Target product profile for tests of neonatal sepsis and possible serious bacterial infections in newborns and young infants

Version 0.1 draft for public consultation, 13 June 2024

Infections among young infants (0–59 days old) including newborns (0–28 days old) are a major cause of mortality and must be identified and treated quickly and adequately to ensure survival and minimize morbidity. An estimated 2.3 million newborns die each year.[1] Low- and middle-income countries (LMICs) bear the greatest mortality burden, with neonatal sepsis being a major contributor in these settings.[2] In 2018, an estimated 15% of all newborn deaths globally were due to sepsis,[3] a common outcome of unmanaged possible serious bacterial infections (PSBIs). Due to the need for early intervention and the lack of diagnostic tools, empirical antibiotic therapy is commonly included in sepsis protocols and results in the overuse of antibiotics. Inappropriate use of antimicrobials is a major contributor to rising antimicrobial resistance globally.[4]

The aim of this target product profile (TPP) is to provide guidance for regulatory authorities, manufacturers, ministries of health, health programmes, and other stakeholders for the development of tests that will enable early and accurate detection of sepsis or exclusion thereof, to ensure appropriate management and antibiotics administration in young infants, including newborns, with the aim of improving patient outcomes, decreasing health-care costs, and supporting antimicrobial stewardship. Once available, these tests should be incorporated into setting-specific clinical algorithms. While clinical judgment remains paramount, objective tests would provide valuable information to health professionals who make treatment decisions.

This TPP addresses two priority use cases:

1. **In non-hospital settings:** The newborn or young infant is being evaluated for PSBI.[5] A positive or negative test result should help health professionals to identify infants who require further evaluation for sepsis and appropriate management according to local guidelines and hospital referral criteria.
2. **In hospitals:** The newborn or young infant is being evaluated for sepsis. A positive or negative test should help health professionals to decide whether to initiate bacterial sepsis management and antibiotics.

Other test purposes and use cases, such as pathogen identification, detection of antimicrobial resistance and the de-escalation, cessation and choice of antibiotic, are outside the scope of this TPP.

This TPP refers to these two types of tests according to the intended setting of each: a **non-hospital test** and a **hospital test**. A statement in this TPP that applies to only one type is preceded by the name of that type in bold.

Regardless of the type of test, this TPP assumes that the test will be delivered as a system consisting of (1) an *instrument* that can be used many times and (2) *consumables* that must be replaced as tests are performed.

For each characteristic of the TPP, a preferred criterion is to be achieved by product developers if feasible and a minimal criterion if the preferred is not feasible. Where the two columns are merged, the preferred and minimal criteria are the same.

Development of this TPP, once complete, will be described in an annex.

Target product profile

Characteristic	Minimal	Preferred	Notes
General			
1. Goal of the test	**Non-hospital test:** As an aid in evaluation for PSBI and in the decision of whether to initiate appropriate management and referral to hospital. **Hospital test:** As an aid in diagnosis of sepsis and in the decision of whether to initiate bacterial sepsis management and antibiotics.		Neither test type is intended for detection of viral or fungal infections or, as stated in the introduction, for pathogen identification, detection of antimicrobial resistance or de-escalation, cessation, or choice of antibiotic.
2. Target use setting	**Non-hospital test**: Level 1 (primary care), level 2 or level 3 health-care facilities. **Hospital test:** Level 2 (e.g. district hospital) or level 3 health-care facilities.		For definitions of levels, see Table 1.
3. Target population	Young infants (0–59 days old), including newborns (0–28 days old),[3] who are: • **Non-hospital test**: being evaluated for PSBI. • **Hospital test**: being evaluated for sepsis.		Includes young infants born at any gestation or birthweight, and includes both early- (≤ 72 h after birth) and late-onset infections.[3]
4. Target user	Using the titles of the International Standard Classification of Occupations[6]: Health professionals: medical doctors and nursing and midwifery professionals. Health associate professionals: medical and pathology laboratory technicians, nursing and midwifery associate professionals, and medical assistants. Some users have requirements for accessibility that must be met by the product.		Throughout, the user is defined as the person who, once trained on this test (see 20. Training for operation), performs the test. This user is not necessarily responsible for specimen collection and clinical care decisions. Accessibility: To design appropriately, see Web Content Accessibility Guidelines.[7]

Characteristic	Minimal	Preferred	Notes
5. Purposes supported by the instrument	Single-purpose: only one type of test (either the *non-hospital test* or the *hospital test*).	Multipurpose: both types of test (the *non-hospital test* and the *hospital test*) and ideally additional tests for other syndromes, diseases and clinical decisions.	
Test procedure			
6. Specimen	≤ 75 µL of capillary whole blood	≤ 25 µL of capillary whole blood using a single collection device	
7. Hands-on time	≤ 10 minutes per test	≤ 3 minutes per test After the user prepares the test, the system requires no further involvement until the test is complete (walk-away operation).	
8. Turnaround time	≤ 30 minutes	≤ 10 minutes	From specimen availability to result. If the instrument utilizes batching, this turnaround time must be met for all specimens in the batch.
Performance			
9. Result format	Qualitative (positive or negative)	Semi- or fully quantitative	

Characteristic	Minimal	Preferred	Notes
10. Clinical sensitivity	**Non-hospital test:** ≥ 90% **Hospital test:** ≥ 85%	**Non-hospital test:** ≥ 95% **Hospital test:** ≥ 95%	**Non-hospital test:** As demonstrated in modelling to be published, exceeding the minimal value for specificity would have less impact than doing so for sensitivity, and settings with high bacterial prevalence and low referral acceptance may require higher sensitivity and specificity than these preferred values to reduce mortality compared to baseline.
11. Clinical specificity	**Non-hospital test:** ≥ 70% **Hospital test:** ≥ 80%	**Non-hospital test:** ≥ 90% **Hospital test:** ≥ 90%	See notes for clinical sensitivity.
12. Non-result rate	≤ 5%	≤ 2%	Non-results include invalid tests (when the instrument detects an error, such as failure of a process control) and indeterminate tests (when the instrument detects no error but cannot interpret a result). Typically, the test should be repeated.

Characteristic	Minimal	Preferred	Notes
Operational			
13. Throughput per site	**Non-hospital test:** ≥ 6 tests per day **Hospital test:** ≥ 15 tests per day	**Non-hospital test:** ≥ 11 tests per day **Hospital test:** ≥ 30 tests per day	Estimated using prevalence (a) of PSBI of 11% in non-hospital settings[8] and (b) of suspected sepsis of 30% in hospitals.[9] Preferred based on a site with 100 births per day, and minimal on 50 births per day. This throughput need may be met by deployment of multiple instances of an instrument module, which, when considered together as a single instrument, must satisfy this document's other instrument characteristics such as size and price.
14. Size of instrument	**Non-hospital test:** Portable table-top device, no larger than 25 x 25 x 25 cm and 2 kg **Hospital test:** Portable table-top device, no larger than 50 x 75 x 50 cm and 10 kg		The product should be designed to be moved easily and to withstand drops and impacts associated with portable (not necessarily handheld) devices (see the latest edition of IEC 61010-1[10]).

Characteristic	Minimal	Preferred	Notes
15. Power	Accepts mains power worldwide (100–240 V AC at 50 Hz and 60 Hz). Accepts local direct-current supplies, such as USB and solar. The instructions for use state the uninterruptable power supply (UPS) capacity necessary to complete in-progress tests.	Same as minimal and the product includes a user-replaceable, rechargeable battery sufficient for an 8-hour shift.	The product's documentation should explain the electrical interfaces, including power consumption, cord length and connector style, so that implementers can plan accordingly.
16. Operating environment	10–40 °C and ≤ 90% non-condensing humidity at ≤ 2500 m elevation; low light to direct sunlight; dusty conditions.	5–45 °C and ≤ 95% non-condensing humidity at ≤ 4000 m elevation; low light to direct sunlight; dusty conditions and water splashes.	Dusty conditions: The test methods for blowing dust in the latest version of MIL-STD-810 may be used.
17. Storage environment	18 months at 2–35 °C (including 3 months at 40 °C) and ≤ 90% non-condensing humidity.	24 months at 2–40 °C and ≤ 95% non-condensing humidity.	These durations apply to consumables. The duration of instrument storage is not expected to be critical.
18. Shipping environment	5 days at 2–50 °C; ISTA 3A.		
19. Training for operation	≤ 4 h with options for remote or self-training.	≤ 1 h with options for remote and self-training; support provided for training of trainers.	

Characteristic	Minimal	Preferred	Notes
20. Language support	For each country in which the product is deployed, one commonly used language, such as the official language or de facto national language, and any language mandated by local regulatory or trade compliance requirements.	Same as minimal plus additional languages to enable use by other residents of that country.	Applies to the text of the instructions for use, training materials, and any other components of the product.
21. Biosafety	Closed, self-contained system operable without a biosafety cabinet under core requirements of laboratory biosafety.[11] Easy decontamination of surfaces with 70% isopropyl alcohol, 70% ethyl alcohol or a bleach solution with 0.5% chlorine.		
22. Service and maintenance	Weekly basic maintenance, including cleaning, of < 5 min by a user. Mean time to failure of ≥ 24 months or ≥ 5000 tests. Automatic self-checks alert the user to instrument errors, warnings or pending software updates. User-involved calibration check at set intervals. Technical support available from the manufacturer or its representative.	No maintenance required. Mean time to failure of ≥ 48 months or ≥ 10 000 tests. Automatic self-checks alert the user to instrument errors, warnings, or pending software updates. No user-involved calibration check required. Technical support available from the manufacturer or its representative.	
23. Internal process control	The product only releases a result if the internal process control(s) for the assay performed as expected.		
24. External controls	Any required positive and negative controls are included in the test's price and are delivered with the tests.		For logistics and stability, controls may be packaged separately from the test kits.

Characteristic	Minimal	Preferred	Notes
25. Quality management system	Compliant with ISO 13485.	Certified to ISO 13485 or equivalent.	
26. Waste disposal	Standard biohazard waste disposal or incineration of consumables.	All components of the kit are designed to minimize the environmental impact during standard biohazard waste disposal.	See [12].
Data features			
27. Data fields	Test results; patient identification; user identification; date and time of tests; quality control results; other for administration and maintenance.		Throughout this section, data features can be provided by integrating the product with a digital health system with those capabilities. When possible, the product should collect data automatically, to reduce the user's workload and avoid errors.
28. Methods for data entry	• Typing with or without protective gloves	• Typing with or without protective gloves • Scanning one- and two-dimensional barcodes	The user can choose one of these methods for entering the types of data listed above.

Characteristic	Minimal	Preferred	Notes
29. Non-volatile memory and storage	≥ 500 patient results ≥ 50 quality control results	≥ 2000 patient results ≥ 200 quality control results	This memory is intended as a log of recent results and a temporary repository of results awaiting transmission to a server using the data connectivity features described later.
30. Role-based access control	Provides configurable access to specific data and product features for users with different roles.		Roles may include data managers at several levels (e.g., supervisor, site administrator, national manager) and users (see 4. Target user).
Data connectivity			
31. Data connectivity methods	A wired connection (Ethernet or USB) and a wireless connection (Wi-Fi or Bluetooth).	All of Ethernet, USB, Wi-Fi and Bluetooth.	
32. Intermittent connections	The user shall be able to perform tests and receive results offline. When back online, the product shall transmit those data automatically, without user action.		
33. Data exchange standards	The product supports either FHIR® or JSON.	The product supports both FHIR® and JSON.	For connections to systems such as laboratory information systems, electronic health records, national registries and surveillance systems according to the health programme's requirements.
34. Data destination	The health programme shall be able to choose the destination(s) of the product's data.		The product's manufacturer and other groups should require permission from the health programme to receive any data.

Characteristic	Minimal	Preferred	Notes
35. Data ownership	The health programme shall be able to manage the product in compliance with local regulations on data ownership.		
36. Security and privacy	To facilitate use by health programmes in accordance with the laws, regulations and policies in their settings and with best practices, the product shall provide configurable features so that personal data can be: (a) gathered transparently to users and patients, including consent, (b) collected and processed only for purposes compatible with the health programme's purposes, (c) limited to what is relevant and necessary, (d) collected accurately, (e) stored in identifiable form no longer than necessary and (f) secured for integrity and confidentiality, with encryption at rest and in transmission.		(a)–(f) are adapted from the European Union General Data Protection Regulation 2016/679 (GDPR), article 5, sec. 1. Note that not all the GDPR is relevant or appropriate to this product in these settings.
Pricing			
37. List price of instrument	To be determined.		Additional research is needed.

Characteristic	Minimal	Preferred	Notes
38. List price of each test	≤ USD 5	≤ USD 3	These prices were informed by impact modelling, to be published, that found that the non-hospital test could be cost-neutral in one low-income country at USD 3 by averting unnecessary hospitalization and healthcare-associated infections. Cost-neutral prices in the other modelled scenarios and settings were higher (up to USD 27). Tailored modelling to inform decision making should be considered in each setting where deployment is considered. Pricing from manufacturers should be as low as sustainably possible while maintaining quality, based on evidence of the cost of goods sold accounting for material, manufacturing process, operational logistics and commercialization efforts. Pricing should also include and clearly define all facets of end-to-end implementation (e.g. support, maintenance). Pricing must account for production at scale with defined volume thresholds. Ultimately pricing should intersect sustainable long-term viability for the manufacturer with affordability to support widespread access to testing in LMICs and should be transparently published.

Table 1: Definitions of use settings in LMICs (adapted from [13])

	Self-testing	Level 0 Community	Level 1 Primary care	Level 2 District hospital laboratory	Level 3 Regional/provincial laboratory	Level 4 Reference/national laboratory
Use setting	• Self-testing	• Community outreach • Home testing	• Primary care facility	• Near-patient laboratory • Referral hospital laboratory • Emergency department testing	• Near-patient laboratory • Referral hospital laboratory • Emergency department testing	• Reference laboratory
Laboratory infrastructure	• No mains power • No water • No laboratory equipment • No environmental control, e.g. temperature, humidity, dust	• No mains power • No water • No laboratory equipment • No environmental control, e.g. temperature, humidity, dust	• No mains power (unreliable) • Minimal laboratory equipment (may not support cold chain) • BSL-1 containment • No environmental control, e.g. temperature, humidity, dust	• Mains power (may be intermittent) • Basic laboratory equipment (biosafety cabinet, centrifuge, calibrated pipettes, refrigerator) • –20 °C freezers (some) • BSL-1/2 containment (some) • Environmental control, e.g. temperature, humidity, dust (some)	• Mains power (may be intermittent) • Basic laboratory equipment (biosafety cabinet, centrifuge, calibrated pipettes, refrigerator) • –20 °C freezers • BSL-1/2 containment • Environmental control, e.g. temperature, humidity, dust	• Mains power (reliable) • Facility with a high level of infrastructure • –20 °C freezers • –80 °C freezers (some) • BSL-2/3 containment • Environmental control, e.g. temperature, humidity, dust
Operator skill	• Self-testing/lay person • Simple reagent/specimen transfer	• Nurse/pharmacist • Community health worker • Simple reagent/specimen transfer	• Nurse • Trained laboratory worker • Minimal specimen processing (≤ 3 steps)	• Laboratory technician (certified for 1–2 years) • Specimen processing with calibrated volumes (≤ 3 steps)	• Laboratory technician (certified for 1–2 years) • Specimen processing with calibrated volumes (≤ 3 steps)	• Scientific research specialist • Laboratory technician (certified for 1–2 years)
Specimen capacity	• Can process minimally invasive samples: fingerstick blood, nasal swabs, saliva, urine	• Can process minimally invasive samples: fingerstick blood, nasal swabs, saliva, urine	• Can process upper respiratory specimens; may not have capacity for lower respiratory, venipuncture or plasma specimens	• Can process most BSL-2 specimens; depends on clinic's specimen capacity	• Can process most BSL-2 specimens; depends on clinic's specimen capacity	• Can process most BSL-2/3 specimens
Test capacity	• True POC MDx (some) • RDTs	• True POC MDx (some) • RDTs	• True POC MDx • Basic microscopy • RDTs	• Near-POC MDx • ELISA with a simple reader (some) • Microscopy • RDTs • Clinical chemistry (some)	• Blood culture and microbiology capacity (some) • Near-POC MDx • ELISA with a simple reader • Microscopy • RDTs • Clinical chemistry	• Blood culture and microbiology capacity • Lab MDx/PCR/LDT • ELISA/EIA/CLIA/PRNT • Fluorescence microscopy • Clinical chemistry • Sequencing (some) • Mass spectrometry (some)

BSL, biosafety level; CLIA, chemiluminescent assay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; LDT, laboratory-developed test; MDx, molecular diagnostic test; POC, point of care; PRNT, plaque reduction neutralization test; RDT, rapid diagnostic test.

References

[1] https://childmortality.org/wp-content/uploads/2023/01/UN-IGME-Child-Mortality-Report-2022.pdf (accessed 22 Sep 2023).

[2] World Health Organization. (28 January 2022). Newborn Mortality. https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-mortality-report-2021 (accessed 22 Sep 2023).

[3] World Health Organization. (2020). Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. World Health Organization. https://iris.who.int/handle/10665/334216 (accessed 22 Sep 2023). License: CC BY-NC-SA 3.0 IGO

[4] Prusakov P, Goff DA, Wozniak PS, Cassim A, Scipion CEA, Urzúa S, Ronchi A, Zeng L, Ladipo-Ajayi O, Aviles-Otero N, Udeigwe-Okeke CR, Melamed R, Silveira RC, Auriti C, Beltrán-Arroyave C, Zamora-Flores E, Sanchez-Codez M, Donkor ES, Kekomäki S, Mainini N, Trochez RV, Casey J, Graus JM, Muller M, Singh S, Loeffen Y, Pérez MET, Ferreyra GI, Lima-Rogel V, Perrone B, Izquierdo G, Cernada M, Stoffella S, Ekenze SO, de Alba-Romero C, Tzialla C, Pham JT, Hosoi K, Consuegra MCC, Betta P, Hoyos OA, Roilides E, Naranjo-Zuñiga G, Oshiro M, Garay V, Mondì V, Mazzeo D, Stahl JA, Cantey JB, Monsalve JGM, Normann E, Landgrave LC, Mazouri A, Avila CA, Piersigilli F, Trujillo M, Kolman S, Delgado V, Guzman V, Abdellatif M, Monterrosa L, Tina LG, Yunis K, Rodriguez MAB, Saux NL, Leonardi V, Porta A, Latorre G, Nakanishi H, Meir M, Manzoni P, Norero X, Hoyos A, Arias D, Sánchez RG, Medoro AK, Sánchez PJ; Global NEO-ASP Study Group. A global point prevalence survey of antimicrobial use in neonatal intensive care units: The no-more-antibiotics and resistance (NO-MAS-R) study. EClinicalMedicine. 2021 Jan 29;32:100727. doi: 10.1016/j.eclinm.2021.100727.

[5] World Health Organization. (2017). WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. World Health Organization. https://iris.who.int/handle/10665/259269 (accessed 22 Sep 2023). License: CC BY-NC-SA 3.0 IGO

[6] International Standard Classification of Occupations (ISCO) [Internet]. 2023 [cited 2024 Jun 4]. Available from: https://ilostat.ilo.org/methods/concepts-and-definitions/classification-occupation/

[7] https://www.w3.org/TR/WCAG21/

[8] Lokangaka A, Ramani M, Bauserman M, Patterson J, Engmann C, Tshefu A, Cousens S, Qazi SA, Ayede AI, Adejuyigbe EA, Esamai F, Wammanda RD, Nisar YB, Coppieters Y. Incidence of possible serious bacterial infection in young infants in the three high-burden countries of the Democratic Republic of the Congo, Kenya, and Nigeria: A secondary analysis of a large, multi-country, multi-centre clinical trial. Journal of Global Health. 2024 Feb 2;14.

[9] Fleischmann-Struzek, Carolin, David M Goldfarb, Peter Schlattmann, Luregn J Schlapbach, Konrad Reinhart, and Niranjan Kissoon. 2018. “The Global Burden of Paediatric and Neonatal Sepsis: A Systematic Review.” The Lancet Respiratory Medicine 6 (3): 223–30.

Narayanan I, Nsungwa-Sabiti J, Lusyati S, Rohsiswatmo R, Thomas N, Kamalarathnam CN, et al. Facility readiness in low and middle-income countries to address care of high risk/ small and sick newborns. Maternal Health, Neonatology and Perinatology. 2019 Jun 18;5(1).

[10] IEC 61010-1. Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 1: General requirements.

[11] World Health Organization. (2020). Laboratory biosafety manual, 4th ed. World Health Organization. https://iris.who.int/handle/10665/337956 (accessed 22 Sep 2023). License: CC BY-NC-SA 3.0 IGO

[12] World Health Organization. Health-care waste. 2018 (https://www.who.int/news-room/fact-sheets/detail/health-care-waste, accessed 5 December 2023).

[13] Ghani AC, Burgess DH, Reynolds A, Rousseau C. Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings. Nature. 2015;528:S50-2.