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GUIDELINE FOR REGISTRATION OF ORTHOPOXVIRUS (MONKEYPOX) IVD TEST KITS

Medical Device Authority
MINISTRY OF HEALTH MALAYSIA

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Preamble

This present guideline serves as guidance for the submission of registration application related with Orthopoxvirus (Monkeypox) IVD test kits via Medc@st.

Irrespective of the requirements of this Guideline Document, MDA has the right to request for information or material, or define conditions not specifically described in this document that is deemed necessary for the purpose of regulatory control.

MDA reserves the right to amend any part of the guideline whenever it deems fit.

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Introduction

A rare disease called Monkeypox is caused by infection of the Monkeypox virus. It belongs to the Orthopoxvirus genus and lies under the Poxviridae family, which also consists of the variola virus that causes smallpox disease[1]. The symptoms of Monkeypox infection are comparable to smallpox symptoms but less severe and rarely result in death. This virus can be spread between individuals or between individuals and particular animals.

Monkeypox virus disease was initially identified in a laboratory research monkey located in Copenhagen, Denmark, in 1958, which is used for Polio vaccine research[2]. The monkey has been priorly infected by other animals, which at last the evolvement of the virus caused it to become susceptible to infecting humans. The first human case of Monkeypox was recorded in the Democratic Republic of the Congo in 1970[3]. Since then, Monkeypox has been reported in people in several central and western African countries[4], which caused it to be announced as endemic in that particular region.

Recently, the outbreak of the Monkeypox virus disease in non-endemic countries has increased an alarm among other non-infected countries worldwide. This situation was supported by the World Health Organisation (WHO) announcement that categorized this Monkeypox virus outbreak as a public health emergency of international concern[5]. This situation brings the appearance of the new or established in vitro diagnostics (IVD) Monkeypox virus test kits to the market.

Due to that reason, this guideline is written to guide the establishment and manufacturer in preparing the documents needed and workflow of the Monkeypox virus IVD test kits registration application.

Glossary

Condition of Use

In Monkeypox virus screening/confirmatory test, it refers to the Professional who used the device and it also covered the environment in which the test was taking place.

- **Professional use**

A condition that describes the respective device can only be used by trained users or personnel that possess good knowledge about the test. It also referred to medical device that can be used under supervision of a qualified personnel[6]. Normally, this type of use is referred to workers that are working in diagnostic, research and health care facilities.

Intended use and Principle of test

- **Monkeypox virus Generic Real-Time PCR Test**

The purpose of this protocol is to describe the procedure used for the detection of Monkeypox virus DNA in clinical specimens by real-time PCR. This assay detects DNA at varying concentrations, providing a qualitative result of either positive, negative, or inconclusive in the identification of Monkeypox virus infections. A diagnostic technique to detect viral genetic material (viral RNA) in a biological sample after having amplified it to allow for its detection[7].

- **Monkeypox virus Antigen detection**

The monkeypox virus antigen test kit is used to detect the protein antigen of monkeypox virus from rash exudates and blood samples of suspected monkeypox virus patients after symptoms. It can be used for clinical auxiliary diagnosis of monkeypox virus infection. Further nucleic acid tests should be conducted for both positive and negative antigen results in the suspected population. Immunodiagnostic test that detects the presence of viral proteins (antigens) expressed by the monkeypox virus in a sample from a rash exudates and blood samples

There are two types of antigen test mechanisms:

1) Lateral flow assays (RTK Antigen)

To detect active infection through directional flow of patient sample over target proteins, usually on a flat card or cassette.

2) Immunoassays (Antigen Assays)

To detect active infection through incubation of patient sample with test proteins, usually in a 96-well plate or similar.

- **Monkeypox virus Antibody detection**

  Monkeypox Virus IgM/IgG Rapid Test is for the rapid, qualitative detection of IgM and IgG antibodies to Monkeypox Virus in human whole blood (fingertip/venous), serum or plasma. The test is for in vitro diagnostic use only. Antibody assay test look for a variation of IgG, and IgM antibodies in venous blood samples in monkeypox virus infected person, either as a separate or combined antibody measurement in laboratory settings using enzyme linked immunosorbent assays (ELISA) or chemiluminescence immunoassays (CLIA)

Note: Detection of viral DNA by polymerase chain reaction (PCR) is the preferred laboratory test for monkeypox disease. The best diagnostic specimens are directly from the rash – skin, fluid or crusts, or biopsy where feasible. Antigen and antibody detection methods may not be useful as they do not distinguish between orthopoxviruses[8].

1 Abbreviation and Acronyms

MDA	Medical Device Authority
CSDT	Common Submission Dossier Template
IFU	Instructions for Use
RTK	Rapid Test Kit
RT-PCR	Reverse transcription polymerase chain reaction
POC	Point of Care
GDPMD	Good Distribution Practice for Medical Devices
QMS	Quality Management System
TAT	Turnaround Time
MDR 2012	Medical Device Regulations 2012
ELISA	Enzyme-Linked Immunosorbent Assay

2 Registration Requirement and Process flow

2.1 The application for registration shall be made to the Authority through an online, web-based system called —Medical Device Centralized Online Application System (MeDC@St 2.0) as per MDA guideline MDA/GL/MD-01 and MDA/GL/IVD-1.

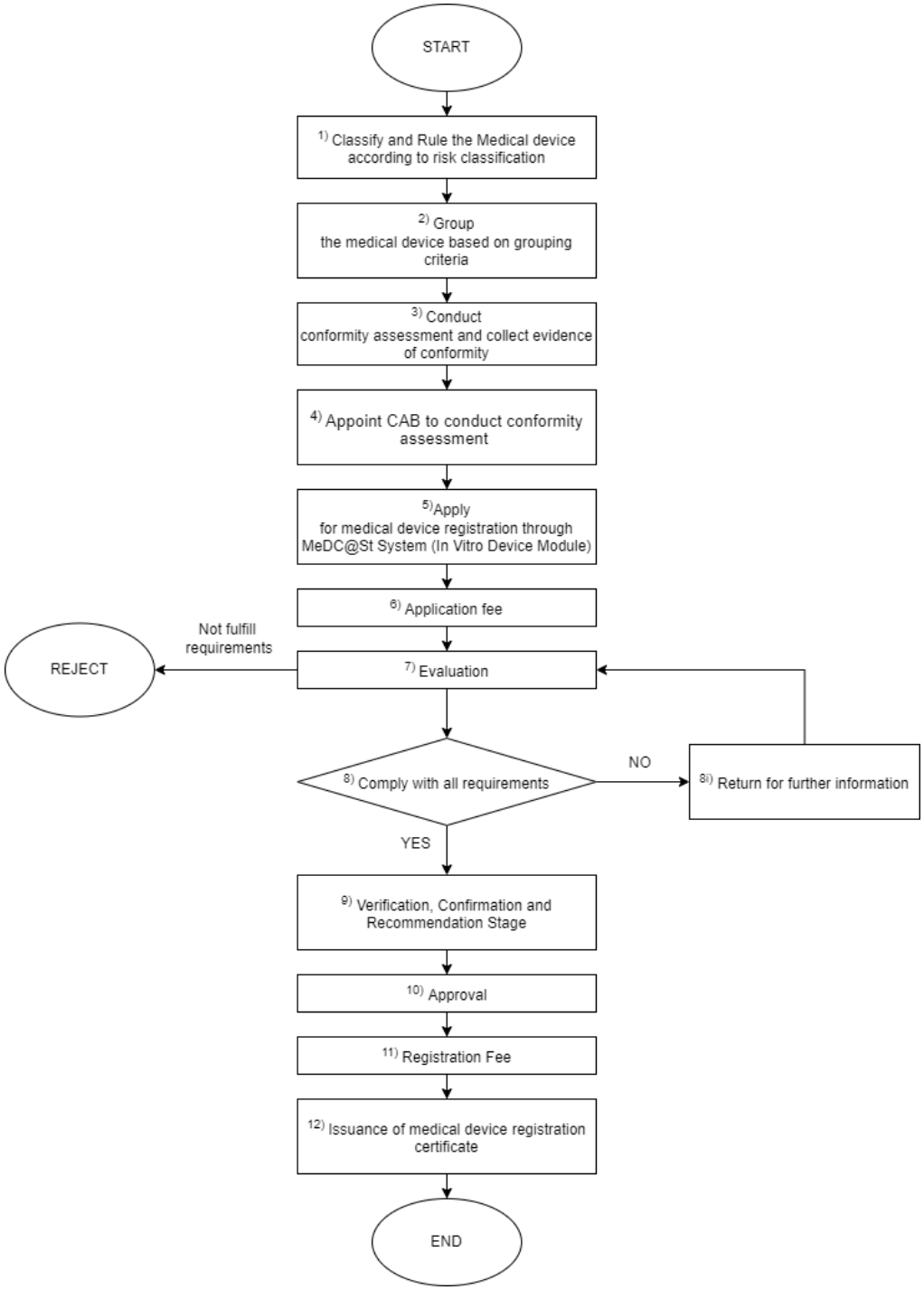

Figure 1: The steps to be taken by an applicant to register a Monkeypox test kit under Act 737.

Table 1: How to register for Monkeypox test kits.

Step	Explanatory Notes
1)Classify and Rule the medical device according to risk classification.	The classification and Rule of medical device is **Class C, Rule 3** according to the rules of medical device classification as specified in First Schedule of Medical Device Regulation 2012 and further elaborated in the Guidance Document on In-Vitro Diagnostic (IVD) Medical Device Classification System (MDA/GD/0001).
2)Group the medical device based on grouping criteria.	The grouping of medical device should be done according to the rules of medical device grouping as specified in Second Schedule of Medical Device Regulation 2012 and further elaborated in the Guidance Document on product Grouping for In Vitro Diagnostic (IVD) Medical Device (MDA/GD/0054).
3)Conduct conformity assessment and collect evidence of conformity.	According to Third Schedule of Medical Device Regulation 2012: (i) the evidence of conformity has to be collected to demonstrate compliance to applicable Essential Principles of Safety and Performance of Medical Device as specified in Appendix 1 of Third Schedule of Medical Device Regulation 2012 and further elaborated in the Guidance Document on Essential Principles of Safety and Performance of Medical Device (MDA/GD-02); (ii) the evidence of conformity has to be compiled according to the Common Submission Dossier Template (CSDT) as specified in Appendix 2 of Third Schedule of Medical Device Regulation 2012 and further elaborated in the Guidance Document on Common Submission Dossier Template (MDA/GD03); (iii) the Declaration of Conformity according to the template in Appendix 1A of Third Schedule of Medical Device Regulation 2012 has to be duly prepared, signed and stamped.
4)Appoint CAB to conduct conformity assessment	• According to 3rd Schedule of Medical Device Regulation 2012 (i) the evidence of conformity has to be verified or validated by the registered CAB; (ii) the CAB has to issue certificate of conformity and the report upon completion of the conformity assessment. • Code for Medical Device Technical Areas of Conformity Assessment Body: (i) IVD 0403 (ii) IVD 0404 • According to the Circular letter 2/2014, any medical device that have undergone conformity assessment and approval for

	placement in the market of the recognized countries, it only needs to undergo a simpler conformity assessment process (By-way of verification on evidence of conformity). • Medical devices which have not obtained any approval by regulatory authorities or notified bodies listed in Circular letter 2/2014 is required to undergo full conformity assessment by any registered CAB in accordance with the requirements stipulated in Section 7(1)(a) of Act 737.
5)Apply for medical device registration through MeDC@St System (In-Vitro Device Module)	Application for registration of medical device may be made after the requirements are met and the information and supporting documents to support the requirement are available. Application for medical device registration shall be made via MeDC@St. Applicant must create an account before making application via MeDC@St.
6) Application fee	According to Table of Fees under Fifth Schedule of Medical Device Regulation 2012
7) Evaluation	Dry Evaluation by MDA: Application that meets the requirements but incomplete documentations will be returned to the applicant for more information/documentation. **Notes: Refer to Table 2 Documents/Information required to be submitted**
8) Comply with all requirements	Comply with the requirements and the information and supporting documents to support the requirements are available
9) Verification, confirmation and recommendation Stage	Verification, confirmation and recommendation by MDA. (please refer to flow chart)
10) Approval	Approval by MDA (Please refer to Flow Chart)
11) Registration fee	According to Table of Fees under Fifth Schedule of Medical Device Regulation 2012
12) Issuance of medical device certificate	Issuance of medical device registration certificate. The registration certificate is valid for five years from the date of issuance.

2.3 The Risk Classification for Monkeypox Test Kit is Class C Rule 3.

2.4 Table 2 specifies the documents required to be submitted for registration of Monkeypox test kits. The Monkeypox test kit registration Checklist for reference Table 2 lists the documentation that must be presented in order for Monkeypox test kits to be registered. For your reference, below is the Monkeypox test kit registration checklist.

Table 2: Documents/Information required to be submitted

Documents/Information required to be submitted	**Remarks (Yes/No)**
i. GDPMD scope for IVD (Attach copy of GDPMD certificate)	
ii. Letter of Authorization from Foreign Manufacturer with list of devices	
iii. Quality Management System Certificate, ISO13485	
iv. Common Submission Dossier Template (CSDT) in accordance with MDR 2012	
v. Essential Principles of Safety and Performance of Medical Devices (EPSP)	
vi. Description and Test Principle of Monkeypox Test Kit • Intended Use (to mention for professional use) • Sample type • Instrument (if applicable)	
vii. List of Configuration (LoC) • Name of Monkeypox test kit • Identifier • Brand/Model	
viii. Pre-Clinical Studies **Analytical Performance** • Analytical Sensitivity -Limit of Detection • Analytical Specificity -Cross-reactivity • Interference • Other Analytical tests	

<table>
<tr><td>ix. Clinical Evidence

Clinical Performance Report

*Testing conducted for Clinical Evidence should have adequate sample size according to prevalence of the disease.

Criteria molecular detection

• Rapid molecular – Point of care testing (Time consumption, gene detection, sample extraction) 1 gene
• RT-PCR – gene detection (at least two genes and channels)

Example of genes and channels:

<table><tr><th>Gene</th><th>Channels</th></tr><tr><td>MPV-1 gene</td><td>FAM</td></tr><tr><td>MPV-2 gene</td><td>VIC/HEX</td></tr><tr><td>Internal control</td><td>CY5</td></tr></table>
*Please refer to Table 3 for extended requirements of clinical evaluation report.</td><td></td></tr>
<tr><td>x. Medical device labelling, IFU & Product brochure

Refer to guidance document MDA/GD/0026: Requirements for Labelling of Medical Devices</td><td></td></tr>
<tr><td>xi. Risk Analysis (according to ISO 14971)</td><td></td></tr>
<tr><td>xii. Manufacturer Information (Manufacturing process; flowchart)</td><td></td></tr>
<tr><td>xiii. Certificate and Reports of conformity assessment from CAB</td><td></td></tr>
<tr><td>xiv. Declaration of Conformity (in accordance to the template provided in MDR 2012)

Refer to guidance document MDA/GD/0025 Declaration of Conformity (DOC)</td><td></td></tr>
</table>

Table 3: Requirements for clinical evaluation report

Criteria	**Notes**	
1- Abstract	Summary of overall study	
2- Introduction	A brief description of the study	
3- Overview of detection	A brief description of the detection applicable in this study	
4- Method / clinical trial procedure	Study objectives	Genes detected and channels used (for PCR only)
		Type of antigen / antibody
		Sample type
	Study design/Study population	Sample size: 50 positive and 50 negative sample (according to prevalence of the disease)
		Inclusion and exclusion criteria
		Location/date of sampling
5- Test kit reagent and/or control kit and/or equipment and/or sample preservatives	Manufacturer	
	Brand	
	Reference	
	Lot number/batch number	
	Manufacturing date	
6- Test principle	The mechanism of the applicable test	
7- Test limitation	Description of test limitation	
8- Specimen blinding	Blinding, or “masking”, is the process by which information that has the potential to influence study results is withheld from one or more parties involved in a research study[9].	
9- Quality control	Test kit	
	Comparator kit	
10- Acceptance criteria for evaluation of clinical result	Authenticity evaluation	
	Reliability	
	Judgemental of clinical result	
11- Statistical method	Calculation for clinical sensitivity and specificity	
12- Result and interpretation of result	PCR: Ct value (<40) considered positive[10].	
	Cross table for the sensitivity and specificity of Monkeypox test kit against comparator test kit.	
13- Conclusion	Final sensitivity & specificity	
14- References	List of bibliography	

3 Evaluation Timeline

3.1 The evaluation timeline for the registration of Monkeypox test kit are 60 working days upon the submission of complete documents.

4 Table of Fees

As per the Fifth Schedule of the Medical Device Regulations 2012, the descriptions of fees for Class C devices are as below:

Application Fee	RM 500
Registration Fee	RM 2000

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