GLOBAL TASK FORCE ON
CHOLERA CONTROL

WHO – Global Task Force on Cholera Control
Target Product Profile (TPP) for the development of improved Cholera rapid diagnostic tests

June 2017

Table of content

Part I Target Product Profile (TPP) for Cholera Rapid Diagnostic Tests

Part II Supplementary Information

Abbreviations

I. Objectives and methodology

II. Introduction

III. Attributes of Cholera rapid diagnostic tests as established by the consultation

a. Preliminary considerations

b. Priority features

c. Test procedure

d. Test characteristics

e. Related equipment

f. Manufacturing process

IV. Members of Cholera RDTs Expert Group

V. References

Part I: Target Product Profile for Cholera rapid diagnostics tests (RDTs)

The product specifications tabled below are called the target product profile (TPP).

This table must be read in conjunction with Part II of this document (Supplementary information) that provides the rationale for the selection of the criteria and proposes refined information on the product attributes and the distinction between "desired" and "acceptable" attributes.

DIAGNOSTIC PRODUCT SPECIFICATIONS TPP CHOLERA		
TARGET POPULATION GROUP/PATIENT: Patients clinically suspect of cholera		
HEALTH FACILITY WHERE THE TEST WILL BE USED: Primary health care level with no access to standard laboratory facility or settings and no access to electricity. Community settings outside health facilities where cholera outbreak is suspected		
ATTRIBUTES definitions	**DESIRED**	**ACCEPTABLE**
Priority features		
Intended use of the test	Early detection, declaration, and monitoring of outbreak without need for cholera confirmation First intention test to be used on a predefined number of cholera suspect cases	Test to declare a cholera alert, to be confirmed by culture and/or PCR
Target molecule classic approach is based on LipoPolySaccharide (LPS) (O antigen), additional markers can be considered provided they show adequate performance	Biomarker for toxigenic *Vibrio cholerae* O1: LPS (O antigen) and cholera toxin marker (CT Monoclonal antibody)	Biomarker for *Vibrio cholerae* O1 and O139 (test will distinguish O1 from O139): LPS (O antigen)
Specimen type	Stool/Rectal swab Or Samples easier to collect (capillary blood if new markers are used)	Stool/Rectal swab
Analytical Sensitivity/Limit of Detection (Identification of positive reference material)	100%	≥ 95%
Clinical/Diagnostic Sensitivity (identification of clinical cases with toxigenic *Vibrio cholerae* only)	≥ 95% 95%CI (90 - 100)	≥ 90% 95%CI (85 – 95)
Analytical Specificity (assessment of cross reactivity with other pathogens)	100%	100%
Clinical /Diagnostic Specificity (identification of the cases not due to toxigenic vibrio cases)	≥ 98% 95%CI (95-100)	≥ 95% 95%CI (93 – 98)
Result output	Qualitative result	Qualitative result
Time to result	< 15 minutes	< 30 minutes

Throughput: number of tests to be performed in an hour	5-6	4-3
Intended users	Health worker from outbreak investigation team with dedicated training, present at community level And Health Community Worker at primary or secondary care levels for early detection of cholera transmission in patients presenting with compatible symptoms"	Non-laboratory trained health personnel
Ease of use	• One-signal test (+ control) • No need of interpretation, result should be self-explanatory • IFU available in all UN languages	• Two-signal test (+ control) • IFU available in English and French
Invalid rate	< 0,1%	< 1%

Test procedure		
Number of steps (use of different reagents/incubation step)	1 - 2	2 – 3
Sample preparation	Not needed/ Fully integrated in use of test device	One step conducted before use of test device
Need for operator to transfer a precise volume of sample or reagents	No	Acceptable if robust transfer device is provided with the test device and if variation do not affect test results
Biosafety requirements	None in addition to standard precautions	None in addition to standard precautions
Internal control • **demonstrating proper migration of sample** • **positive and negative controls**	• Included in test device • Provided with the kit, ideally embedded in each single test	• Included in test device • To be purchased separately
Result recording	Permanent via a reader	Manual transfer
Connectivity	Adaptable to generic reader and digital data transfer	Same
Tests Characteristics		
Operating conditions	10°C – 50°C	10°C - 40°C
Format of test	• Cassette • Sufficient space to write patient ID • Biodegradable plastic • Easy and safe to mail (after inactivation) and used for further molecular testing	• Dipstick • Sufficient space to write patient ID
Volume of sample required	No need to measure volume < 0,1 ml (rectal swab)	< 1ml

In use stability	≥ 1 hour after opening of individual pouch	≥ 30mn after opening of individual pouch
End-point stability (time window during which signal remain valid)	1 hour	≥ 30mn
Shelf-life	24 months	12 months
Storage conditions for test device (stability)	• 2°C - 40°C, relative humidity up to 98%, no cold chain required • Should be able to tolerate stress during transport (cycles of temperature of 30 to 50°C) without affecting the labelled expiry date	• Up to 35°C, no cold chain required • Should be able to tolerate stress during transport cycles of temperature of 30 to 50°C without affecting the labelled expiry date
Lot to lot variation - **Sensitivity** - **Specificity**	- SE: up to 50% in end-point sensitivities with all lots meeting the sensitivity specification - SP: no variation	Same
Reader to reader variation	90% of readers should detect a positive result near the limit of detection	Same
Reagents reconstitution (need to prepare the reagents prior to utilization)	Not needed	Not needed
Disposal requirements	None, device and accessories should be disposed in standard biological waste containers – no sharps or glassware – Or be biodegradable or combustible	Device and accessories should be disposed in standard biological waste containers
Training needs (time dedicated to training session for end users)	• Less than half a day • Job aid provided in test kit	• Less than one day of any type of end-user.
Kit presentation	• 5 test kit allowing use in exploratory mission with minimal wastage • Test components individually packed • Accessories not too small to be used with regular gloves • Include all required components and accessories to perform the test • Abbreviated IFU	• 10 test kit • Accessories not too small to be used with regular gloves • Include all required components and accessories to perform the test • Abbreviated IFU
Related equipment	•	•
Equipment needed	None (optional: use of a separate generic reader)	Small dedicated device, portable
Power source	None	Battery operated
Need for maintenance	None	Once a year, on site
Manufacturing process		
Cost of test device	< 1.00$	< 5.00$

Cost of reader (optional and if available)	< 1 000$	< 1 500$
Expected scale of manufacture	100 000 tests to be prepositioned in 25 at risk settings/countries	25 000 tests to be piloted in 5 priority countries
Lead time for production	1 month maximum	< 3 months
Required QMS standard for production	ISO 13485	ISO 13485

Part II: Target Product Profile (TPP) for Cholera rapid diagnostic tests

Supplementary Information

Abbreviations

CDC	Center for Disease Control
CFU	Colony Forming Unit
CI	Confidence Interval
GFTCC	Global Task Force on Cholera Control
GHTF	Global Harmonization Task Force
ID	Identification
IFU	Instructions For Use
ISO	International Organization for Standardization
LPS	Lipo Poly Saccharide
MSF	Médecins sans Frontières
O1	Serogroup 1
O139	Serogroup 139
PCR	Polymerase Chain Reaction
PQ	Pre-Qualification
QMS	Quality Management System
R&D	Research and Development
SE	Sensitivity
SP	Specificity
TPP	Target Product Profile
VC	Vibrio *cholera*
WHO	World Health Organization

I. Introduction

Surveillance efforts to detect and react to the appearance of cholera in at-risk populations require the rapid identification of toxigenic *V. cholerae* in patients presenting with acute watery diarrhoea.

There is an international consensus in the scientific community, supported by the recommendations issued by the WHO[1] that culture of the bacteria or its detection by PCR remains essential for the confirmation of the presence of the etiologic agent of cholera. Nevertheless, the timely and safe referral of specimens collected from cholera suspect cases to laboratory facilities where these techniques are available has been documented as challenging or just impossible due to the lack of capacity for classical microbiological and molecular testing in many areas at risk for cholera outbreaks. These barriers lead to loss of specimens, delayed results and late declaration of outbreaks.

Therefore, reliable cholera rapid diagnostic tests (RDT) are critical to quickly alert medical authorities to the start of a potential outbreak. Due to its characteristics, such as ease of use, quick turnaround time for results, and robustness, the added value of a cholera RDT is expected to be important for resource-constrained settings. Unfortunately, while they are several cholera RDTs on the market with others under development, the most recent published evaluations (8-17) have shown their diagnostic accuracy to be less than optimal.

Because of these limitations, the use of cholera RDTs has been erratic and insufficient in most of the settings at risk for cholera epidemics. The adoption of cholera RDTs will take place when good quality and performing diagnostic products are developed and made available to the teams facing suspicions of cholera outbreaks. New diagnostic products are needed to meet the specific requirements of health workers operating in harsh conditions.

Several tests are probably required to answer all these needs but the priority was given to a test able to support an early detection of a cholera outbreak, this has been the scope of an consultation dedicated to cholera RDTs. All along the consultation process, the group of experts has tapped into its solid field experience and highly specialized knowledge and aligned their recommendations on the Common Technical Specifications usually considered by stringent regulatory authorities for the same category of diagnostic products namely a class A product according to the Global Harmonization Task Force (GHTF) classification (18).

[1] http://www.who.int/cholera/technical/prevention/control/en/index1.html

II. Objectives and Methodology

Objectives

In 2016, The World Health Organization (WHO) published its vision of the pathway leading to the development and the production of the most needed health products to fight epidemic outbreaks. In a document entitled “An R&D Blueprint for Action to prevent Epidemics” (1), WHO and partners describe a set of tools meant to foster the delivery of new products matching the unmet public health needs in the domain of epidemic prone diseases, one of them being the definition of Target Product Profiles (TPPs). For health products, such as diagnostic tests and vaccines (2), the publication of TPPs is meant to guide research and development (R&D) teams and foster the delivery of new products answering the priority unmet needs.

In this context, a consultation with a group of experts was organised to support the definition of Target Product Profiles for Cholera rapid diagnostic tests. cholera rapid test specifications to inform a Target Product Profile, focussing on the detection target (VC O1 and/or VC O139) and expected targets for acceptable sensitivity and specificity.

The objectives of this group of experts were to:

- Support transparent and pragmatic consultation of experts and stakeholders involved in the use and development of cholera rapid diagnostic tests
- Provide scientific and R&D community with key characteristics to guide the development of improved rapid diagnostic tests for cholera, allowing for early detection of cholera outbreaks
- Review the knowledge gaps and foster R&D efforts that facilitate the production and uptake of affordable quality cholera RDTs at country level

Methodology

The proposed TPPs presented in this document outline two sets of attributes for cholera rapid diagnostic tests, both “desired” and “acceptable” product criteria have been considered, in line with the approach used by WHO and partners for other diseases, such as diagnostic tests for Ebola disease, Zika, and to differentiate bacterial and non-bacterial infections (3, 4, 5). While “acceptable” attributes set the minimum requirements for a cholera rapid diagnostic test to answer the user needs and procurement obligations in terms of quality, the “desired” attributes are aspirational and intend to foster the competition among RDT manufacturers leading to the development of new products demonstrating improved performance. It is hoped that the use of new technological approaches together with a clear vision of what the test would ideally bring to the cholera programme can enhance the revision of the existing versions of cholera RDTs and result in improved test performance and alignment on end-user specific needs.

These TPPs for cholera RDTs constitute the outcome of a joint-collaboration between WHO (6) and the Global Task Force on Cholera Control (GTFCC) (7). Together with a group of partners, the GFTCC Secretariat has set up group of experts, where individuals from different technical areas were invited to debate the profile of cholera RDTs answering the burning public health needs such as early detection of cholera outbreak in at risk settings. The group of experts is made of 14 highly specialized experts[2] in the domain of cholera disease, outbreak management, implementation and use of RDTs in underserved settings, development and production of antibodies and rapid tests, evaluation of RDTs and quality assessment of diagnostic products. WHO and the GTFCC paid special attention to reflect the opinion and the needs of the field end-users. For that, several representatives of cholera

[2] See composition of the Expert Group in Section IV of the document

national programs from countries regularly facing cholera outbreaks were invited to join the group.

The GFTCC Secretariat convened a series of consultations aiming at drafting the TPP for cholera RDTs. An initial set of characteristics was drafted to facilitate the discussion and the definition of TPPs for cholera RDT. Several rounds of mail exchanges took place between February and June 2017, resulting in a draft TPP document which was then shared with the members of the Epidemiology and Laboratory Working Group of the GFTCC in May 2017. All the suggestions but also the discordances were discussed until consensus was reached for each of the product attribute.

The present TPP for cholera RDTs are also developed within a broader strategy aiming at improving the quality of the products made available to the stakeholders. WHO and its Pre-Qualification unit has developed a comprehensive assessment scheme[3] for the review of product dossiers. It is foreseen that this approach will convince the manufacturers of existing and new products to approach WHO for submission of data and product dossiers. A pre-qualification awarded to any cholera RDT will be considered as a critical asset by the teams in charge of procurement of these products.

[3]WHO Pre-Qualification scheme for diagnostic products.
http://www.who.int/diagnostics_laboratory/evaluations/en/

III. Attributes of improved cholera rapid diagnostic tests

A. Preliminary considerations

The procurement of cholera RDTs by WHO and the main organizations involved in the management of cholera epidemic outbreaks is based on the assessment of priority attributes as described below. To support the use and the selection of the cholera RDTs, the GTFCC has issued a temporary guidance document on the use of cholera RDTs[4].

Of paramount importance are the populations to be tested and the health facilities where the tests will be deployed. If a cholera outbreak is suspected and for surveillance purposes, the cholera RDTs will be used on a small number of patients clinically suspect of cholera[5], typically patients presenting with acute watery diarrhoea. A positive result found in several patients in the same area will trigger a cholera alert, informing the health authorities and enhancing preparedness. It is only when the RDTs positive results are confirmed by positive culture or molecular testing that the outbreak is declared and relevant interventions initiated.

To support this strategy, the selected cholera RDTs will be made available to health personnel and staff present in facilities where standard laboratory might not be present. The test must be suitable for end-users with limited knowledge on traditional laboratory testing.

TARGET POPULATION GROUP/PATIENT: Patients clinically suspect of cholera
HEALTH FACILITY WHERE THE TEST WILL BE USED: Primary health care level with no access to standard laboratory facility or settings and no access to electricity. Community settings outside health facilities where cholera outbreak is suspected

B. Priority attributes

While a cholera test may not meet all the attributes presented in the TPP, a restricted set of attributes are considered as critical for the selection of the best adapted cholera RDTs. This encompasses the intended-use for the test, its detection targets, its performance, and several additional characteristics.

Basically, the cholera RDTs are intended to be used for early outbreak detection facilitating its management and reducing transmission. The diagnostic test presented in this document is not meant to be used for individual diagnostic of cholera among a general population. With improved technology and performance, the cholera RDT could be used within a “test and act” approach where positive cholera RDT results would allow a cholera outbreak to be declared without further confirmation. This context is referred to in the “desired” section. For the time being, the best cholera RDTs still need to be confirmed by culture or PCR for any positive result.

Acceptable detection targets are biomarkers for detection of Vibrio *cholerae* O1 and O139 with the capacity of distinguishing between the two subgroups. The test must also distinguish these serogroups from the non-O1 and non-O139 ones. Currently, available cholera RDTs have been using lipopolysacharride (LPS) antigen O, unfortunately it is not sufficient to conclude that a VC strain is toxigenic. So, in addition to LPS biomarkers, it is highly desirable

[4] Interim Technical Note: The Use of Cholera Rapid Diagnostic Tests. GTFCC. 2016. http://www.who.int/cholera/task_force/Interim-guidance-cholera-RDT.pdf?ua=1

[5] Guidance on cholera surveillance. GTFCC. 2017. http://www.who.int/cholera/task_force/GTFCC-Guidance-cholera-surveillance.pdf?ua=1

that the test detects toxigenic VC species using a cholera toxin marker to detect the strains with high potential for epidemic outbreaks.

Because of the cost implications of having two markers attached to the same test and because the circulation of VC O139 has been limited in Africa so far, a test offering a single target molecule (VC O1) will be preferred. That being said, if the test is used for environmental surveillance as it is already the case in some countries and contexts, the presence of non-toxigenic VC O1 or non-toxigenic non-O1/non-O139 species will be interesting for background literature research.

Regarding the expected minimal performance for a cholera RDT, the clinical sensitivity and specificity were intensively discussed in by the Expert Group. Sensitivity was felt as less important than specificity in the context of a test used to allow an outbreak alert to be declared. In the case of suspicion of an outbreak the current practice is to test a small number of patients presenting with cholera symptoms in the same area, therefore a test with a sensitivity of 90 – 95% will likely detect patients with high level of organisms. Unlike sensitivity, specificity will be the main parameter to consider as the end-user would not accept a high percentage of false positive results leading to the need of confirmatory testing or triggering unnecessary outbreak interventions or even distribution of cholera vaccines. In addition, prior to procurement, the manufacturer is expected to provide data demonstrating that the test does not cross react with a list of organisms for which differential diagnosis is crucial based on clinical evidence from historic records of outbreak and infections. As monoclonal antibodies can be very specific, we present here an indicative list of organisms to be tested for selection of the most specific ones: Vibrio parahaemolyticus, Vibrio alginolyticus, Vibrio mimicus, Vibrio fluvialis, Vibrio cholerae non-O1/non-O139, Plesiomonas shigelloides, Escherichia coli, Yersinia enterolitica, Shigella sonnei, Shigella flexneri, Salmonella typhi, Salmonella enteritidis, Salmonella typhimurium, Aeromonas hydrophila, Aeromonas sobria, Campylobacter coli, Campylobacter jejuni and additional Enterobacteriaceae responsible for diarrhoeal diseases.

Should an ideally sensitive and specific cholera RDT be developed and validated, the recommendation on the use of cholera RDTs might be reviewed and amended accordingly.

In addition, limits of the confidence intervals are indicated here for clinical sensitivity and specificity to guide the manufacturers in their validation studies and to suggest the number of tests to be conducted to reach statistically valid results. The limit of detection which is usually accepted is around a concentration of less than 10^6 CFU/mL and/or LPS at a concentration inferior to 100 ng/ml (referring to in-vitro cultured reference and clinical strains).

The group of experts has also stressed the importance of the test attributes related to the ease of use for health workers with little or no knowledge of classical laboratory techniques. Cholera RDTs will be distributed in countries and settings affected with cholera outbreaks, most of them occurring in rural areas where trained health workers are often missing or not familiar with laboratory techniques. This deployment strategy will allow cholera alerts to be timely declared, this context of use has major consequences in terms of test attributes and kit presentation. The way the reading system of the test is built must prevent the end-user to interpret the result, this should be self-explanatory, thus a single or dual signal (one line or one spot) will be the most desired option. To facilitate the distribution of the cholera RDTs and its adoption, manufacturers must design clear Instructions for Use (IFU) with pictures and drawing rather than written explanations, available in the languages spoken in the countries where cholera outbreaks are likely to happen (English, French being the minimal requirement).

ATTRIBUTES definitions	DESIRED	ACCEPTABLE
Intended use of the test	Early detection, declaration, and monitoring of outbreak without need for cholera confirmation First intention test to be used on a predefined number of cholera suspect cases	Test to declare a cholera alert, to be confirmed by culture and/or PCR
Target molecule classic approach is based on LipoPolySaccharide (LPS) (O antigen), additional markers can be considered provided they show adequate performance	Biomarker for toxigenic *Vibrio cholerae* O1: LPS (O antigen) and cholera toxin marker (CT Monoclonal antibody)	Biomarker for *Vibrio cholerae* O1 and O139 (test will distinguish O1 from O139): LPS (O antigen)
Specimen type	Stool/Rectal swab Or Samples easier to collect (capillary blood if new markers are used)	Stool/Rectal swab
Analytical Sensitivity/Limit of Detection (Identification of positive reference material)	100%	≥ 95%
Clinical/Diagnostic Sensitivity (identification of clinical cases with toxigenic *Vibrio cholerae* only)	≥ 95% 95%CI (90 - 100)	≥ 90% 95%CI (85 – 95)
Analytical Specificity (assessment of cross reactivity with other pathogens)	100%	100%
Clinical /Diagnostic Specificity (identification of the cases not due to toxigenic vibrio cases)	≥ 98% 95%CI (95-100)	≥ 95% 95%CI (93 – 98)
Result output	Qualitative result	Qualitative result
Time to result	< 15 minutes	< 30 minutes
Throughput: number of tests to be performed in an hour	5-6	**4-3**
Intended users	Health worker from outbreak investigation team with dedicated training, present at community level And Health Community Worker at primary or secondary care levels for early detection of cholera transmission in patients presenting with compatible symptoms"	Non-laboratory trained health personnel

Ease of use	• One-signal test (+ control) • No need of interpretation, result should be self-explanatory • IFU available in all UN languages	• Two-signal test (+ control) • IFU available in English and French
Invalid rate	< 0,1%	< 1%

C. Test procedure

Additional attributes related to the test procedure are important to consider for the selection of the best adapted cholera RDTs.

As the cholera RDTs will be used in a context of emergency by health workers in basic facilities, a simplified procedure is highly desired with a limited number of steps which will decrease the risk of user errors. Here, we indicate a maximum of steps for each of the version of the TPP with a step being defined as a short preparation phase (a simple transfer, a couple of minutes) which is different from a 6-hour enrichment steps (not acceptable for the intended -users).

Regarding the bio safety requirements, standard precautions assume the use of gloves together with the provisions for waste management, hand hygiene and splash protection. Anything more demanding will be considered as a non-appropriate option.

The presence of internal controls must be carefully assessed for the selection of the best adapted diagnostic product. It is expected that a control demonstrating a proper sample flow is included in the test format, acknowledging that this might be a challenge for the test developers especially on stool samples. In addition, the availability of negative and positive controls within the test kit is a highly-appreciated attribute, alleviating the need for the end-user to store scarce cholera positive and negative samples.

ATTRIBUTES definitions	DESIRED	ACCEPTABLE
Number of steps (use of different reagents/incubation step)	1 - 2	2 – 3
Sample preparation	Not needed/ Fully integrated in use of test device	One step conducted before use of test device
Need for operator to transfer a precise volume of sample or reagents	No	Acceptable if robust transfer device is provided with the test device and if variation do not affect test results
Biosafety requirements	None in addition to standard precautions	None in addition to standard precautions
Internal control • **demonstrating proper migration of sample** • **positive and negative controls**	• Included in test device • Provided with the kit, ideally embedded in each single test	• Included in test device • To be purchased separately
Result recording	Permanent via a reader	Manual transfer
Connectivity	Adaptable to generic reader and digital data transfer	

D. Test characteristics

In alignment with the recommendations issued for the improvement and harmonization of malaria RDTs (10), the Expert Group has highlighted several attributes for in-depth review. Because of the usual context of use in cholera prone areas, the cholera RDTs are expected to present specific characteristics in terms of robustness and composition of test kits. This section outlines the key attributes that would be reviewed by any stringent regulatory authority to which a cholera RDT would be submitted for product assessment.

A cassette version is preferred to a strip one as it is considered as more user-friendly although the cost would probably be higher.

To cope with the field operating conditions, the proposed range of temperature for stability is wide enough to accommodate cases where the test kits are accidently stored in a fridge although it is not required to do so ("desired" column).

Available products do not have sufficient space on the top of the cassette (even less on a strip version) allowing the identification of the patient to be recorded, this has been considered as a drawback by field users. Thus, it is recommended that the design of the new cholera RDTs presents a dedicated space for ID record. Given the conditions of use at the beginning of an outbreak it is important to avoid any mistake in the reporting of the test results.

Regarding the requirements for disposal of the cholera RDTs, an acceptable approach would state that "device and accessories should be able to be disposed in standard biological waste containers – no sharps or glassware (note: glass cannot be incinerated). Accompanying non-infectious waste should be biodegradable or combustible.

Stability and reproducibility are essential components for manufacturers to consider as specific data will be reviewed by the teams in charge of product selection leading to procurement. The expected stability during storage presents a range of temperatures covering the locations where air conditioning is not available especially in areas where ambient temperature is very high (over 37°C). The test must sustain these high temperatures, allowing the pre-positioning of the products at regional or district levels in the areas most at risk for cholera outbreaks.

For stability attributes, the device must tolerate temperature stress without affecting the labelled expiry date. Testing on cycles of temperatures between 30 and 50°C is recommended as these modifications of temperature mimic transportation conditions more accurately and are more stressful.

Reproducibility has been highlighted by the Expert Group as an important attribute, acknowledging that expressing reproducibility for a qualitative assay is somehow challenging. Lot to lot variation is a key component to investigate as it reflects a robust and regular quality of production. It is foreseen that no more than 50% difference in end-point sensitivities measured by logistic or probit analysis and all lots meeting the sensitivity specification would be acceptable. In any case, specificity should not change with all the different tested lots meeting the specification. The reader to reader reproducibility should reach 90% with typical, not expert, readers who should be able to detect a positive result near the limit of detection.

The kit presentation is equally an important attribute, the ideal products would include clear bench aids (in addition to the IFU) describing the use of the individual test together with clear guidance on the interpretation of the test results which is known to be prone to errors for basically trained end-users.

ATTRIBUTES definitions	DESIRED	ACCEPTABLE
Operating conditions	10°C – 50°C	10°C - 40°C
Format of test	• Cassette • Sufficient space to write patient ID • Biodegradable plastic • Easy and safe to mail (after inactivation) and used for further molecular testing	• Dipstick • Sufficient space to write patient ID
Volume of sample required	No need to measure volume < 0,1 ml (rectal swab)	< 1ml
In use stability	≥ 1 hour after opening of individual pouch	≥ 30mn after opening of individual pouch
End-point stability (time window during which signal remain valid)	1 hour	≥ 30mn
Shelf-life	24 months	12 months
Storage conditions for test device (stability)	• 2°C - 40°C, relative humidity up to 98%, no cold chain required • Should be able to tolerate stress during transport (cycles of temperature of 30 to 50°C) without affecting the labelled expiry date	• Up to 35°C, no cold chain required • Should be able to tolerate stress during transport cycles of temperature of 30 to 50°C) without affecting the labelled expiry date
Lot to lot variation - **Sensitivity** - **Specificity**	- SE: up to 50% in end-point sensitivities with all lots meeting the sensitivity specification - SP: no variation	- SE: up to 50% in end-point sensitivities with all lots meeting the sensitivity specification - SP: no variation
Reader to reader variation	90% of readers should detect a positive result near the limit of detection	90% of readers should detect a positive result near the limit of detection
Reagents reconstitution (need to prepare the reagents prior to utilization)	Not needed	Not needed
Disposal requirements	None, device and accessories should be disposed in standard biological waste containers – no sharps or glassware – Or be biodegradable or combustible	Device and accessories should be disposed in standard biological waste containers
Training needs (time dedicated to training session for end users)	• Less than half a day • Job aid provided in test kit	• Less than one day of any type of end-user.
Kit presentation	• 5 test kit allowing use in exploratory mission with minimal wastage • Test components individually packed • Accessories not too small to be used with regular gloves • Include all required components and accessories to perform the test • Abbreviated IFU	• 10 test kit • Accessories not too small to be used with regular gloves • Include all required components and accessories to perform the test • Abbreviated IFU

E. Related equipment

In the case an equipment is required to perform the cholera RDT (which is not considered as an advantage), it must be extremely simple to use without any constraint for the power source and the maintenance. This is most desired condition for the product to be used outside of classical laboratory premises and allow detection of cholera outbreaks.

ATTRIBUTES definitions	DESIRED	ACCEPTABLE
Equipment needed	None (optional: use of a separate generic reader)	Small dedicated device, portable
Power source	None	Battery operated
Need for maintenance	None	Once a year, on site

F. Manufacturing process

The indicated unit prices for the cholera RDTs are only indicative. In the absence of benchmark price for cholera tests, the Expert Group has used price information available for equivalent products implemented in similar contexts. Current versions are not expected to be procured in high volumes because of their limitations and the public health approach (testing of a small number of suspect cases), should the new cholera RDTs be massively improved they could be used for individual diagnostic therefore their unit price would be expected to decrease substantially.

A rough estimate for production has been derived from historic procurement data from WHO and MSF, which are the main funders for this category of products in cholera endemic areas. Again, new cholera RDTs showing all the attributes listed in the desired section of this TPP document would likely trigger an increase demand as they would be able to support individual diagnosis outside of outbreak episodes.

The lead time for production is critical attribute to know in advance as very few countries have stocks of tests available at national level even less at their periphery. This information is essential to ensure smooth procurement and delivery operations up to areas facing suspicions of cholera outbreaks.

The requirement for ISO 13485 standard for Quality Management System is the benchmark for any diagnostic products to be procured by WHO and its affiliated partners.

ATTRIBUTES definitions	DESIRED	ACCEPTABLE
Cost of test device **Cost of reader (optional and if available)**	< 1.00$ < 1 000$	< 5.00$ < 1 500$
Expected scale of manufacture	100 000 tests to be prepositioned in 25 at risk settings/countries	
Lead time for production	1 month maximum	< 3 months
Required QMS standard for production	ISO 13485	ISO 13485

IV. Members of Cholera RDTs group of experts

Members

- Jerome Ateudjieu, Université de Dschang, Cameroon
- Maurice Bangombe, Community Health Sciences Unit, MOH, Lilongwe, Malawi
- Bhabatosh Das, Translational Health Science and Technology Institute, Haryana, India
- Julian Duncan, diagnostic R&D expert, consultant
- Jan Jacobs, Institute of Tropical Medicine, Antwerp, Belgium
- Pierre Lafaye, Pasteur Institute, Paris, France
- Jose Paulo Langa, Instituto Nacional de Saude, Maputo, Mozambique
- Gisele Mbuy, DLM/MOH, Kinshasa, Democratic Republic of Congo
- John Mwaba, University of Zambia, Lusaka, Zambia
- Piero Olliaro, WHO/TDR, Geneva, Switzerland
- Anne-Laure Page, Epicentre, MSF, Paris, France
- Michele Parsons, CDC/OID, Atlanta, USA
- Erwan Piriou, MSF, Amsterdam, The Netherlands
- Anita Sands, Pre-Qualification Team – Diagnostic, WHO, Geneva, Switzerland

WHO/GTFCC Secretariat

- Johanna Fihman, WHO/GTFCC Secretariat, Geneva, Switzerland
- Dominique Legros, WHO/GTFCC Secretariat, Geneva, Switzerland
- David Olson, WHO/GTFCC Secretariat, Geneva, Switzerland
- Martine Guillerm, WHO/consultant, Geneva, Switzerland

Acknowledgements

Marie-Laure Quilici, National Reference Laboratory for Vibrio and Cholera, Pasteur Institute, Paris, France

Contact : GTFCCsecretariat@who.int

V. References

1. WHO (2016) An R&D blueprint for action to prevent epidemics. http://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf?ua=1
2. The process for developing WHO PPCs and TPPs for vaccines. WHO. http://www.who.int/immunization/research/ppc-tpp/developing_ppcs_tpps/en/
3. Ebola Diagnostics TPP. WHO. (2014) http://www.who.int/medicines/publications/target-product-profile.pdf?ua=1
4. Zika Diagnostics TPP; WHO (2016). http://www.who.int/entity/blueprint/what/research-development/zika-tpp.pdf?ua=1
5. Target Product Profile for a Diagnostic Assay to Differentiate between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus. Dittrich S, et all. (2016). PLOS ONE 11(8): e0161721. https://doi.org/10.1371/journal.pone.0161721
6. WHO. Cholera website http://www.who.int/cholera/en/
7. The Global Task Force on Cholera Control http://www.who.int/cholera/task_force/en/
8. Field Evaluation of Crystal VC Rapid Dipstick test for cholera during a cholera outbreak in Guinea-Bissau (Trop Med Int Health. 2009)
9. Evaluation of a rapid dipstick test for identifying cholera cases during the outbreak (IJMR, 2012)
10. Performance and utility of a rapid diagnostic test for cholera: notes from Haiti (Diagn Microbiol Infect Dis, 2013)
11. Evaluation of a rapid immunochromatographic Dipstick Kit for Diagnosis of Cholera emphasizes its outbreak utility (Jpn. J. Infect. Dis. 2010)
12. Evaluation of a rapid dipstick (Crystal VC) for the Diagnosis of Cholera in Zanzibar and a comparison with previous studies (Plos ONE 2012)
13. Evaluation of a Rapid Test for the Diagnosis of Cholera in the Absence of Gold Standard (PLoS ONE 2012)
14. Rapid Detection of Vibrio Cholerae O1 and O139 in stool samples by one-step immunochromatographic dipstick test (Int J Biol Med Res. 2015)
15. Development and testing of monoclonal antibody-based rapid immunodiagnostic test kits for direct detection of vibrio cholerae O139 Synonym Bengal (J. Clin. Microbiol. 1995)
16. Evaluation of the monoclonal antibody -based kit Bengal SMART for rapid detection of vibrio cholerae O139 synonym Bengal in stool samples (J. Clin. Microbiol. 1995)
17. A novel kit for rapid detection of vibrio cholerae O1 (J. Clin. Microbiol. 1994)
18. A risk based approach for the assessment of in-vitro diagnostics. WHO. (2014). http://www.who.int/diagnostics_laboratory/evaluations/140513_risk_based_assessment_approach_buffet.pdf?ua=1
19. Jacobs, J. et al. (2014). Harmonization of malaria rapid diagnostic tests: best practices in labelling including instructions for use. Malaria Journal **13**(1): 505.