SALDA

SOUTHERN AFRICAN LABORATORY DIAGNOSTICS ASSOCIATION

Good morning ladies and gentlemen,
Thank you for inviting me to talk about the IVD industry.

We are entering a new era of much needed regulatory oversight which might seem a daunting task at first. I am glad to say that there are already countries that have managed this before us and we hope to learn from their mistakes.

So to begin, what are in vitro diagnostic devices, which always seem to hang off the end of the expression “medical devices and IVDs”?
Why are international IVD regulations and guidelines different to Medical Devices?
What is the current self-regulatory framework in laboratories?
How do the vulnerabilities of IVDs affect the patient?
What are the risks?
What is the vision for IVD regulation and guidelines?

In Vitro Diagnostic Devices or IVD’s are a specific type of diagnostic device used for the in-vitro examination of specimens in order to provide information for diagnostic, monitoring, and compatibility purposes. IVD’s may also be used in the public health environment for the monitoring of food and water contaminants. They may also be used for non-clinical purposes without any medical objective.
Since draft Medical Device and *In Vitro* Diagnostic Regulations and Guidelines were published, it has been our intention to view these regulations and guidelines specifically in relation to *In Vitro* diagnostic assays to ensure that adequate and appropriate provisions are made for *In Vitro* Diagnostic Device product registration and regulation. Currently these regulations and guidelines lean heavily towards Medical Devices and most of which do not relate to IVDs. In the current drafts of Regulations and Guidelines there is **no definition** for IVDs or **classification rules** specifically for IVDs. Although, on the face of it, it seems that the same set of regulations could possibly fit both IVDs and Medical Devices. However there are fundamental and obvious differences that would prescribe the need for separate regulations and guidelines for IVDs.

Take the case of combination medical devices. Antibiotics are required to be registered and follow regulations and guidelines specifically for pharmaceuticals. If you have a drug eluting stent then that product would require registration using Medical Device and IVD regulations

and guidelines. But when you look at an antimicrobial assay used to determine the sensitivity and resistance of an antibiotic to a specific bacteria causing infection in the body, you will find a classic combination medical device which is a device containing a scheduled substance whose action is ancillary to the purpose of the medical device (such as our drug eluting stent). However in the case of a combination IVD, both the antibiotic and the medical device are not in contact with the patient. The volume of antibiotic used is significantly smaller than that of an administered antibiotic. So in order to properly classify and register antimicrobial tests we can neither use Pharmaceutical or classical combination Medical device regulations.

So perhaps this is a good time to tell you all about our industry.

The Pillars of the *In* Vitro Diagnostic Industry including the Southern African Laboratory Diagnostics Association's (SALDA), the National Pathology Group (NPG), the Health Professions Council (HPCSA) and the Society for Medical Laboratory Technologists of South Africa (SMLTSA) have reviewed the landscape of IVD's and how regulations will impact our industry within South Africa, given that IVD's are already self-regulated to a certain extent. Internationally *In vitro* diagnostic devices are regulated by means of a separate set of regulations within the greater context of medical device regulation, as in the EU Directive 98/79 EC for *In vitro* diagnostics. Our recommendations are based on global and African harmonization, international best practices, experience within the industry and the necessity for change to ensure quality, performance and safety of *in vitro* diagnostics (IVDs) balanced with the need for sustainability of the IVD industry and to ensure patient accessibility to proven as well as cost-effective technologies.

"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. (This includes reagents, calibrators, control materials, specimen receptacles, and software relating to a specific IVD). This 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. This also excludes IVDs where the intended use is for non-clinical purposes without any medical objective and "RUO - Research use only" IVD Devices.

Unlike other forms of medical technology, IVDs never interact directly with the human body. Their purpose is not to have a direct therapeutic effect, but rather to provide valuable information on a patient's health status. Their value stems from the information they provide. This means that the appropriate qualification and expertise of the healthcare professional in using the IVD is crucial to ensure the correct decision making for patient treatment and care. This sets IVDs apart from medical devices and pharmaceuticals, and is part of what makes them unique amongst health technologies.

In this context we can also say that In Vitro diagnostic assays are simply tools to help us with clinical and non-clinical assessments of a target analyte in humans, animals and the environment. So the intended purpose of an IVD is not always directly related to a patient for clinical assessment but to a specific analyte wherever it may be found.

As an example, to distinguish IVDs from other medical devices, one might consider the use of medical devices for the diagnosis of TB in a patient:

- The IVDs used in the diagnosis of TB may consist of more than one component. They could include more than one laboratory instrument and various reagents, techniques and skills, applied to specimens obtained from the patient (e.g., sputum) The risk does not lie primarily in the equipment or the test itself, but in the manner in which the testing is performed and in the correct interpretation of the results.
- In contrast, other medical devices may also be used to diagnose TB. For example, an X-ray machine involves direct contact with the patient, and involves a high degree of risk. Such devices are clearly distinct from IVDs and should be governed by a separate set of regulations.

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.

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:

(a) Class A - Low Risk: Individual and Public health risk
(b) Class B - Low-moderate Risk: Individual and Public health risk
(c) Class C - Moderate-high Risk: Individual and Public health risk
(d) Class D - High Risk: Individual and Public health risk
(e) "RUO - Research use only" for IVDs in development phase.
(e) "Laboratory Developed Tests (LDT) for in-house testing" where health institutions develops, evaluates and validates tests, and does not place those on the market, but puts those 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.

Then we come to the issue of **near patient testing** and **self-patient testing**, which I believe are vulnerable to abuse and exposing the patient to a very high risk of misinterpretation which could cause untold misery. The device itself is unlikely to cause direct harm but the misinterpretation of a result in the absence of a trained professional could have very critical consequences for the patient. This is the only area of IVDs that are not self-regulated and would need the immediate attention of SAPHRA or the MCC. Analysis of specimens in an accredited laboratory pose little or no risk to patients safety since there are currently more checks and balances.

(f) Near Patient or self -testing

1) **Near patient testing** uses ICU blood gases monitors, doctor's room analysers for urine and blood tests, and rapid tests for sexually transmitted diseases.

2) **Self-testing** (e.g. Pregnancy tests, malaria drugs of abuse).
: For these categories, the risk is increased due to the:

i) Use by lay persons, where risk relates to the competence of the patient or user,
ii) inadequate post market surveillance and vigilance, reporting of adverse events, lot traceability, complaints handling, quality control and correct disposal of contaminated material.

3) **Companion testing**: e.g. Glucometers

IVDs for POCT should not be confused with the task of a registered nurse, which monitors patients with **IN VIVO** diagnostic tools in the form of blood pressure and temperature monitoring, which is done on the human body and which would fall under medical device regulations. Lay persons often confuse the responsibilities of in vitro diagnostics with the responsibilities of in vivo diagnostics.

For IVDs intended for use for self- testing, it is important to note when the user should consult with a healthcare professional. For near patient testing the healthcare professional must be registered with the Health Professions Council of South Africa in accordance with the Health Professions Act. Such persons may only operate within their chosen scope of practice for example Cytology, Microbiology, Haematology or General Clinical Pathology. Registered Nurses must be registered with the Nursing Council in accordance with the Nurses Act and would require additional accredited qualification for near patient testing.

Since IVDs are currently unregulated, some IVD assays have crept into the pharmacies and are freely available for sale to lay persons. I have seen vending machines capable of dispensing one off tests. I have seen, pregnancy tests, fertility tests, malaria tests, bacterial detection for urinary tract infection, HIV tests and many more.
Although companion IVDs such as Glucometers and blood pressure monitors have always been freely available, these have always been used in conjunction with the frequent evaluations by a clinician.
Pregnancy tests are also freely available, which poses a risk, because they do not quantify high levels of Bhcg which is also used as a gynaecological tumour marker. Strangely, you cannot just walk into a laboratory requesting a pregnancy test, it has to accompany a written request form from a clinician.
Just because a test is “easy to use” it does not mean that it can be used outside the scope of a medical technologist or pathologist. A lot of these strip assays have what we call “an internal control”. This control is used to indicate the progression of fluid so that it proceeds unhindered to the end point. This does not replace the compulsory test controls which governs the test band sensitivity or specificity. These test controls are not supplied with the self-testing kits. In all laboratories additional tests are performed frequently to monitor this. These self-tests are used in individual isolation, so false positives or false negatives are hard to detect. Laboratories usually run batches of specimens so a “lot” defect or specimen defect is picked up very quickly. An even greater risk to patient self-testing is the correct and accurate sample collection. This is currently done by professional phlebotomists who are also registered by the HPCSA.

South Africa has desperate need for Point of Care testing and self-testing to be done in rural clinics, so obviously POCT will relieve a huge burden on reference hospitals but it is very important to provide a robust regulatory framework that properly supervises and addresses its specific needs.

Apart from self-testing, IVD's performed in accredited laboratories already manage patient safety, and quality and performance of assays in the absence of regulations and guidelines. I am happy to say that the South African Blood Transfusion Service has led the way in this regard, and currently supplies South Africa with one of the safest blood and blood products in the world.

With the practice of self-regulation, the IVD and Pathology industry adopts international laboratory set standards . In addition , apart from self-testing, IVDs are currently only available for sale to pathology laboratories or similar and are largely not open to the wholesale market place or the public. This makes current post marketing activities such as lot traceability, handling of adverse events, complaints handling, product training , quality control and material disposal possible.

- The technicians and technologists that use IVD products are highly qualified and meet with the standards laid out by the Health Professions Act and regulated by the HPCSA. The test results are verified additionally by a pathologist and then assessed by the clinician.
- All IVD products used, come with an internal certificate of analysis, and are manufactured by accredited laboratories ISO 13485/ or equivalent.
- Medical Laboratories that are accredited by SANAS, the National Accreditation Body of South Africa, are compliant against the International ISO 15189:2012 standard.
- The ISO 15189 Standard has been designed specifically for Medical Laboratories for Quality and Competence.
- The Ethics code is implemented as part of all the policies and procedures.
- All Policies and processes are documented, managed, used for Training and read by staff.
- There is an advisory service and consulting to all clients to assist with the relevant tests and interpretations of results.
- Internal audit processes give an opportunity of finding non-conformances, being proactive with corrective actions to ensure continual improvement.
- Risk assessment is done within the laboratories as well as patient risk management.
- The Waste Management Act is implemented and monitored very closely.
- Bio hazardous and Liquid waste is removed by compliant companies
- Sample collection of patients is documented in procedures and monitoring of sample requirements and suitability of procedures and requests is done.
- A (Order for testing) Request form from the Referring Clinician must be received.
- There are procedures in place for verbal requests
- Sample transportation is monitored closely.
- Sample handling, preparation and storage are implemented.

- Appropriate facilities, securing patient information and samples and to avoid deterioration
- All (IVDs) Equipment and Reagents (test kit) used within the laboratory are thoroughly investigated before being bought and put to use.
- Supplier International and National Compliance and Accreditation records are evaluated
- IVDs compliance certificates with full validations are obtained.
- IVDs are verified within the laboratory before use
- IVDs are all traceable from receipt with serial numbers, lot/batch numbers and expiry dates
- Full documentation, name, make, model, serial no, date of purchase etc. of each IVD is kept on record
- Controls both Internal and External are used to assure correctness of the complete process until the attained result
- Maintenance and temperature control is done where applicable
- All IVDs interfaced with the computer system and validated, verified before use
- IVDs are stored in relevant and regulated storage areas.
- Result Reports to clinicians contain all patient and client information.
- Requested tests, normative values and Pathologist comments
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An Independent Accreditation, Quality and Safety Department evaluates and monitors the compliance of this system.

Relevant Regulatory Bodies Used:

- Constitution and Code of Conduct – NPG
- Ethical Ruling – HPCSA
- Health Professions Act 1974
- Marketing Code Authority
- Occupational Health and Safety Act and Regulations 83 of 1993
- National Environmental Management Waste Act 2008
- Accreditation for Conformity Assessment, Calibration and Good Laboratory Practice Act19 of 2006
- OHSA Regulations for Hazardous Biological Agents – Department of Labour
- South African National Accreditation System – SANAS
- National Health Act 2003, National Health amendment act 2013

South Africa is a member of the Asian Harmonisation Working Party, an organisation that facilitates international harmonization and is in consensus with the Global Harmonisation Task Force (GHTF) guidance documents. The GHTF, which is widely regarded as the international forum for consensus has published the latest developments in IVD regulation and harmonisation which provides guidance to new regulatory bodies. By adopting the GHTF guidance as the basis for regulation, South Africa will ensure that it is harmonized with the rest of the world. This will:

- Ensure ease of recognition and MOUs between South Africa and its peers
- Ensure shorter regulatory timelines and reduced expenses

- Assist local companies already in or wishing to enter international markets.

We similarly believe that it is imperative that SAPHRA have dedicated staff for dealing with IVD issues, in order to ensure appropriateness and efficiency in the review processes. SALDA promotes cross-mentorship and a transfer of knowledge between the Authority and all stakeholders of the IVD industry. *In vitro* diagnostics are very different to medical devices and will require special considerations for regulations and guidelines. We acknowledge that all participants in these regulations have limited experience in regulating In Vitro Diagnostics in South Africa and would like to share our knowledge of the industry gained by our experience in self- regulating.

Thank You!

SALDA In Vitro Diagnostics in South Africa

Welcome

October 2014

A new era of regulatory oversight

What are In Vitro Diagnostic Devices

How do they differ from Medical Devices

The current self-regulatory framework in laboratories

What are the real risks to the patient

What is the vision for IVD regulation and guidelines

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What are In Vitro Diagnostic Tests

The examination of specimens taken from the body

Or the environment

Provide information for diagnostic, monitoring, surveillance and compatibility purposes.

Public health environment

Non-clinical purposes

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Draft MD and IVD Regulations and Guidelines

Regulations and guidelines need to be viewed specifically in relation to IVDs.

They need to be robust, adequate and appropriate.

Currently lean heavily towards Medical Devices.

No provisions made for IVD definition and classification rules in the regulations or guidelines.

Fundamental differences between MDs and IVDs.

The need for separate regulations and guidelines for IVDs.

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Combination IVDs

Antibiotics = medicine= Pharma regulations and guidelines.

Combination medical devices = drug eluting stent = Medical Device regulations and guidelines.

Combination IVD = antibiogram for bacteriology IVD containing an antibiotic=no patient contact at all= ?

Pillars of the IVD Industry

Southern African Laboratory Diagnostics Associations (SALDA) representing the “trade” commercial sale of IVDs.

National Pathology Group (NPG) representing Pathologists.

Health Professions Council (HPCSA)representing qualification and regulation of Medical Technologists and Phlebotomists.

The Society for Medical Technologists of Southern Africa (SMLTSA) representing the continued education of Medical Technologists.

Why Regulate?

Global and International Harmonization.

International Best Practices

Experience within the industry

The necessity for change to ensure quality, performance and safety of IVDs

The sustainability of the IVD industry

To ensure patient access to proven cost effective technologies

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IVD Definition and concept

IVDs are a specialised type of medical device.

They can be used alone or in combination with other IVDs, laboratory procedures or techniques.

The examination of specimens derived from the human body or the environment.

To provide information for diagnostic, monitoring and compatibility purposes.

Why are IVDs different to MD?

Never interact directly with the patient.

No direct therapeutic effect

Provides information on the patients status.

Qualification of the health care professional is crucial.

Used in clinical and non-clinical assessments.

Targets a specific analyte found in humans, animals and the environment.

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An example of TB Testing

IVD TB Diagnosis:

- Laboratory instruments
- Various reagents
- Techniques and technologists skills
- The intrinsic risk lies in the manner in which it is performed

MD TB Diagnosis

- X ray machine in direct contact with the patient
- A high degree of risk due to exposure.

Classification considerations for IVDs

They are not in direct contact with the patient.

There are different risk criteria to MDs.

Class A – Low risk to the individual and the public health

Class B – Low to moderate risk to the individual and the public health

Class C – Moderate to high risk to the individual and public health

Class D – High risk to the individual and public risk

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Non Clinical IVD Considerations

IVDs can be used in other industries:

- Agriculture
- Bio fuels

The testing and monitoring of Cholera in environmental water.

Food industry:

- Early and accurate detection of bacterial contaminants

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" RUO "

Research Use Only IVDs

IVDs in the development phase

Reagents are researched outside the human body.

No indication for "classical " clinical trials.

LDT's

Laboratory developed tests

Laboratories develops, evaluates and validates in-house tests or "home brews".

Not for sale on the market but are used within the context of the laboratories professional activity

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The risks relating to near patient and self-patient testing

Vulnerable to abuse and misinterpretation in a non-regulated environment.

IVDs do not cause direct harm.

The misinterpretation of a result, for whatever reason, and in the absence of a trained professional, could have very critical consequences for the patient.

This is the only area of IVDs that is not self-regulated.

There is a need for urgent regulation in POCT.

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Near patient testing

- ICU Blood Gas Monitors
- Urine and blood chemistry
- Sexually transmitted diseases
- Liver enzymes
- Glucometers

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IVD Self-Testing

- Glucometers
- Pregnancy Tests

The risk is increased due to the use by lay persons

The risk will vary due to the competence of the lay person.

In adequate post market surveillance, reporting of adverse events, lot traceability, complaints handling, quality control and disposal of contaminated material.

IVD Self-Testing

Consult with a health care professional.

Registration with the HPCSA
- Operate within your scope of practice

Registration with the Nursing Council
- Additional accredited qualifications

Currently unregulated

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IVD Self-Testing

Freely available in pharmacies, not behind the counter.

The sale of High Risk Tests:

- Pregnancy Tests – also used in the labs as a gynaecological tumour marker.
- Fertility tests
- Malaria Tests
- Bacterial detection for urinary tract infections
- HIV tests, indicating HIV 1&2 but not subtype O

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“Easy to use” ?

The ease and speed of a result does not place it outside of the scope of practice for Medical Technologists and into the hands of lay persons.

False sense of security ignoring false positives, false negatives and incorrect sample preparation.

No compulsory quality control performed. Not supplied with the test sold.

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POCTs : The future

Relieve diagnostics burden and access direct patient healthcare.

ROBUST REGULATORY FRAMEWORK TO ADDRESS THE SPECIFIC NEEDS OF POCT.

Self-Regulation – An interim Measure

Accredited laboratories – ISO 15189

Adopting of international laboratory standards

Sale of IVD directly to healthcare professionals

Quality assurance programmes

Qualified and registered technologists

Code of ethics

Marketing Code Authority

Bio-hazardous and liquid waste management

Phlebotomists for sample collection

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Self-Regulation – An interim Measure

Order request form issued by a doctor

Monitoring sample transportation

Pre validation of reagents

Accredited manufacturers by international accepted standards – ISO 13485

Results reviewed and issued by a Pathologist or Medical Technologist.

The integration of relevant and supporting legislation

GHTF harmonisation

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SAPHRA Wish List

Dedicated trained staff for dealing with IVD issues.

Cross mentorship and transfer of knowledge between SAPHRA and the IVD Industry.

Special IVD considerations in the regulations, guidelines and the principal act as amended.

Learn from the experience of others.

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THANK YOU

Presented by Robyn Howes SALDA Regulatory Committee