Dossier Assessment

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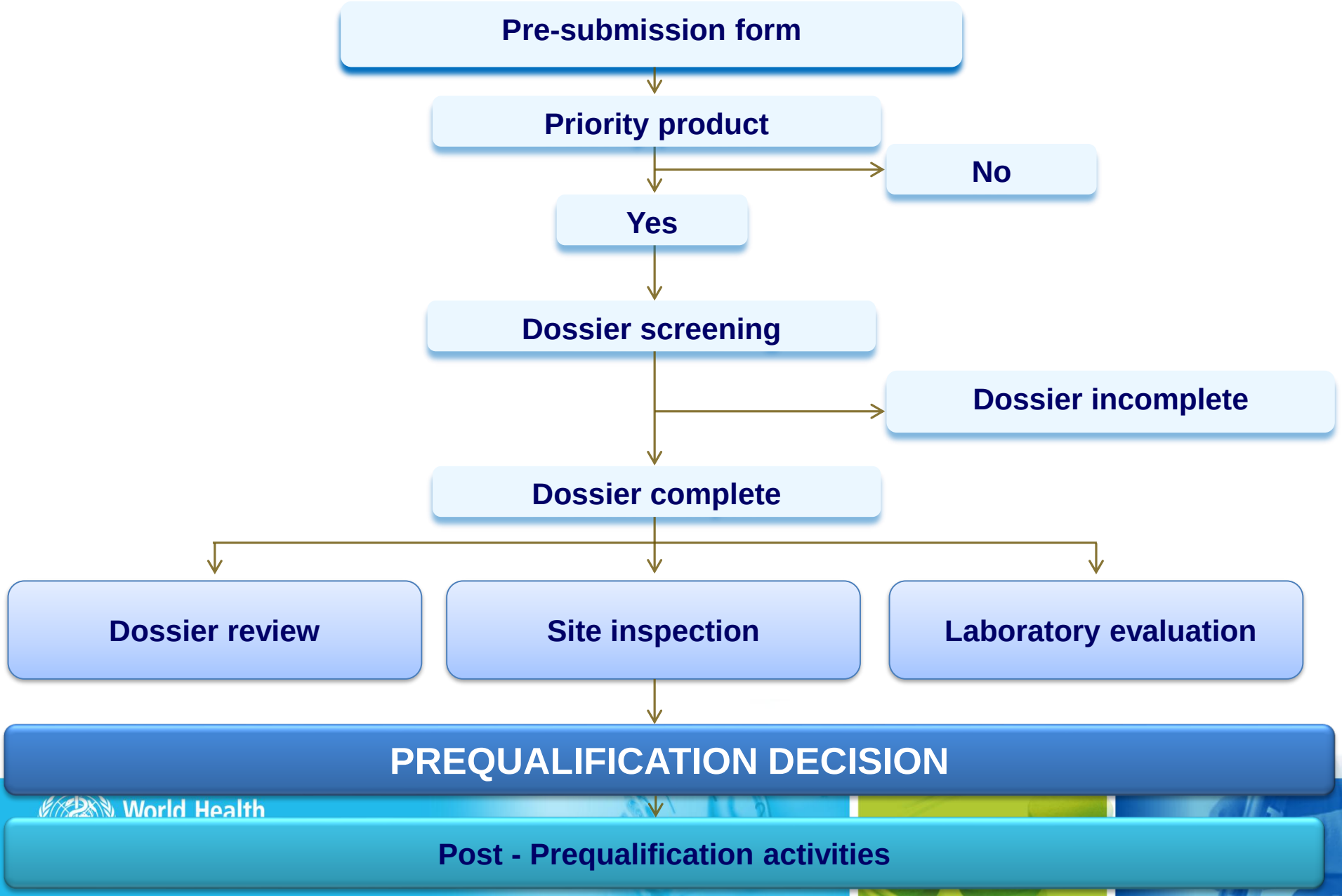
WHO PQ Team – Diagnostics Assessment

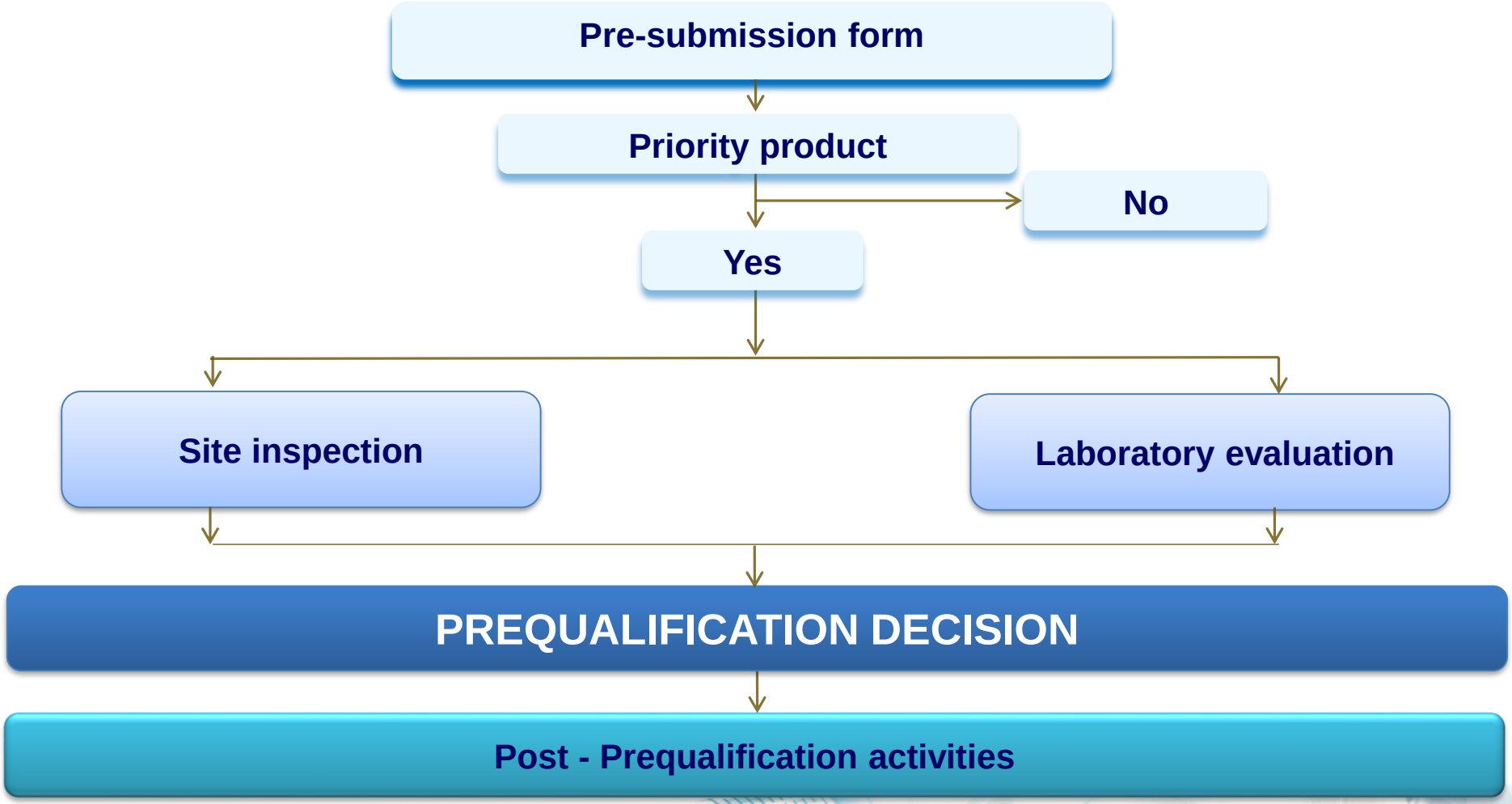
Dossier Assessors and Inspectors Meeting
Geneva Switzerland
19 – 21 March 2016

World Health Organization

PREQUALIFICATION PROCEDURE



ABBREVIATED PROCEDURE



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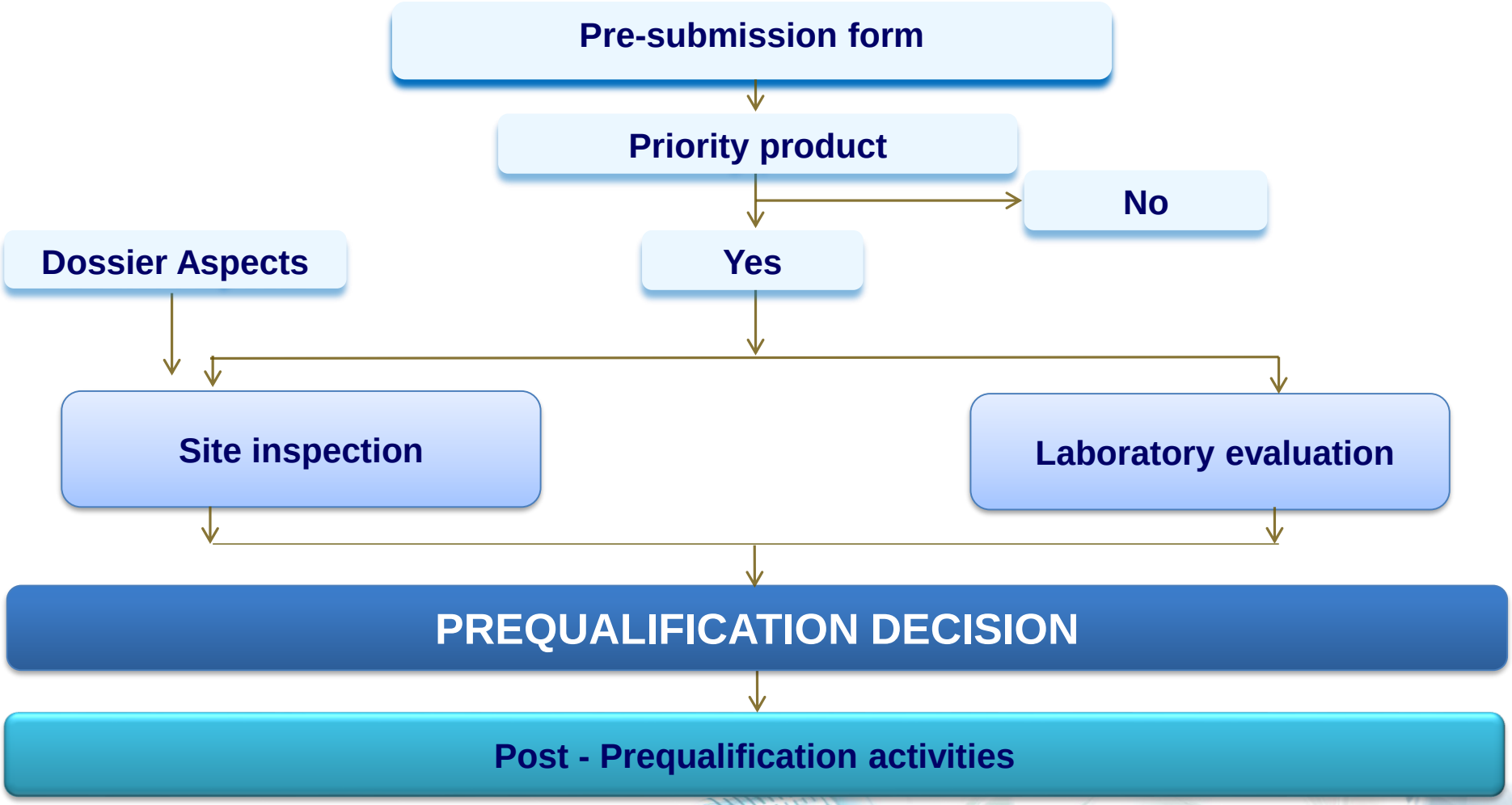

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Purpose of the dossier

- The dossier contains a subset of the technical documentation held by the manufacturer
  - to demonstrate that the IVD to which it applies conforms to the “Essential Principles of Safety and Performance of Medical Devices” as defined by GHTF
- The dossier reflects the status of the IVD at a particular moment in time

Purpose of the dossier

- It should also provide sufficient information to inform the PQ Inspection team regarding:
  - Sites responsible for design and manufacture to enable planning of inspection/s
  - Information regarding the maturity of the manufacturer's QMS
- It should provide sufficient information to determine the **regulatory version** submitted to PQ and to ensure the data in the dossier is relevant to this version
- It should demonstrate that the Mx has considered the safety and performance in WHO Member States.

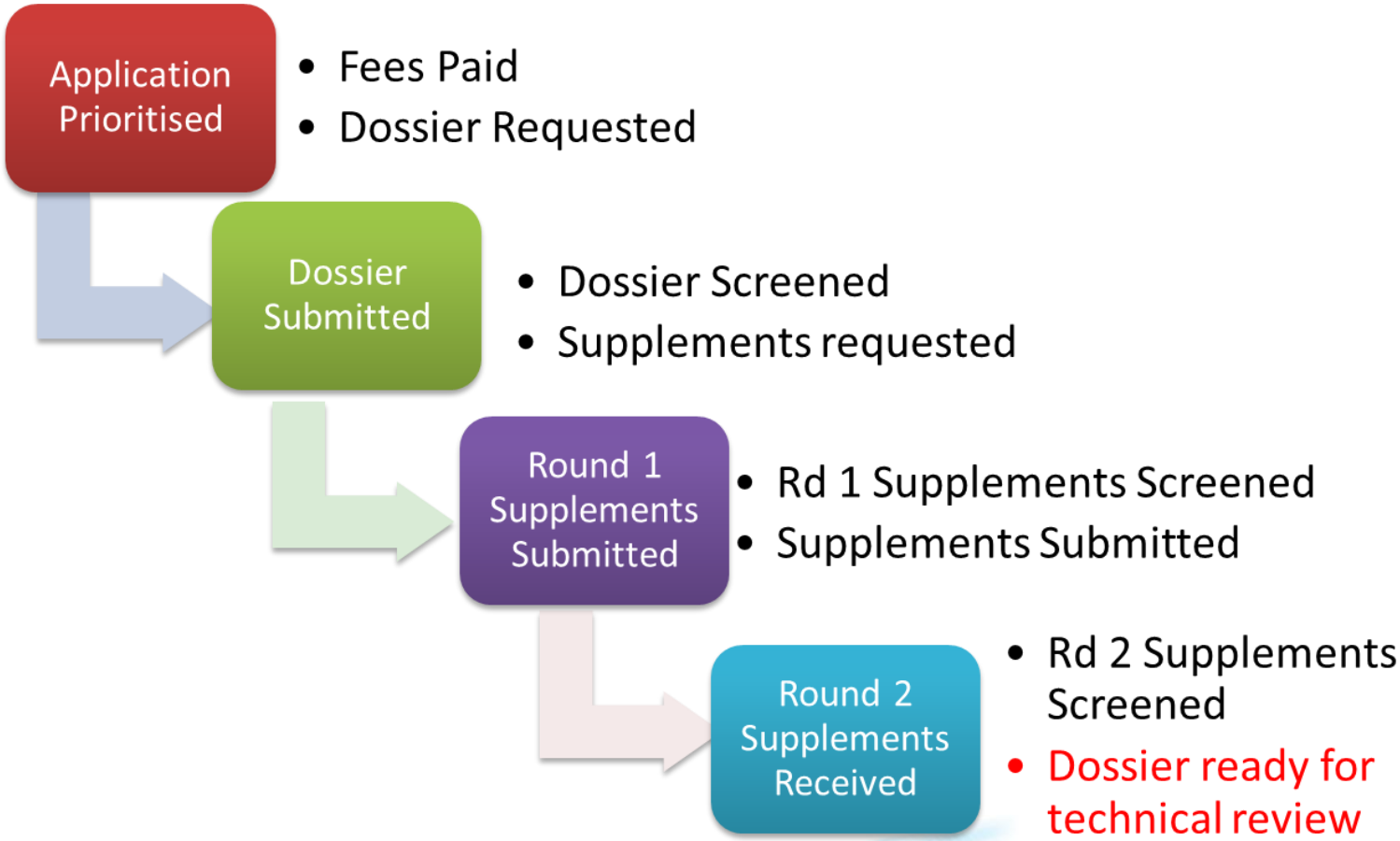
How and when to submit a dossier

- Required, on request by WHO, for applications undergoing full assessment
- Must be submitted according to WHO PQDx_018 “Instructions for Compilation of a Product Dossier”
- The first page should be the original signed Letter of Agreement
- The “Product Dossier Checklist” WHO PQDx_049 must be completed and used as a Table of Contents for the dossier documentation
  - Sample Product Dossiers available on website – example of type of documentation to be submitted in a Product Dossier

Dossier Requirements

- Based on best international practice (ISO, EN, GHTF, IMDRF, CLSI…)
- Follows the content of the IMDRF MA IVD ToC (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140630-rps-ivd-toc.pdf)
- Dossier must demonstrate that the IVD conforms to the Essential Principles of Safety and Performance of Medical Devices (GHTF/SG1/N41R9:2005)
- Looks into critical aspects for WHO Member States often not dealt with from a local perspective by SRAs
  - stability, risk assessment, instructions for use, etc.

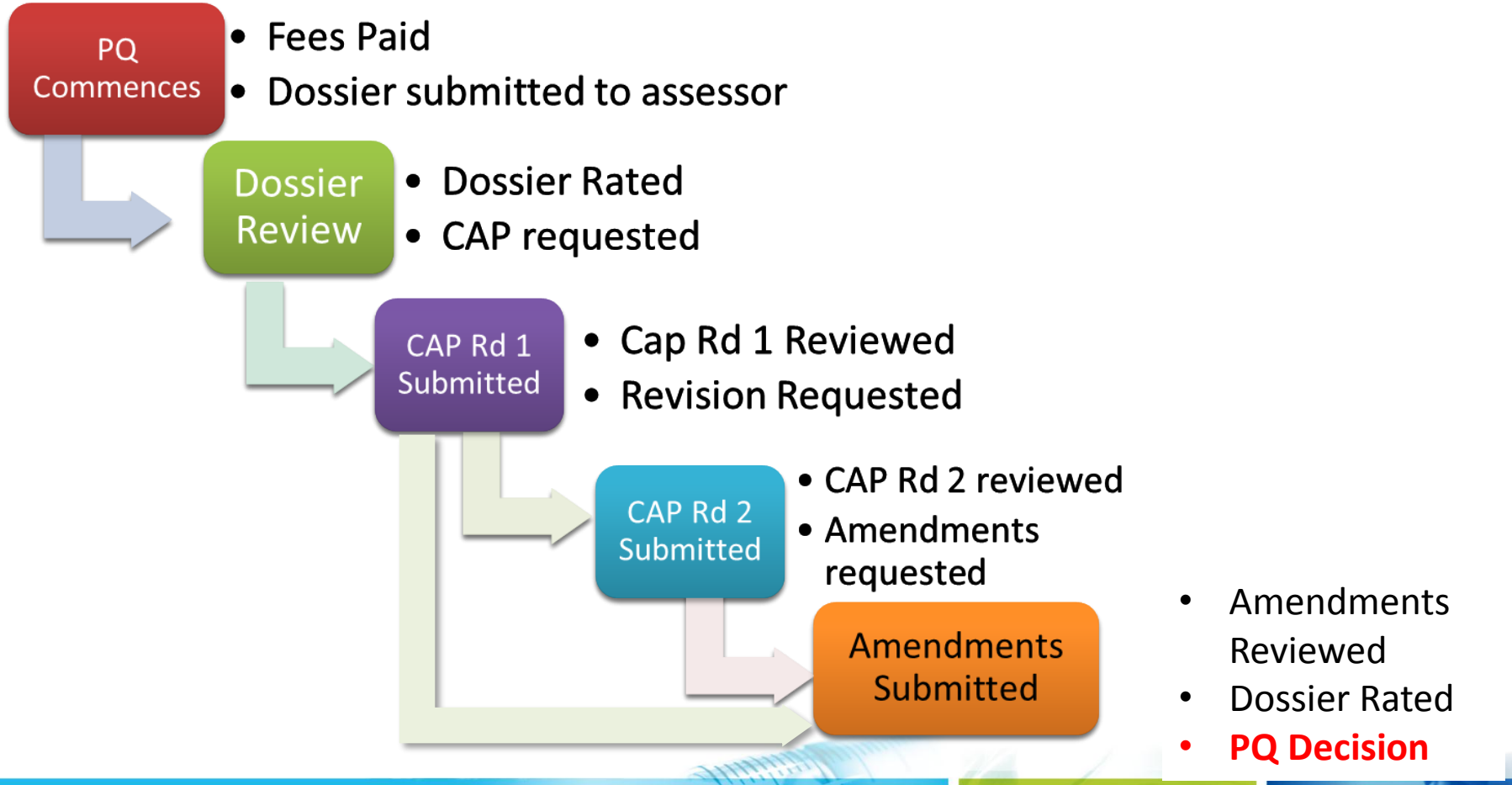
Dossier Screening



Dossier Screening – Recurrent Problems

- Layout and format
- No clear identification of the product being submitted to PQ in the dossier documentation and reports
- Photos of the kits components are unclear/missing
- Some sections are not documented (e.g. design changes)
- Full study reports not submitted or too summarised
- Information on training and support network not available for countries where the assay is supplied
- Certificates requested are not certified
- No inspection reports submitted

Dossier Assessment



Prequalification Team - Diagnostics

World Health Organization

INSTRUCTIONS FOR COMPILATION OF A PRODUCT DOSSIER

Prequalification of In Vitro Diagnostics Programme

PQDx_018 v3 27 August 2014

IMDRF/RPS WG/N13FINAL:2014

IMDRF International Medical Device Regulators Forum

Final Document

Title: In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)

Authoring Group: Regulated Product Submissions Table of Contents Working Group

Date: 30 June 2014

Jeffrey Shuren, IMDRF Chair

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2015 PQ Dossier related statistics

PQ	2015
Number of applications	22
Number of dossiers received	16
Number of dossiers reviewed	15
Number of new manufacturers	3
Number of reviewers	15

Dossier challenges

- Dossier submissions quality is increasing
- Mx with minimal experience in submitting to mature regulatory bodies in general still struggle to understand basic requirements
- A number of RDT manufacturers who failed in previous attempts are responding with greatly improved new submissions.
- The lack of both general and product specific guidance remains a major issue.

Dossier challenges: major issues with screening

- Providing all required/requested information
  - Especially “confidential” information
- Incomplete study reports
- Certified copies
- Poorly compiled dossiers
- Regulatory versions*
- Stability*
- Risk Management

Regulatory Versions

You may not be getting identical twins!

- Relates to the information associated with a submission for approval by a regulatory authority.
- The submitted version is defined by all of the documentation related to development, manufacture, and intended use, labelling and post market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission.
- Any difference is considered to be a different regulatory version.
- Need to be sure how the data in the dossier relates to the product undergoing review.
- The FDA approved product may be different to the Rest of World (ROW) model!

Data Integrity

Maintaining and assuring the accuracy and consistency of data over its entire life-cycle

Data Quality

Analysing the relevance of the data in the dossier

Data integrity and quality

Data may be generated by

- Paper based record of an observation (manual)
- Equipment or computerised

Risk to data integrity depends on

- the system used, and
- the possibility it can be potentially manipulated

Data integrity requirements apply equally to manual (paper) and electronic data

There must be appropriate data integrity controls

Data integrity principles are reflected in…

Aspects that will ensure traceability

- Comprehensive protocols
- Evidence of control eg
- User access rights and other evidence of data governance
    - Controlled blank paper templates for results recording
    - Control of intended and unintended changes
    - Evidence of verification that documentation a true record eg senior management sign off
- Other evidence of good recording practice…

Good recording practice

Data for a study must be

- Attributable to the person generating the data
- Legible and permanent
- Contemporaneous
- Original record
- Accurate

[redacted] INVESTIGATIONAL PERFORMANCE TESTING

DCN 20272	QI Form 101-2	Rev.: B	Pg. 1 of 2

Device Description:	[redacted] Membrane Units	Lot Number:	B3G181
Part Number:	NA	Exp. Date:	2014-06-11

Device Components			
Description	Part Number	Lot Number	Exp. Date
Sample Diluent	80-1048	B3H168-1	2015-03-01
Colour Developer	80-1017	B3K113-1	2014-10-07
Clarifying Solution	80-1050	B3J129-1	2015-03-13
[redacted]ultiplex Membrane Units	NA	B3J181	2014-06-11

Contrived Sample #	[redacted] Whole Blood ID	[redacted] Sample ID	Expected Result [redacted]	Expected Result [redacted]	Result [redacted]	Result [redacted]	Comments
133.	B6266	HA16	-	+	−	+	
134.	B6266	HA18	-	+	−	+	
135.	B6267	HA19	-	+	−	+	
136.	B6267	HA20	-	+	−	+	2013-11-07
137.	B6267	HA26	-	+	−	+	
138.	B6267	HA27	-	+	−	+	N/A
139.	B6267	HA29	-	+	−	+	
140.	B6267	HA30	-	+	−	+	
141.	B6267	HA38	-	+	−	+	
142.	B6268	HA39	-	+	−	+	
143.	B6268	HB03	-	+	−	+	
144.	B6268	HB06	-	+	−	+	
145.	B6268	HB10	-	+	−	+	
146.	B6268	HB11	-	+	−	+	
147.	B6268	HB17	-	+	−	+	
148.	B6268	HA12	-	+	−	+	
149.	B6270	HA24	-	+	−	+	

RESULT: (+) reactive (-) non-reactive (ind) indeterminate (inv) invalid (nt) not tested

Performed by (initial & date):	AB 2013-11-07		
Results verified by (initial & date):	CR 2013-11-07	Document checked by (initial & date):	AB 2013-11-07

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ANNEX 21 Stability Study
File No. WHO-HIV-21-01-1411
Ver. 02

[redacted] HIV 1+2 [redacted]

1. Objective

The objective is to determine the stability of the [redacted] HIV 1+2 [redacted] through real time stability study, shipping study, usage stability study, and heat accelerated stability study.

2. Materials

2.1 20 HIV positive samples: P1-P18 (HIV-1 Reactive), P19 and P20 (HIV-2 Reactive) from NICPBP
2.2 20 HIV negative samples: N1-N20 from NICPBP
2.3 [redacted] HCV Test Cassette: Lot: 20100920, Lot: 20100921, and Lot: 20100922.
[redacted]
2.4 IFU for HIV (Ver.1.0)

3. Test Arrangement

Tester: [redacted]

Test Location: The laboratory of production technology department.

Test start time：2010.09.22
Test end time：2012.12.22

4. Reference standard：

[redacted]8.2-D-ZL-010-HIV Colloidal gold product inspection operation procedure-HIV
Q/CPKUR0016-2009 [redacted] HIV 1+2 [redacted] Enterprise Standard

5. Experiment Design

5.1 Real Time Stability Study

5.1.1 Three lots of the [redacted] HIV 1+2 [redacted] were stored at 2°C and 30°C.
5.1.2 These devices were tested with 20 HIV positive samples (P1-P18 (HIV-1 Reactive), P19 and P20 (HIV-2 Reactive)) and 20 HIV negative samples (N1-N20) at Time 1, 2, 3, 6, 12, 18, 21, 24, 25, 26 and 27month.
5.1.3 Each sample was tested with one device from each lot.

5.2 In-use Stability Study

5.2.1 One lot of the [redacted] HIV 1+2 [redacted] was used in this study.
5.2.2 Two sets of 40 devices were tested with the 20 HIV positive samples and 20 HIV negative samples. One set of device were opened and tested immediately. The other set of device were opened and exposed to the laboratory lighting at 20-24°C for 16-24 hours before testing.

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ANNEX 21 Stability Study
[redacted]
Ver. 02

[redacted] HIV 1+2 [redacted]

samples	NEG	0	0	0	0	0	0	0	0	0	0	0
20 HIV negative samples	POS	0	0	0	0	0	0	0	0	0	0	0
	NEG	20	20	20	20	20	20	20	20	20	20	20

Table 3: 2°C Stability Results (Lot 20100922)

Sample Panel		1st month	2nd month	3rd month	6th month	12th month	18st month	21th month	24th month	25th month	26th month	27th month
20 HIV positive samples	POS	20	20	20	20	20	20	20	20	20	20	20
	NEG	0	0	0	0	0	0	0	0	0	0	0
20 HIV negative samples	POS	0	0	0	0	0	0	0	0	0	0	0
	NEG	20	20	20	20	20	20	20	20	20	20	20

Table 4: 30°C Stability Results (Lot 20100920)

Sample Panel		1st month	2nd month	3rd month	6th month	12th month	18st month	21th month	24th month	25th month	26th month	27th month
20 HIV positive samples	POS	20	20	20	20	20	20	20	20	20	20	20
	NEG	0	0	0	0	0	0	0	0	0	0	0
20 HIV negative samples	POS	0	0	0	0	0	0	0	0	0	0	0
	NEG	20	20	20	20	20	20	20	20	20	20	20

Table 5: 30°C Stability Results (Lot 20100921)

Sample Panel		1st month	2nd month	3rd month	6th month	12th month	18st month	21th month	24th month	25th month	26th month	27th month
20 HIV positive samples	POS	20	20	20	20	20	20	20	20	20	20	20
	NEG	0	0	0	0	0	0	0	0	0	0	0
20 HIV negative samples	POS	0	0	0	0	0	0	0	0	0	0	0
	NEG	20	20	20	20	20	20	20	20	20	20	20

Table 6: 30°C Stability Results (Lot 20100922)

Sample Panel	1st month	2nd month	3rd month	6th month	12th month	18st month	21th month	24th month	25th month	26th month	27th month

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1. Objective

The [redacted] HIV 1+2 [redacted] should be stored at 2-30ºC avoiding humidity and the device operation environment temperature should be 15-30ºC. This study evaluates the robustness of the device under simulated transportation conditions and operation environment outside the specified required temperatures.

2. Involved Departments and Responsibility

Involved Departments:

Production Technology Department, Quality department.

Responsibility:

Production Technology Department is responsible for providing [redacted] HIV 1+2 [redacted] for research.

Quality department is responsible for testing to verify that products meet quality requirement and can be used in this study. The researchers in the Production technology department are in charge of the specific operation of this trail.

Testing Director: [redacted]

Test Location: The laboratory of production technology department.

3. Document reference

No.	Document reference
1	[redacted] Colloidal gold product manufacturing operation procedures- HIV
2	[redacted] Colloidal gold product inspection operation procedure-HIV
3	[redacted] HIV 1+2 [redacted] Enterprise Standard

4. Materials

4.1 20 HIV positive samples: P1-P18 (HIV-1 Reactive), P19 and P20 (HIV-2 Reactive) from NICPBP [redacted]
4.2 20 HIV negative samples: N1-N20 from NICPBP.
4.3 [redacted] HCV Test: Lot: 20130307.
4.4 IFU for HIV (Ver. 2.1)

5. Experiment Design

5.1 Simulated transportation temperature test:

Data Quality

Analysing the relevance of the data in the dossier

- Reports should be complete and transparent
- WHO assessment of a study report will assess it for bias and for generalisability of the results
- For accuracy studies (eg diagnostic sensitivity and specificity), recommend the use of STARD list "Standards for Reporting Diagnostic accuracy studies"
- Study authors can use the list to write informative study reports

Data Quality

http://www.stard-statement.org/

Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
METHODS		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	6	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test methods	10a	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy
	15	How indeterminate index test or reference standard results were handled
	16	How missing data on the index test and reference standard were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	18	Intended sample size and how it was determined
RESULTS		
Participants	19	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21a	Distribution of severity of disease in those with the target condition
	21b	Distribution of alternative diagnoses in those without the target condition
	22	Time interval and any clinical interventions between index test and reference standard
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	25	Any adverse events from performing the index test or the reference standard
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27	Implications for practice, including the intended use and clinical role of the index test
OTHER INFORMATION		
	28	Registration number and name of registry
	29	Where the full study protocol can be accessed
	30	Sources of funding and other support; role of funders

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Any questions?