution, wholesaling and the sale of medical devices or IVDs.

Provide to SAHPRA documentary proof of:

- the particulars of the owner of the business;
- the particulars of the authorized representative; and
- evidence of accreditation to a Quality Management System for medical devices and IVDs as determined by SAHPRA,
- must specify, as determined by SAHPRA, the medical devices or IVDs or group or family of medical devices or IVDs to be manufactured, imported, exported or distributed and sold; and
- must pay the application fee.

Application Requirements

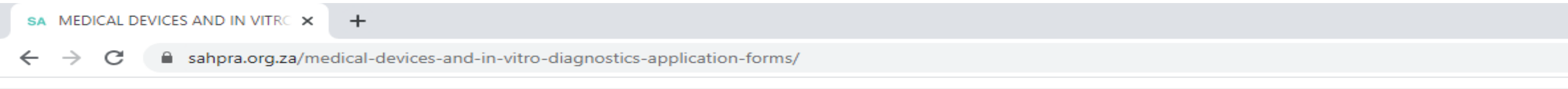
- Application form
- Originating approvals
- Certificate of free sale
- Technical dossier
- Product listing
- Application fee

Global Approvals

Originating approvals

- Australia
- Brazil
- Canada
- EU (CE)
- Japan
- US FDA
- WHO PQ

Application Forms



MEDICAL DEVICES AND IN VITRO DIAGNOSTICS APPLICATION FORMS

Show 10 entries Search:

Number	File Name	Year	Version	Document Type	Download
6.21	Licence Application Medical Device Manufacture	2016	3	Application Form	DOWNLOAD FORM
6.22	Licence application to distribute (import/export) medical devices	2016	1.2	Application Form	DOWNLOAD FORM
6.26	Licence application to wholesale medical devices	2017	2	Application Form	DOWNLOAD FORM

Showing 1 to 3 of 3 entries Previous

Application Forms

It is important to make use of the correct form.

The type of license that you will need will depend on the activities that you are performing.

- If you are doing any packaging, labelling, servicing or refurbishment of medical devices at the establishment, you will be required to apply for a Manufacturer's license.
- If you are doing any distribution activities, such as importation or exportation of medical devices to and from the premise, you will be required to apply for a Distributor's license.
- If you are doing any wholesaling activities, such as sale, storage, transportation and/or the onward dispatch of medical devices from the premise, you will be required to apply for a Wholesaler's license.

SAHPRA Fees

FEE FOR NEW LICENCES

4. (a) An application for a new licence in terms of Section 22C (1)(b) of the Act:

(i) Manufacture: R25 200;

(ii) Distribute: R15 000 [Holder of certificate of registration (HCR)];

(iii) Wholesale: R15 000;

(iv) Import: R15 000 (Holder of certificate of registration); and

(v) Export: R15 000 (Holder of certificate of registration).

(b) An application for the renewal of a licence in terms of Section 22D of the Act, the licensing of which has been approved by the Authority in terms of Section 22C(1)(b) of the Act:

(i) Manufacture: R22 000;

(ii) Distribute: R12 600 (Holder of certificate of registration);

(iii) Wholesale: R12 600;

(iv) Import: R9 200 (Holder of certificate of registration); and

(v) Export: R9 200 (Holder of certificate of registration).

(c) Annually, in respect of the retention of a licence issued in terms of Section 22C(1)(b) of the Act: R4 200, and this fee is payable on or before the last working day of June that year, failing which registration may be cancelled.

Retention Fees

The SAHPRA annual retention fee must be paid before 30 June every year depending on when your license was issued. Please note the below example for payment of the Retention Fee:

- If your license was issued in May 2020 - you have to pay the retention fee in June 2021
- If your license was issued in June 2020 - you have to pay the retention fee in June 2021
- If your license was issued in December 2020 - you have to pay the retention fee in June 2021
- If your license was issued in January 2021 - you have to pay the retention fee in June 2022

- NB SAHPRA does not send reminders for retention fees

License Amendment

Do I need to submit an amendment when I add a new product to my license listing?

Licensees are not required to make application for amendment of a medical device establishment license in the event of a change in the product listings provided in section 4.1, 4.2, 4.3, 4.4 and 17.3 of the manufacturers and distributors license application form and section 3 of the wholesaler's application form: Provided that the **class** of medical device/s for which the licensee has been licensed is not affected and does not change.

- In the event of a change to section 4.1, 4.2, 4.3, 4.4 and 17.3 of the manufacturers (6.21) and distributors (6.22) license application form and section 3 of the wholesalers (6.26) application form that does not affect the class of medical device/s for which the licensee has been licensed, the licensee is required to **notify** the Authority in writing – subject to the criteria set out by SAHPRA.
- No fees will be levied in this regard.
- All other changes to the product listing are subject to an amendment and associated fees
- In the case of a **new Class** of device being added to the listing of your Medical Device Establishment License, you will need to apply for a full amendment with associated fees

License Amendment

Do I need to apply for an amendment to my Medical Device Establishment License if the product is repacked and registered under another jurisdiction?

- It is important that South African labelling criteria be met/adhered to.
- If the name/kit composition change or the product is re-labelled, you will need to apply for a full amendment with associated fees
- The regulatory conditions of the market approvals you have indicated with SAHPRA must still be met.

COVID PCR /Serology Kits

What is the classification on serological/rapid test kits?

- These are class D and you will need to apply for a full amendment with associated fees (visit the SAMED website for the fee schedule) regardless on the highest classification on your Medical Device Establishment License.

What are the limitations on the sale of serological/rapid test kits?

- SAHPRA is only allowing the sale of serological test within National Testing setting. This will need to follow the National Testing algorithm which the National Department of Health will publish.

If I want to bring in a serological/rapid test kit or PCR test kit for Research Use Only (RUO), what must I do?

- You will need to submit the clinical trial protocol to SAHPRA for approval before any RUO tests will be permitted for import.

***What are the turnaround times for COVID-19 product applications*?**

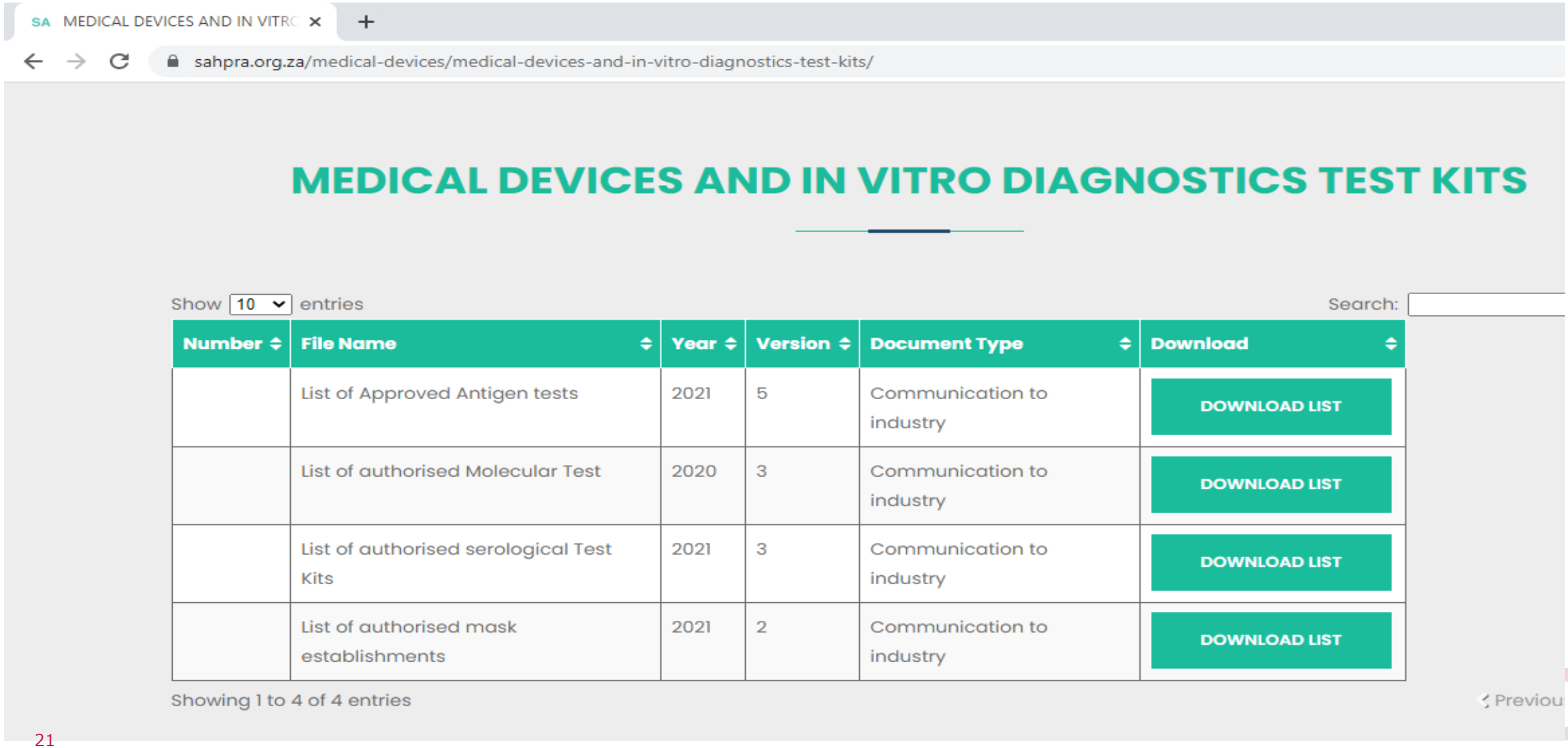
- General: 7-10 Working days, however, this will depend on the completeness of the application and support documentation as well as the response times to any SAHPRA queries with the applicant. Application for serological kits may take 6-8 weeks as these require greater technical scrutiny and validation

Section 21

What is the process for Section 21 authorization and new license documents for IVDs?

- To apply for Section 21 approvals, you will need to follow the guidance as set out in the SAHPRA communications MD0011, MD0013 and MD0015.
- At the same time you can apply for your new/updated license document through the relevant application channels.
- You will receive section 21 authorization and new/updated medical device establishment license from SAHPRA.

Test kits listing



MEDICAL DEVICES AND IN VITRO DIAGNOSTICS TEST KITS

Show 10 entries Search:

Number	File Name	Year	Version	Document Type	Download
	List of Approved Antigen tests	2021	5	Communication to industry	DOWNLOAD LIST
	List of authorised Molecular Test	2020	3	Communication to industry	DOWNLOAD LIST
	List of authorised serological Test Kits	2021	3	Communication to industry	DOWNLOAD LIST
	List of authorised mask establishments	2021	2	Communication to industry	DOWNLOAD LIST

Showing 1 to 4 of 4 entries

Certificate of Free Sale (MD020)

- A certificate, issued by SAHPRA, which serves as confirmation that the listed medical devices are legally sold or distributed in the open market in South Africa, freely without restriction, and approved by the regulatory authority (SAHPRA) in the country of origin (South Africa).
- Serves as confirmation by SAHPRA that the manufacturer is:
  - the legal original manufacturer; and
  - licensed by SAHPRA to manufacture the medical device/s.

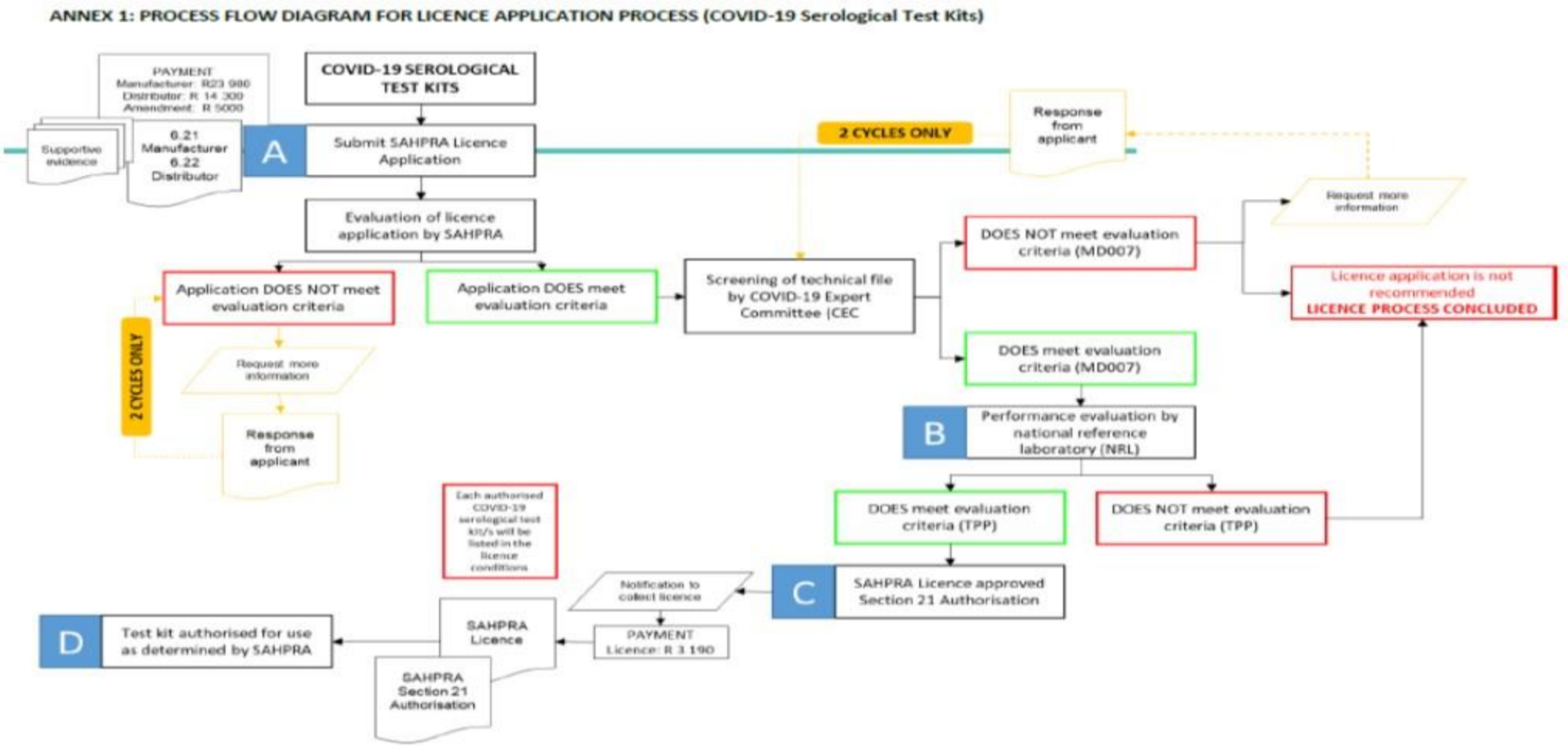
  Note: the medical device/s has/have not been assessed for safety and performance by SAHPRA.
- Aim to meet the needs of the importing country.
- Before applying for a certificate SAHPRA recommends that the applicant contact the relevant foreign government through their consulate to ascertain what information must be supplied in order to facilitate the export of the medical devices to their country.
- Only medical device/s that are listed in Sections 4.1, 4.2, 17.1 and/or 17.2 of the current SAHPRA license application of the manufacturer, are eligible for inclusion in the application for a certificate of free sale.
- The application for a Certificate of Free Sale may include multiple medical devices and multiple recipient countries. It is not necessary to apply for a certificate of free sale for each listed medical device and/or recipient country
- The Certificate of Free Sale will be valid for a maximum period of **one year** and will be void when medical device/s are called up for registration, in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965

Certificate of Free Sale con.

The following information will be included on the Certificate of Free Sale:

- Name, site address, license number and MDF number of SAHPRA licensed manufacturer of medical device
- Details of medical device/s intended for export and listed in this application including
- GMDN code
- GMDN descriptor
- Name and/or group and/or family of the medical device
- South African risk class of medical device
- Recipient Country/ies
- Name and contact details of the authorized representative
- Any additional particulars required to facilitate the export of the listed medical device/s to the relevant foreign government.

Process Flow – kits (MD002)



Validation of Kits

- NHLS Labs – **sole lab** authorised by SAHPRA to do validations
- Timelines differ for each validation
  - 6-8 weeks for antigen kits;
  - 2-4 weeks for molecular kits;
  - 4-5 weeks for antibody kits

MD027 –RUO (Research Use only IVDs) – 29 March 2021

1. The Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended, ("the Medicines Act"), read in conjunction with the Regulations relating to medical devices and in-vitro diagnostic medical devices ("the Medical Devices Regulations"), published in Government Gazette Notice 40480, No.1515 of 9 December 2016, provides for the regulatory oversight of medical devices including in- vitro diagnostics (IVDs) in South Africa.

2. **"Research use only"** ("RUO") is defined in the regulations as "an IVD labelled for "research use only", and "for investigational use only" and may not be used for clinical diagnostic purposes.

3. A RUO product may be an IVD device that is:
   a. in the laboratory research phase of development; **or**
   b. intended for use in the conduct of non-clinical laboratory research with goals other than the development of a commercial IVD product, i.e., these products are used to carry out research and are not themselves the object of the research.

4. RUO IVDs are neither used nor intended to be used for clinical diagnosis, or support thereof, of a clinical condition in a human or an animal.

5. An IVD device labelled for RUO is thus limited to use in the conduct of laboratory research that is either related or unrelated to the development of IVDs, providing instructions for correctly using the product in a research manner (for example, mixing proportions, incubation times, storage conditions, etc.) and is consistent with "research use only" labelling.

6. With respect to IVD products that are appropriately labelled RUO, the RUO classification and label serves as a warning, to prevent such products from use in clinical diagnosis or patient management.

7. In terms of Section 21 of the Medicines Act, the Authority may authorise the sale of unregistered medicines, medical devices or IVDs for certain purposes—
   (1) The Authority may in writing authorise any person to sell during a specified period to any specified person or institution a specified quantity of any particular medicine, medical device or IVD which is not registered.

RUO con.

SUBMITTING A SECTION 21 APPLICATION FOR IMPORTATION OF RUO IVD

10. Any entity or person, located in South Africa, intending to conduct non-clinical laboratory research may submit a section 21 application to SAHPRA to import a RUO IVD.

11. An application form (refer **Annexure A**) for the purpose of obtaining the section 21 authorisation to import a Research Use Only (RUO) In Vitro Diagnostic (IVD) medical device in terms of the provisions of the Medicines Act read in conjunction with the Medical Device Regulations, must be submitted to SAHPRA.

12. The application must include the following attached documentation:
    a. Classification of the IVD in other jurisdictions recognised by SAHPRA; (Australia; Brazil, Canada; European Community; Japan; USA & WHO);
    b. Product / component label(s) and kit label, where relevant;
    c. Information for Use / User manual;
    d. Proof of payment for a section 21 authorisation

13. Please ensure that on submission to the Authority all relevant fields are completed and all supporting documentation is attached. Incomplete applications will be identified as deficient and review will not be progressed until deficiencies are addressed.

14. The prescribed section 21 application fee and proof of payment must accompany the application. For the current fee payable, refer to the latest fee schedule as published in the Government Gazette and published on the SAHPRA website.

15. Payments should be made as per 17.05 "Guideline on the payment of fees to SAHPRA", accessible here: https://www.sahpra.org.za/wp-content/uploads/2021/01/SAHPRA-Payment-Guideline-Nov-2020.pdf

RUO con.

- The current fee for the Section 21 RUO application falls under the section 3b(iii) – R 350
- If the product is already listed on the product list as part of the applicants license – then a separate RUO application is not required.
- If the product has not been listed previously as an RUO or registered product, then the RUO pathway must be followed

Recall and Vigilance

SAHPRA : GUIDELINE FOR RECALL / WITHDRAWAL, ADVERSE EVENTS & POST-MARKETING VIGILANCE REPORTING OF MEDICAL DEVICES AND IVDs

A reference document detailing the regulatory requirements for reporting and describes the information to be supplied to the Regulatory Authority in South Africa.

- to assist licensed manufacturers and distributors and Holders of a Certificate of Registration (HCR) of Medical Devices and IVDs in

➢ the reporting of adverse events associated with the use of medical devices and IVDs,

➢ the post-marketing vigilance for medical devices and IVDs. (This includes the management of safety data which arises during post-registration and post-marketing performance and clinical trials.) and

➢ the recall of a medical device or IVD from the market place

Recalls

- The recall must be reported to SAHPRA by the local distributor.

An excerpt from the SAHPRA recalls & vigilance guideline:

- When initiating a recall, the HCR / licensed manufacturer / licensed distributor should take the extent of public warnings and the successfulness of the recall into consideration.
- It is imperative that before or upon initiating a recall, the HCR (holder of certificate of registration)/ licensed manufacturer / licensed distributor immediately on becoming aware of a problem, notifies the CEO or in his/her absence his/her designate of the potential recall.
- Therefore, it is advisable that no recall, regardless of the level, should be undertaken without consultation with the Regulatory Authority and without agreement on the recall strategy.
- In case of a potential significant health hazard to patients, the HCR / licensed manufacturer / licensed distributor may within 24 hours disseminate information on the recall. This includes precautionary measures to quarantine stock pending the initiation of the recall.

ISO 13485

- The internationally accepted quality standard for medical device establishments is called ISO 13485. While SAHPRA requires companies to provide details of their quality management systems, it has provided a grace period to companies applying for medical device establishment licenses to certify that ISO 13485 standards have been met.
- “SAHPRA license holders will [only] be required to provide evidence of ISO13485 certification upon application for renewal of the SAHPRA license”, - “licenses are valid for five years”.
- A major barrier for companies seeking to gain ISO 13485 certification is the dearth of companies and groups accredited by the South African National Accreditation System (SANAS) to provide this certification.
- Awaiting transition plan from SAHPRA :

The requirement is stipulated in guidance documents, however the amendment to the regulations (where the ISO13485 becomes mandatory) has not been published, and is awaiting publication. The company is however mandated to be ISO13485 compliant insofar as the company has a robust QMS in place, as signed by the AR in the Section 23 declaration.

Clinical Trials

SAHPRA requires sponsors to monitor the conduct and progress of their clinical trials because effective monitoring of clinical trials by sponsors is critical to the protection of human participants and the conduct of high-quality studies.

It is expected of Sponsors of clinical trials involving human medicines, biological products, medical devices, and or other combinations, to provide oversight to ensure adequate protection of the rights, welfare, and safety of human participants and the quality of the clinical trial data submitted to SAHPRA.

SAHPRA has drafted a guideline for the **oversight and monitoring of clinical trials**, launched in March 2021: **Version 3.**

- This guideline focuses principally on monitoring, which is one aspect of the processes and procedures needed to ensure clinical trial quality and participant safety.
- Monitoring is a quality control tool for determining whether study activities are being carried out as required so that deficiencies can be identified and corrected.
- SAHPRA's stances that Monitoring or oversight alone cannot ensure quality. Rather, quality is an overarching objective that must be built into the clinical trial enterprise

Any Questions ?