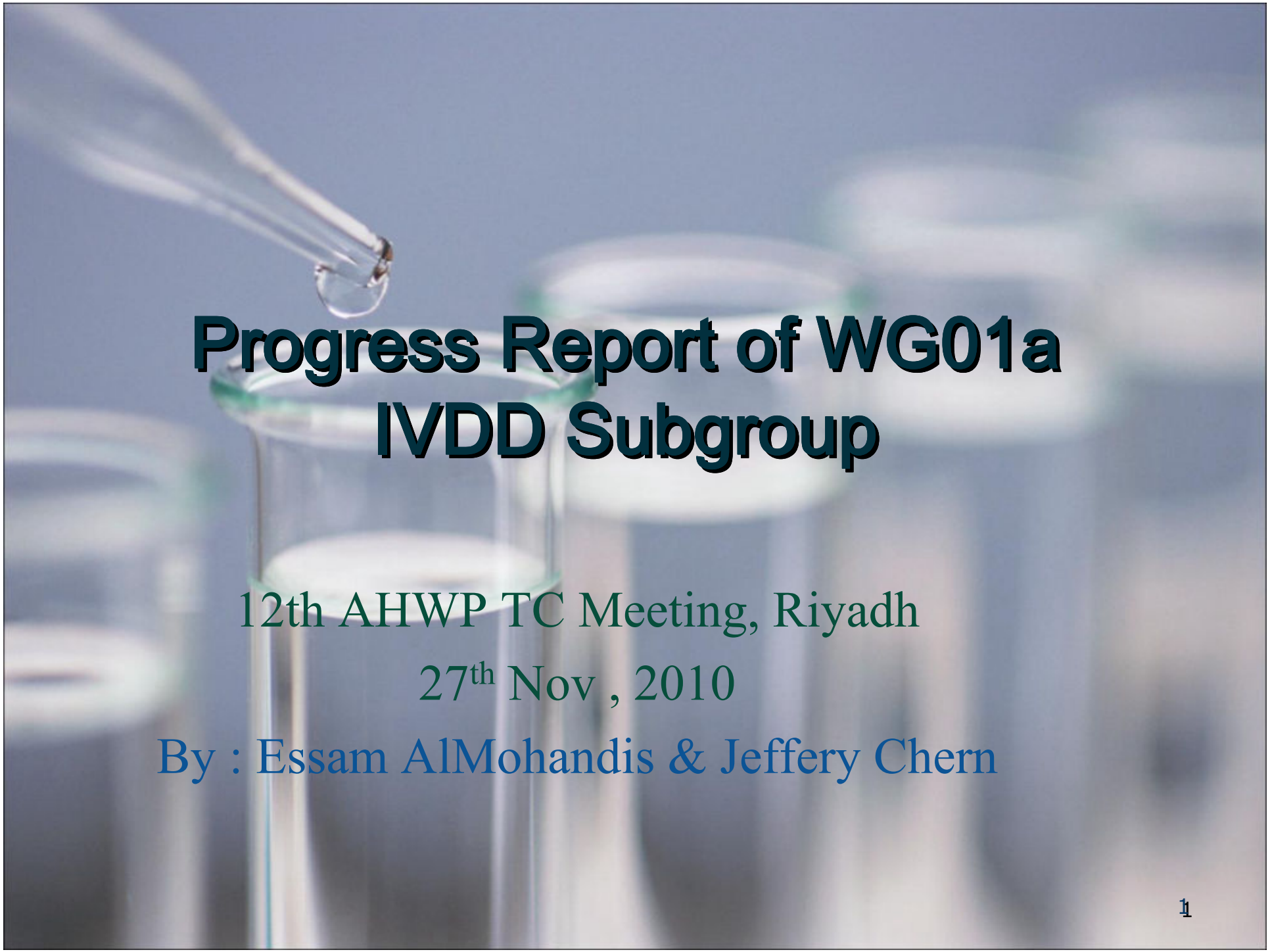


Progress Report of WG01a IVDD Subgroup

12th AHWP TC Meeting, Riyadh

27th Nov , 2010

By : Essam AlMohandis & Jeffery Chern

AHWP WG01a IVD Subgroup

Chair:	Eng. Essam Mohammed Al MOHANDIS Saudi Food & Drug Authority Kingdom of Saudi Arabia	Regulator
Co-Chair:	Mr. Jeffrey Jiin Feng CHERN Industrial Technology Research Institute Chinese Taipei	NON-Regulator
Member:	Mr. Lun AU YEUNG Medical Device Control Office, Department of Health Hong Kong SAR, China	Regulator
Member:	Dr. Phana CHHIENG Ministry of Health Cambodia	Regulator
Member:	Mrs. SAR Kuy HEANG Ministry of Health Cambodia	Regulator
Member:	Ms. Jeong Jin JO Korea Food & Drug Administration Korea	Regulator

AHWP WG01a IVD Subgroup

Member:	Ms Maria Cecilia MATIENZO Department of Health Philippines	Regulator
Member:	Ms Suhoung THITISATTHAYAKORN Medical Devices Control Division Food and Drug Administration Thailand	Regulator
Member:	Dr Rama Sethuraman Health Science Authority Singapore	Regulator
Member:	Mr Alan CHANG Director of President Office Taiwan Medical and Biotech Industry Association Chinese Taipei	Regulator
Member:	Ms Pauline LAW Siemens Healthcare Diagnostics Singapore	Non-Regulator
Member:	Mr Benjamin CHAN MediConcepts Ltd Hong Kong SAR, China	Non-Regulator

AHWP WG01a IVD Subgroup

Member:	Mr Alan CHANG Director of President Office Taiwan Medical and Biotech Industry Association Chinese Taipei	Non-Regulator
Member:	Mr Shekhar GANU Ortho-Clinical Diagnostics India	Non-Regulator
Member:	Mr Bryan SO Hong Kong Productivity Council Hong Kong SAR	Non-Regulator
Member:	Mr Ming-Che WANG Center for Drug Evaluation Chinese Taipei	Non-Regulator
Member:	Ms. Susan Chan Sanofi-Adventis Singapore	Non-Regulator

2010-2011 Work Plan

Work Item	Deadline
● Gap analysis of IVD medical devices regulations in member economies ● Feasibility study on adoption of the classification and conformity assessment of IVD medical devices proposed by GHTF	Mar 28, 2010 (Extended to Jul 31, 2010)
Liaise to GHTF in developing related documents on clinical evidence for IVD medical devices	Jul 31, 2010
Liaise to GHTF in developing related documents on the Essential Principles and labeling of IVD medical devices	Dec 31, 2010
Holding workshop on GHTF documents on IVD medical devices regulations	During 15th AHWP meeting Sunday 28th Nov 2010 by:Dr.Petra Wiele
Feasibility study on the adoption of the IVD STED, definition and concepts on clinical evidence of IVD medical devices proposed by GHTF	Sep, 2011

Ever since the foundation of this subgroup, we have been working closely with GHTF in the harmonization of IVD medical devices regulations

Achievements

- AHWP-WG01a has been cooperating with GHTF-SG01a to review or draft the following documents:
  - SG1-N45:2008 Principles of In Vitro Diagnostic (IVD) Medical Devices Classification
  - SG1-N46:2008 Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices
  - SG1(PD)/N063 “Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices”
  - “Clinical Evidence for IVD medical devices–Key Definitions and Concepts” (Draft)
  - ”Clinical Evidence for IVD medical devices–Clinical utility and performance evaluation” (Draft)

The documents were subject to the review of WG01a and comments were consolidated and reflected in GHTF SG1 IVD Subgroup working meetings.

Progress (1)

Work Item	Deadline	Status
●Gap analysis of classification and conformity assessment of IVD medical devices in member economies ●Feasibility study on adoption of the classification and conformity assessment of IVD medical devices proposed by GHTF	Mar 28, 2010 (Extended to Jul 31, 2010)	**Inputs from 5 member economies have been consolidated.**

Survey on IVD Medical Devices Regulations

Country / GHTF	China	Chinese Taipei	Hong Kong	India	KSA	Singapore
Definition	Yes	Yes	Yes	Yes*	Yes	Yes
Classification	Yes	Yes	Yes	Yes*	Yes	Yes
QMS	ISO13485: 2003	ISO13485: 2003	ISO13485: 2003	ISO13485: 2003*	ISO13485: 2003	ISO13485: 2003
Risk Management	Yes	Yes	Yes	Yes*	Yes	Yes
Performance Evaluation	Yes	Yes	Yes	Yes*	Yes	Yes
Use of Standards	Yes	Yes	Yes	Yes*	Yes	Yes
STED/CSDT	N/A	N/A	N/A	N/A	N/A	CSDT
Clinical Evidence	Yes	Yes	Yes	Yes*	Yes	Yes
PMS and vigilance	Yes	Yes	Yes	Yes*	Yes	Yes

* Prepare to adopt related practices

Our finding : Survey on IVD Medical Devices Regulations

- Definition and classification have been established
- Standard for QMS is ISO13485:2003
- Risk management has been adopted in TPLC
- Performance evaluation is required-but how to use appropriate standards needs more guidance (in terms of conducting safety and performance evaluation, e.g., analytical performance, clinical utility, clinical performance)
- Harmonized premarket submission has been adopted

*TPLC: Total Product Life Cycle

Progress (2)

Work Item	Deadline	Status
Liaise to GHTF in developing the following documents: ●"Clinical Evidence for IVD medical devices–Key Definitions and Concepts" (Draft) ●"Clinical Evidence for IVD medical devices–Clinical utility and performance evaluation" (Draft)	Jul 31, 2010 (Postponed to Nov 30, 2010)	**Underway** : collecting comments & will be discuss during 6-10 Dec 2010 Ca-meeting.

Both draft guidance are available upon request. (For internal circulation only.)

Analytical Performance

- Analytical studies for trueness usually are based on one or more of the following:
  (a) methods described in a **recognized standard**
  (b) comparison with an **international reference method**
  (c) comparison with a **reference material** of a higher order
- Where the aforementioned methods are not readily available, a comparison with an already available IVD medical device (**method comparison**) or a recognized method, may be used.
- In most circumstances analytical performance testing using **human specimens** is needed. If specimens are of limited availability or do not cover the desired range of the assay or presence of the analyte (measurand), the use of **contrived samples** would be acceptable.
- Analytical performance is always expected for **all IVD medical devices**. However for **novel assays** it may not be possible to demonstrate **trueness**.
- For a well established and standardized analyte (measurand) information about analytical performance is sufficient to allow a test to be placed on the market as an IVD medical device.

Reference: CLSI EP9-A Method comparison and bias estimation using patient samples;
CLSI EP14-A2 Evaluation of matrix effects

Clinical Performance

- **Diagnostic specificity**: the effectiveness of an examination in correctly classifying patients that do not have a particular disease or condition

- **Diagnostic sensitivity**: the efficiency of the examination in correctly identifying patients who have a particular disease or condition

Both characteristics depend on the choice of a cutoff value for the examination.

Reference: ISO18113-1:2009

Clinical Performance

- **Positive predictive value**: the effectiveness of an examination in separating true positive results from false positive results for a given attribute in a given population

- **Negative predictive value**: the effectiveness of an examination in separating true negative results from false negative results for a given attribute in a given population

Predictive values generally depend on the prevalence of the disease or condition in the population of interest.

Reference: ISO18113-1:2009

Clinical Performance

- Clinical performance should only be performed once the **analytical performance of the device has been established and determined to be acceptable**. Clinical performance represents the true clinical assessment, where the test performance is evaluated in the target population.
- Ideally, the diagnostic sensitivity and specificity will be validated through studies conducted at **multiple sites in different health care and geographical settings**. The aim is to substantiate performance claims.
- Clinical performance *may be* required for '**established and non standardized tests**' while clinical performance *should always be* required for '**novel tests**'.
- For high risk IVD medical devices, **design changes** that may affect the performance claims of the IVD medical device may also require clinical performance studies.

Clinical Performance

- Manufacturers are able to draw on *any one or combination of the following data* sources to demonstrate clinical performance:

  - ✓ **Literature**
  - ✓ **Clinical Performance Studies**
  - ✓ **Experience gained by routine diagnostic testing**

Progress (3)

Work Item	Deadline	Status
Liaise to GHTF in developing documents on the following topics : ●Essential principles for demonstrating the safety and performance of IVD medical devices ●Labeling (including graphical symbols) of IVD medical devices	Dec 31, 2010	**Underway:** ▫ Conducting exercises on the EP for IVD medical devices ▫collected comments will be discussed during CA-meeting

Essential Principles (EP)

- GHTF/SG1/N41R9:2005 Essential Principles of Safety and Performance of Medical Devices
- Six general requirements of safety and performance that apply to all medical devices (including IVD medical devices).
- A comprehensive list of design and manufacturing requirements of safety and performance, some of which are relevant to each medical device.
- *GHTF is revising GHTF/SG1/N41R9:2009, focusing on the EP for demonstrating the safety and performance of IVD medical devices*

Essential Principles (EP)

EP	Clauses in SG1/N41R9:2005	Applicability to IVD
General Requirements	5.1~5.6 Intended use, safety, effectiveness, risk management, performance, risk-benefit balance	Applicable：Product information and risk management
Design and Manufacturing Requirements	5.7 Chemical, physical and biological properties	Applicable：Reagents containing microbial agents, carcinogens, toxic substances, tissues/cells derived from human or animal sources, etc.
	5.8 Infection and microbial contamination	Applicable： ▫ Substances or microbial agents identification / concentration per unit ▫ Sterility of vacutainers ▫ Clinical lab practices
	5.9 Medical devices incorporating a substance considered to be a medicinal product/drug	Not applicable

Essential Principles (EP)

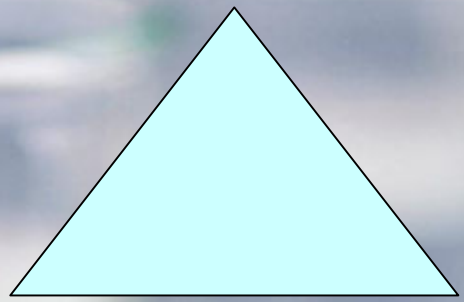
EP	Clauses in SG1/N41R9:2005	Applicability to IVD
Design and Manufacturing Requirements	5.10 Medical devices incorporating materials of biological origin	Applicable：Product containing tissues/cells derived from human or animal sources, etc.
	5.11 Manufacturing and environmental properties	Applicable： ▫Compatibility between reagent and instruments, orientation, connections, etc. ▫Handling, processing and disposal of hazardous materials ▫Clinical laboratory practices
	5.12 Devices with a diagnostic or measuring function	Applicable： ▫**Analytical and clinical performance characteristics** ▫Use scenario (professional, OTC, etc.)

Essential Principles (EP)

EP	Clauses in SG1/N41R9:2005	Applicability to IVD
Design and Manufacturing Requirements	5.13 Protection against radiation	Applicable：Proper handling, processing, labeling of RIA kits
	5.14 Requirements for medical devices connected to or equipped with an energy source and medical software	Applicable： ▫Instruments containing software or stand-alone software ▫Validation according to analytical and clinical performance characteristics of specific assays
	5.15 Protection against mechanical risks	Applicable：Instruments
	5.16 Protection against the risks posed to the patient by supplied energy or substances	Applicable：Self-testing devices which indicate parameters by means of visual system
	5.17 Protection against the risks posed to the patient for devices for self-testing or self-administration	Applicable：**Proper labeling including instruction for use and use of symbols**
	5.18 Information supplied by the manufacturer	Applicable：**Proper labeling including instruction for use and use of symbols**
	5.19 Performance evaluation including, where appropriate, clinical evaluation	Applicable： ▫**Analytical and clinical performance characteristics** ▫Use scenario (professional, OTC, etc.)

Progress (4)

Work Item	Deadline	Status
Holding workshop on IVD medical devices regulations	(28th Nov 2010)	**Dr. Petra Carls Wiele will be the speaker**
Feasibility study on the adoption of the IVD STED, definition and concepts on clinical evidence of IVD medical devices proposed by GHTF	Sep, 2011	



Thank you for your attention!


Attachments

IVD Medical Devices Regulatory Elements and Related GHTF Guidances

Regulatory Element	Status	Posted on
Definition and Classification	SG1/N045:2008	June 23, 2008
Conformity Assessment	SG1/N046:2008	Aug 26, 2008
Declaration of conformity and Technical Documentation	SG1(PD)/N063	Mar 26, 2009 (Open for Public Comments by Jan 7, 2010)
Clinical Evaluation and Investigation	"Clinical Evidence for IVD medical devices–Key definitions and concepts" (Working Draft)	N/A
	"Clinical Evidence for IVD medical devices–Clinical utility and performance evaluation" (Working Draft)	N/A

Definition

IVD medical device: a device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

Note: In some jurisdictions, some IVD medical devices may be covered by separate regulations.

Reference: SG1/N045:2008 Principles of In Vitro Diagnostic (IVD) Medical Devices Classification

Classification

Risk-based Classification and 7 classification rules

CLASS	RISK LEVEL	DEVICE EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser , prepared selective culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

Reference: SG1/N045:2008 Principles of In Vitro Diagnostic (IVD) Medical Devices Classification

Principles of IVD Classification

- Intended use and indications for use as specified by the manufacturer
- Technical/scientific/medical expertise of the intended user
- The importance of the information to the diagnosis, taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician
- Impact of the result (true or false) to the individual and/or to public health

Reference: SG1/N045:2008 Principles of In Vitro Diagnostic (IVD) Medical Devices Classification

Classification Rule 1

- IVD medical devices intended for the following purposes are classified as Class D:
  - Devices intended to be used to detect *the presence of, or exposure to, a transmissible agent in blood*, blood components, *blood derivatives, cells, tissues or organs* in order to assess their *suitability for transfusion or transplantation*, or
  - Devices intended to be used to detect *the presence of, or exposure to, a transmissible agent that causes a life-threatening often incurable disease* with a high risk of propagation

Classification Rule 2

- IVD medical devices *intended to be used for blood grouping , or tissue typing* to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation, are classified as *Class C*, except for *ABO system (A (ABO1), B (ABO2), AB (ABO3), rhesus system (RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e) , Kell system (Kel1 (K), Kidd system (JK1 (Jka), JK2 (Jkb) and Duffy sytem (FY1 (Fya), FY2 (Fyb) determination* which are classified as *Class D*.

Classification Rule 3

- IVD medical devices are classified as Class C if they are intended for use:
  - in detecting the presence of, or exposure to, a *sexually transmitted agent*.
  - in detecting the presence in cerebrospinal fluid or blood of an *infectious agent* with a risk of limited propagation.
  - in detecting the presence of an *infectious agent* where there is a significant risk that an erroneous result would cause death or severe disability to the individual or fetus being tested.
  - in screening pre-natal women in order to determine their immune status towards *transmissible agents*.
  - in determining infective disease status or immune status, and where there is a risk that an erroneous result will lead to a *patient management decision* resulting in an imminent life-threatening situation for the patient.

Classification Rule 3 (Contd.)

- IVD medical devices are classified as Class C if they are intended for use:
  - in screening for selection of patients for *selective therapy and management*, or for *disease staging*, or in the diagnosis of cancer, (NOTE: those IVD medical devices where the therapy decision would usually be made only after further investigation and those used for monitoring would fall into class B under rule 6.)
  - in *genetic testing*
  - to *monitor levels of medicines, substances or biological components*, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient.
  - In the *management of patients* suffering from a life-threatening infectious disease.
  - In *screening for congenital disorders* in the fetus.

Classification Rule 4

- IVD medical devices intended for *self-testing* are classified as *Class C*, except those devices from which the result is not determining a medically critical status, or is preliminary and requires follow-up with the appropriate laboratory test in which case they are Class B.
- IVD medical devices intended for blood gases and blood glucose determinations for near-patient testing would be Class C. Other IVD medical devices that are intended for near-patient should be classified in their own right using the classification rules.

Classification Rule 5

- The following IVD medical devices are classified as Class A:
  - *Reagents or other articles which possess specific characteristics*, intended by the manufacturer to make them suitable for in vitro diagnostic procedures related to a specific examination.
  - *Instruments* intended by the manufacturer specifically to be used for in vitro diagnostic procedures
  - *Specimen receptacles*

Classification Rule 6 and 7

- Rule 6: IVD medical devices *not covered in Rules 1 through 5* are classified as *Class B*.
- Rule 7: IVD medical devices intended to be used as *controls without a quantitative or qualitative assigned value* will be classified as a *Class B.*

Conformity Assessment

Elements of Conformity Assessment	Proposed Practice
Quality Management System	A QMS based on risk management
Post-Market Surveillance System	Integrated as part of the QMS
Declaration of Conformity	***Utilizing the Essential Principles and Recognized Standards***
Registration of Manufacturers and Their Devices	Different practice in each country
Technical Documentation	***IVD STED***

Reference: SG1/N046：2008 Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices

Use of EP and recognized standards in the safety and performance evaluation of medical devices

STEP 1: Device classification	Determine the class of the device based on risks
STEP 2: Conformity assessment	Determine the premarket and the post-market requirements of the device according to its class
STEP 3: Safety and performance evaluation	Determine which essential principles (EP) should be used Locate appropriate recognized standards and/or other standards
STEP 4: Technical Documentation	Prepare technical documentation based on the result of safety and performance evaluation

Essential Principles and Recognized Standards

EP	Clauses in SG1/N41R9:2005	Recognized Standards
General Requirements	5.1~5.6 Intended use, safety, effectiveness, risk management, performance, risk-benefit balance	ISO 14971:2007; other applicable standards
Design and Manufacturing Requirements	5.7 Chemical, physical and biological properties	ISO 10993 series; EN ISO 15193:2009; EN ISO 15194:2009; other applicable standards
	5.8 Infection and microbial contamination	EN 13641:2002; other applicable standards
	5.9 Medical devices incorporating a substance considered to be a medicinal product/drug	Not applicable
	5.10 Medical devices incorporating materials of biological origin	Applicable standards
	5.11 Manufacturing and environmental properties	IEC 60601-1-6:2006; EN 62366:2008; other applicable standards
	5.12 Devices with a diagnostic or measuring function	***CLSI standards on performance characteristics; EN13612:2002; other product specific standards**

Essential Principles and Recognized Standards

EP	Clauses in SG1/N41R9:2005	Recognized Standards
Design and Manufacturing Requirements	5.13 Protection against radiation	IEC 60601-1:2005; IEC 61010-2-101:2002
	5.14 Requirements for medical devices connected to or equipped with an energy source and medical software	IEC 62304:2006; *CLSI standards on performance characteristics; EN 13612:2002; other product specific standards
	5.15 Protection against mechanical risks	IEC 60601-1:2005; IEC 61010-2-101:2002
	5.16 Protection against the risks posed to the patient by supplied energy or substances	IEC 60601-1-6:2006; EN 62366:2008; other applicable standards
	5.17 Protection against the risks posed to the patient for devices for self-testing or self-administration	EN ISO18113-4:2009; EN ISO 18113-5:2009; EN 13532:2002
	5.18 Information supplied by the manufacturer	**EN ISO18113-1~3:2009; EN 980:2008**
	5.19 Performance evaluation including, where appropriate, clinical evaluation	***CLSI standards on performance characteristics; EN 13612:2002; EN 13640:2002; other product specific standards**

Analytical Performance Characteristics and Recognized Standards

Performance Characteristics	Recognized Standards
Accuracy (trueness and precision)	CLSI EP5-A, CLSI EP12-A, CLSI EP15-A
Analytical sensitivity	CLSI EP12-A
Analytical specificity	CLSI EP7-A2
Linearity and measuring range	CLSI EP-6A
Limit of detection, limit of quantification of the method	CLSI EP-17A
Assay cut-off	CLSI GP10-A
Laboratory error, total analytical error	CLSI EP18-A, CLSI EP21-A
Stability	EN13640:2002
Interference	CLSI EP7-A2

CLSI –Clinical & laboratory standards Institute

Performance Evaluation for Blood Glucose Meter

Performance Characteristic	New Device	Predicate	Standard used	SE/NSE
Accuracy	95% of the readings in < 75mg/dL, ±15mg/dL or > 75mg/dL, ±15%	95% of the readings in < 75mg/dL, ±15mg/dL or > 75mg/dL, ±15%	CLSI EP9-A2	SE
Range of measurement	10~600mg/dL	10~600mg/dL	CLSI EP6-P	SE
Precision	CV<5%	CV<5%	CLSI EP5-A	SE
Analytical Sensitivity	0.5mg/dL	1mg/dL	CLSI EP6-P	SE
Etc....				

Preparation of Technical Documentation

GHTF SG1-N11:2008

Summary Technical Documentation

For Demonstrating Conformity to Essential Principles of Safety and Performance of Medical Devices (STED)

Posted on May 29, 2008

PROPOSED DOCUMENT

Global Harmonization Task Force

Title: Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices

Authoring Group: Study Group 1 of the Global Harmonization Task Force

Date: March 26, 2009

Contents of the IVD STED

Table of Contents

Contents of the IVD STED

PART 2 - CONTENTS OF THE STED

Contents of the IVD STED

The Function of the IVD STED

- STED is prepared from the technical documentation of the manufacturer, which is quite similar to an index of the subsystems of the QMS.

- It is a “snapshot” of the product prior to the premarket submission.

Premarket Use of the IVD STED

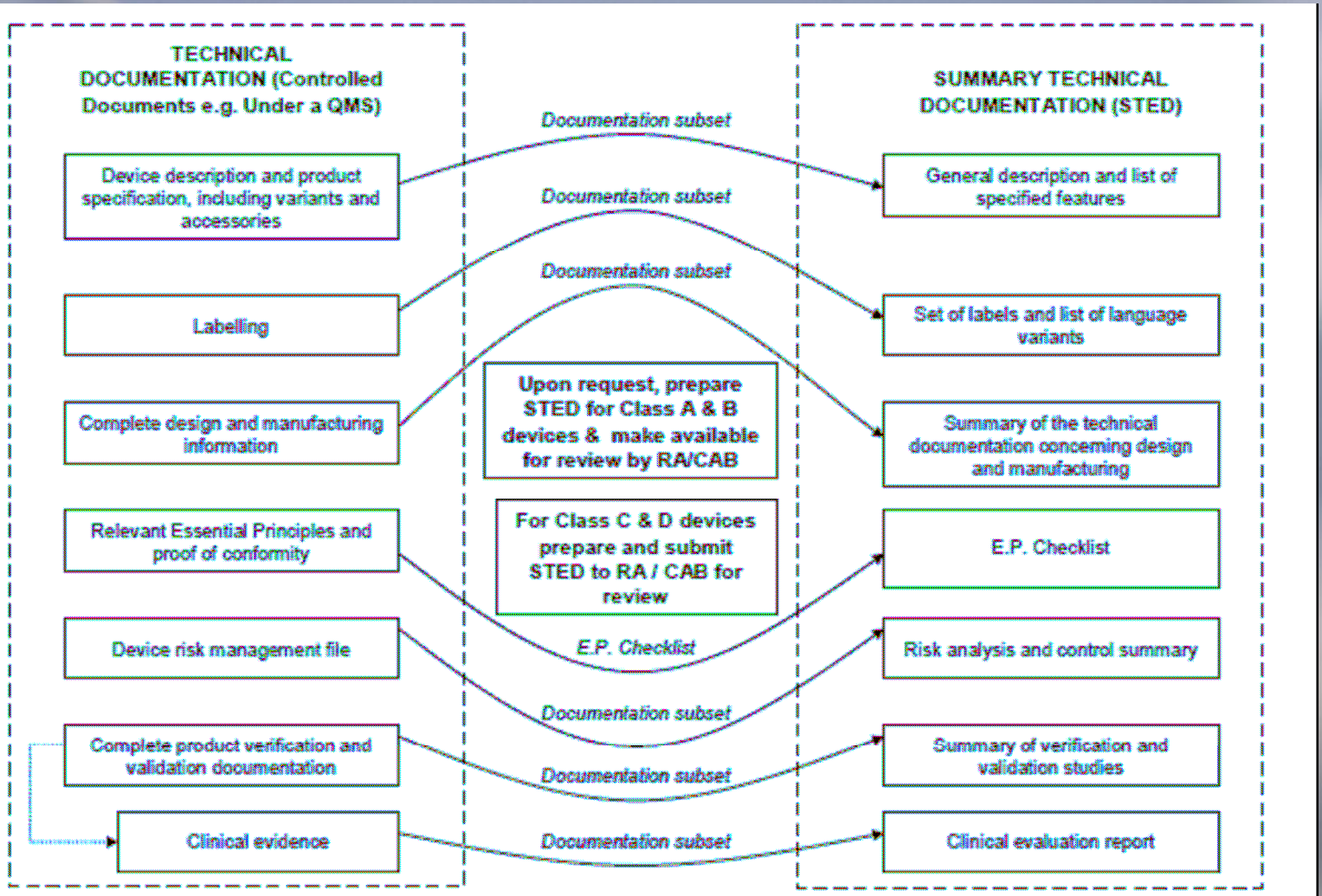


FIGURE 1: PREMARKET USE OF THE STED

Reference: GHTF SG1(PD)/N063

Post-market Use of the IVD STED

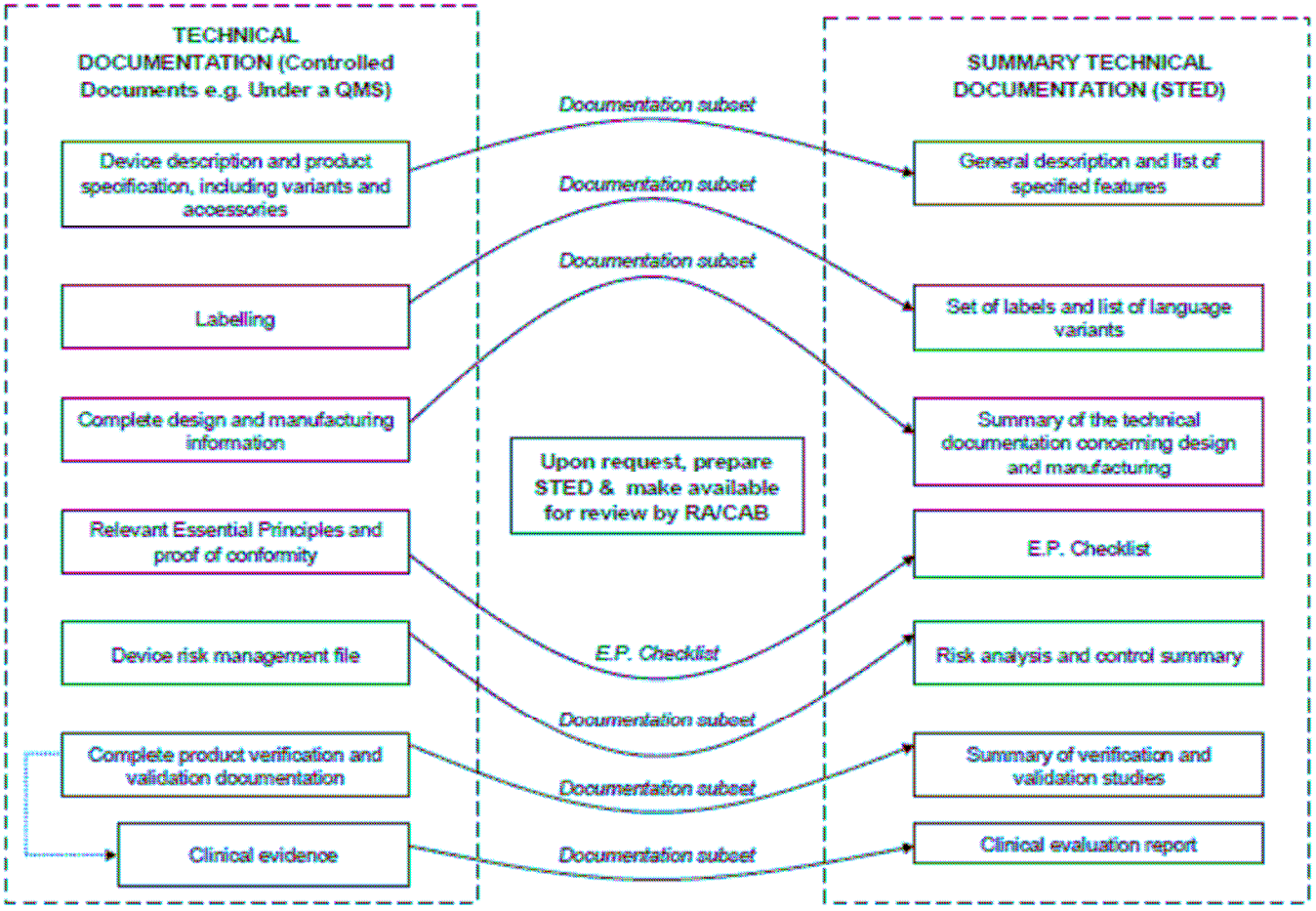


FIGURE 2: POST-MARKET USE OF THE STED

Reference: GHTF SG1(PD)/N063

Acceptance Criteria of Summary Documentation

- If a **recognized standard** ***including*** **specific acceptance criteria** is used, declaration of conformity could be accepted.
- If a **recognized standard** ***without*** **specific acceptance criteria** is used, justification of using that standard as well as arranged and analyzed data should be submitted.
- If a **professional guideline/standard** or **in-house standard** is used, the rationale of using the standard, method of the experiment, arranged and analyzed data as well as conclusion of the experiment should be submitted.

Contents of Detailed Documentation

- Study design
- Methods, procedure, including acceptance criteria
- Study report including arranged and analyzed data (where appropriate, the report should include raw data/ line listing, e.g. in the case of a Class D product)
- Conclusion of the study
- All claims mentioned in the submission should be verified and validated (e.g. intended use and performance characteristics).

Related Issues

- The **depth and details** of the documentation depend on the **classification** of the device.
- Manufacturers may be asked by the RA's to submit related information on performance characteristics of the device.
- Under an **effective QMS**, at the stage of design control, the manufacturer should have completed product **verification and validation**.
- Related documents and records could be accessed from a regulatory audit.

Related Issues

- **Verification and validation** of IVD medical devices consist of four parts :
  - Analytical Performance Data
  - Clinical Performance Data
  - Traceability of Calibrators and Control Materials
  - Stability

  Note: If a device contains **software**, information on software verification and validation is required.
- Information on the **uncertainty of measurement** is not required so far.

- Requirements on product verification and validation of IVD medical devices based on different intended uses have not been thoroughly discussed (e.g. qualitative analysis, quantitative analysis, semi-quantitative analysis, OTC, POC, ect.)

Demonstration of Conformity to the EP

Essential Principal	Applicable to the device?	**Method of Conformity**	Identity of Specific Documents
General Requirements			
5.1 Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.			
5.2 The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed: ▪ identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse, ▪ eliminate risks as far as reasonably practicable through inherently safe design and manufacture, ▪ reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms, ▪ inform users of any residual risks.			