View in the context of the Performance Evaluation Consultation Procedure (PECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert view

This scientific view reflects the opinion of independent experts (MDR Article 106.1) on the performance evaluation report (PER) of the manufacturer. The advice is provided in the context of the performance evaluation consultation procedure (PECP), which is an additional element of conformity assessment by notified bodies for specific high-risk in vitro diagnostic devices (IVDR Article 48.6).

When making its conformity assessment decision, the notified body is obliged to give due consideration to the opinions expressed in the scientific view of the expert panel, where applicable (Annex IX, Section 4.9 or, as applicable, Annex X, Section 3, point (j)).

For class D devices, the notified body must provide a full justification in the case of divergent views between the notified body and the experts. This justification shall be included in the notification to the competent authority (IVDR Article 50; mechanism for scrutiny of class D devices)

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	09/02/2024
Notified Body number	2962
Internal PECP dossier # (e.g. 2021-000201)	IVD-2024-000020
***In vitro* diagnostic medical device** *(descriptive text, no nomenclature use)*	A non-automated IVD real-time PCR test for the qualitative detection of foetal RHD DNA from extracted human maternal plasma of non-immunized RhD negative pregnant women (non-invasive prenatal determination of foetal RHD status, NIPT-RHD). The test detects exons 5, 7 and 10 of the RHD gene.

2 INFORMATION PROVIDED BY THE NOTIFIED BODY

Intended purpose (P)		
P1	what is detected and/or measured *please specify the analyte(s) or marker(s), e.g. SARS-CoV-2 spike protein, Kel1 (K)*	Fetal RHD status (exons 5, 7 and 10 of the RHD gene)
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	Aid to decide if a prepartum anti-D prophylaxis should be administered to RhD-negative pregnant women
P3	the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate *e.g. hepatitis C infection, exposure to SARS-CoV-2, risk of HIV transmission in blood transfusion etc.*	RHD status of the fetus, as a RhD-positive fetus causes the formation of anti-D IgG antibodies in an RhD-negative mother
P4	whether it is automated or not	Non-automated assay
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative assay
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	Extracted human maternal plasma
P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	Non-immunized RhD-negative pregnant women

P8	intended user	For Professional Use Only (trained users)
Technology (T)		
T1	principle of the assay method or principles of operation of the instrument *e.g. real-time PCR, qualitative PCR, digital PCR, sandwich immunoassay, competitive immunoassay, immunoturbidimetric assay etc.*	Real-time polymerase chain reaction (PCR) – amplification of the specific Target Sequence using fluorescence-labelled oligonucleotide probes

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group (where relevant)

Date of views	24/04/2024
Expert panel name	IVD expert panel
Sub-group of expert panel (where relevant)	IVD sub-group 2024-20

3.2 Summary of expert panel views

The device under PECP assessment is an IVD designed for non-invasive prenatal testing (NIPT) to determine foetal Rhesus D (RhD) status in RhD-negative pregnant women. The device utilizes real-time Polymerase Chain Reaction (PCR) technology to determine in maternal plasma the presence or absence of the RHD gene in foetal DNA, aiming to guide the administration of anti-D prophylaxis and prevent Haemolytic Disease of the Foetus and Newborn (HDFN).

The comprehensive overview provided on the biological and genetic foundations underlying the Rhesus factor, acknowledging the robust scientific rationale for targeting the RHD gene is noted. The connection between RhD status and the risk of HDFN is well-established, underscoring the scientific validity of the device's intended application.

It is noted that the terminology is sometimes not harmonized. For example, the use of the terms "diagnostic sensitivity and specificity" in some parts of the text and "clinical sensitivity and specificity" in others. A better harmonization of terms and adherence to ISO/IEC Guide 99:2007 International vocabulary of metrology (VIM) is recommended, as well as the citation of the terms used.

The panel recognizes the device's high analytical sensitivity and specificity as critical strengths, highlighting the reliable detection capabilities of real-time PCR technology. However, the experts note a lack of detailed references to standard evaluation protocols, suggesting an area for improvement in documentation to bolster the report's robustness. In fact, the lack of references and the information given does not allow to recognize the statistical approaches used in analytical and clinical performance assessment. Generally, evaluation protocols recognized in the field are mostly published by the Clinical and Laboratory Standards Institute (CLSI). However, no CLSI protocols are mentioned in references. These shortcomings found in the performance evaluation report (PER) extend to the instructions for use (IFU), limiting the understanding of the approaches used by end users.

The clinical performance report is viewed positively for demonstrating the device's effectiveness in real-world settings. The clinical study and its outcomes support the kit's utility. However, it is recommended that the literature review is expanded and the adherence to clinical evaluation guidelines is explicitly detailed for a more comprehensive presentation. The literature search methodology, protocol, and report are considered adequate but would benefit from a broader scope and deeper analysis. Expanding the review to encompass a wider range of studies could reinforce the device's positioning within the current state of art in prenatal diagnostics. As already mentioned, the limitation in the literature review is the lack of references to standard evaluation protocols, such as those from CLSI.

The expert panel agrees with the manufacturer's multifaceted approach to gathering clinical evidence, combining laboratory validation with clinical studies. The strategy is deemed appropriate for establishing the device's efficacy and safety, although a more explicit connection to established guidelines is recommended.

The panel views the use of real-time PCR technology as highly appropriate for the device's intended purpose, supporting the manufacturer's claims regarding performance and safety. The non-invasive nature of the test is highlighted as an innovative aspect, reducing risks associated with traditional invasive procedures.

The clinical evidence presented is deemed acceptable, sufficiently supporting the device's intended clinical benefits. However, continuous update and expansion of this evidence base are recommended to keep pace with advancements in the field.

Without Common Specifications (CS) in place for this type of device, the manufacturer's chosen approach to evaluate and ensure the device's performance and safety is considered adequate. The proactive incorporation of both analytical and clinical validations aligns with regulatory expectations, though enhanced documentation and adherence to recognized protocols are suggested for improvement.

The performance evaluation report of the device under PECP assessment effectively demonstrates the device's capability to fulfil its intended purpose, supported by solid scientific, analytical, and clinical foundations. To further bolster confidence in the device's performance and safety, the expert panel recommends:

- Enriching the report with direct references to internationally recognized evaluation protocols and standards.
- Broadening the literature review to include a wider array of relevant studies.
- Continuously updating the clinical evidence base to reflect advancements in prenatal diagnostics.
- Enhancing transparency and detail in the methodology for post-market surveillance.

In summary, the expert panel views the device under PECP assessment as a valuable addition to prenatal care, with recommendations focused on enhancing documentation and evidence reporting to improve completeness and compliance with regulatory standards.

3.3 Views on the specific reports included in the performance evaluation report (PER)

(IVDR, Annex XIII, Section 1.3.2, first paragraph)

Views of the expert panel on the performance evaluation report of the manufacturer (PER)
1. Expert views on the scientific validity report[1]
The manufacturer's report on the device under PECP assessment, as detailed in the Performance Evaluation Report, provides a comprehensive overview of the scientific and technical foundation supporting the kit's claims regarding its ability to non-invasively determine foetal RHD status from maternal plasma. This evaluation covers various aspects crucial for demonstrating scientific validity, such as the biological and genetic basis of the Rhesus factor D, the implications of HDFN (haemolytic disease of the foetus and newborn), and the principles of circulating cell-free foetal DNA (cffDNA) and non-invasive prenatal testing (NIPT). The scientific validity of the device under PECP assessment is supported by an extensive literature review, technological insights, the device's intended purpose, performance claims, analytical and clinical performance reports, stability studies, specimen collection, and sample handling procedures. Notably, the scientific validity report outlines the biological and genetic considerations of RhD, providing a solid foundation for the test's rationale. The importance of accurately determining the foetal RHD status to prevent HDFN by administering targeted anti-D prophylaxis to RhD-negative pregnant women is well-

[1] Annex XIII, Section 1.2.1 of Regulation (EU) 2017/746 - Demonstration of the scientific validity

established within the report, reinforcing the test's intended purpose and clinical significance. The manufacturer's assessment of scientific validity and performance claims are grounded on a detailed literature review and methodological rigor, reflecting a comprehensive approach to validate the kit's intended purpose. This includes a systematic methodology for literature review, adherence to recommended performance requirements, and validation of analytical and clinical performance based on specific sensitivity and specificity metrics. The performance evaluation also considers potential limitations and the importance of testing multiple RHD gene exons to account for genetic variations, ensuring a high diagnostic accuracy.

Exon 10 is usually very conserved, but there are some DEL and partial variants that have an exchange in exon 5 and exon 7 to the CE exons. These variants may create an immunogenic D epitope. While the documentation and the IFU (instructions for use) only outline cases where the mother carries these haplotypes, it is important to note that the presence of these variant RHD genes will mask the foetal RHD. This makes it difficult to predict the foetal D type. Additionally, foetuses carrying a D-expressing-RHD variant may be missed by foetal genotyping, leading to false-negative results. In multiethnic populations, foetal genotyping assays need to be reliable e.g. for D negative pregnant women of Asian origin. As a result, additional attention should be given to decisions based on RHD exon 10. For example, in samples taken early in pregnancy (11w), the low foetal DNA concentration could result in only 2 out of 3 exons 10 specific reactions being positive, which is interpreted as a negative result according to the algorithm but is in fact a false negative result.

Examples for such variants, resulting in weak-D, partial D or DEL while still immunogenic are:

RHD*14:01 (RHD-CE(5-7)-D) (exon 5,6,7 RHCE, all other exons (1-4 and 8-10 RHD), partial D,

RHD*14:02 (RHD-CE(5-9)-D), partial D,

RHD*41 (D-CE(5-7)-D), weak D,

RHD*01EL.23 (RHD-CE(5-7)-D), Del or partial D,

RHD*01EL.44 (RHD-CE(4-9)-D) Del (weak D expression primarily detectable only by adsorption and elution).

In addition, if only two of the exons (5,7,10) are present as RHD (e.g. 5 and 10) and one as RHCE (e.g. 7), a lower LOD can also be assumed. For example:

RHD*04.03 (D-CE(6-9)-D) partial D (DIV type 3),

RHD*04.05 (D-CE(7-9)-D) partial D (DIV type 5),

RHD*05.02 (D-CE(5)-D) partial D (DV type 2),

RHD*05.10 (D-CE(5-6)-D) partial D (DV type 10),

RHD*06.01 (D-CE(4-5)-D) partial D (DVI type 1),

RHD*06.02 (D-CE(4-6)-D) partial D (DVI type 2),

RHD*06.03 and RHD*06.03.02 (D-CE(4-6)-D) partial D (DVI type 3/3.2), prevalence in Caucasians 1.24%,

RHD*06.04 (D-CE(3-5)-D) partial D (DVI type 4),

RHD*13:01 (D-CE(5)-D) partial D,

RHD*46 (D-CE(5-6)-D) partial D,

RHD*58 (D-CE(7)-D) partial D.

There a appears to be a need to strengthen the evidence related to populations of non-Caucasian origin, particularly women that have had multiple pregnancies.

Furthermore, the report demonstrates a keen awareness of the clinical and ethical implications of the test, such as the optimization of RhD immunoglobulin use and the consideration of rare gene variants. The thorough investigation into the technology used for the device, including real-time PCR technology and the rationale behind the choice of gene targets for RHD detection, underscores the scientific validity of the device under PECP assessment.

In summary, the manufacturer's scientific validity report for the device under PECP assessment, as detailed in the PER, provides a solid and comprehensive demonstration of the kit's scientific basis, analytical and clinical performance, and its potential to contribute to the targeted management of HDFN risk in RhD-negative pregnant women. The extensive documentation supports the conclusion that the manufacturer's scientific validity report provides sufficient data, underpinned by robust scientific sources, to demonstrate the scientific validity of the device under PECP assessment for its intended use.

2. Expert views on the analytical performance report[2]

The analytical performance report of the device under PECP assessment meticulously details several key parameters critical to demonstrating the analytical validity of the device, covering aspects such as analytical sensitivity and specificity, trueness, precision (including repeatability and reproducibility), linearity, and limit of detection (LoD). These parameters are fundamental for assessing the kit's ability to accurately and reliably detect foetal RHD status in maternal plasma samples. The manufacturer's approach in evaluating these parameters is comprehensive, reflecting a strong commitment to aligning with regulatory standards and ensuring the device meets clinical needs.

The manufacturer has conducted extensive validation studies to establish the kit's analytical sensitivity and specificity, which are paramount for determining the kit's ability to correctly identify the presence of RHD gene sequences in maternal plasma. The report's indication of high sensitivity and specificity rates, alongside the clinical relevance of these metrics, underscores the kit's capability for accurate detection of foetal RHD status, which is crucial for the targeted management of HDFN in RhD-negative pregnancies. The inclusion of data on trueness and precision, encompassing both repeatability and reproducibility, supports the kit's reliability across different runs and laboratory settings. This aspect is vital for ensuring that the test results are consistent and dependable, thus providing healthcare professionals with confidence in the test outcomes for making clinical decisions. The evaluation of linearity and LoD offers insights into the kit's performance across a range of target DNA concentrations, confirming its ability to accurately quantify the foetal RHD gene in a linear fashion and detect it at low levels. This is particularly important early in pregnancy, where foetal DNA concentrations in maternal plasma may be minimal. In cases analytical performance parameters were omitted from the report, it would be crucial for the manufacturer to provide a robust justification, possibly highlighting the specific challenges or the irrelevance of certain parameters to the kit's intended clinical use. For instance, parameters like analytical specificity and selectivity might be

[2] Annex XIII, Section 1.2.2 of Regulation (EU) 2017/746 - Demonstration of the analytical performance

more emphasized over others due to the high homology between RHD and RHCE genes and the importance of accurately distinguishing between them.

The manufacturer's rigorous assessment of analytical performance data demonstrates a methodical approach to validation. By systematically addressing each analytical performance parameter, the manufacturer not only ensures compliance with regulatory requirements but also enhances the clinical utility and reliability of the device under PECP assessment.

It should be noted that an important flaw in this section is the lack of reference to standard evaluation protocols, such as those from CLSI. In fact, the statistical models used are not traceable, since they are not cited. For example, CLSI evaluation protocols EP06-A2, E05-A3, and EP17-A2 can be cited. Some further comments on the provided documentation are included below. Moreover, on page 50 of the PER, the NTC negative should be negative in only 7/9 replicates which should be clarified. The starting value for 50 copies seems to be missing (page 55, Table 56 of the PER). It is also noted that the clinical sensitivity of exon one increases during storage, but the decrease in exon 10 is unexplained. Furthermore, a Blant-Altman comparison/plot could be used (pages 72-74 of the PER). Additionally, on page 82 of the PER, there is no clear distinction between water probes and true negative samples.

In conclusion, the analytical performance report for the device under PECP assessment appears to provide a comprehensive and detailed evaluation of the device's performance characteristics, ensuring that it meets the necessary standards for accuracy, reliability, and clinical relevance. Assuming all relevant parameters have been appropriately addressed and any omissions sufficiently justified, the report substantiates the analytical validity of the device, supporting its use in clinical practice for the non-invasive determination of foetal RHD status in RhD-negative pregnancies.

3. Expert views on the clinical performance report[3]

The manufacturer's clinical performance report for the device under PECP assessment, as presented in the provided Performance Evaluation Report (PER), emphasizes several key aspects necessary to establish the clinical utility and reliability of the device. This includes its diagnostic sensitivity and specificity, the determination of clinical cut-offs, and the execution of a clinical study. The clinical performance of a device like the one under PECP assessment is crucial for its intended use in non-invasively determining foetal RHD status in RhD-negative pregnant women.

The report's inclusion of data on diagnostic sensitivity and specificity is fundamental to demonstrating the device's ability to accurately identify foetal RHD status. High sensitivity ensures that the device can detect the presence of the RHD gene in foetal DNA when it is present, while high specificity ensures that the device can correctly identify the absence of the RHD gene when the foetus is RhD-negative. The mentioned high rates for both parameters indicate a strong clinical performance, crucial for making informed clinical decisions regarding anti-D prophylaxis in RhD-negative pregnant women. The establishment of a clinical cut-off and the execution of a clinical study are critical components for assessing the kit's performance in a real-world setting. The determination of a clinical cut-off, which indicates a positive foetal RHD status, is essential for translating the test's analytical sensitivity and specificity into clinically meaningful results. The conduct of a clinical study, especially in an ethnically diverse population and across multiple stages of pregnancy, provides concrete evidence of the kit's utility and reliability.
Even if the manufacturer's report partially relies on literature reviews or previously published studies for its clinical performance data, this approach can be justified by the consistency and robustness of existing

[3] Annex XIII, Section 1.2.3 of Regulation (EU) 2017/746 - Demonstration of the clinical performance

evidence supporting the technology's efficacy. Non-invasive prenatal testing (NIPT) for foetal RHD status is well-established, with numerous studies demonstrating its accuracy and clinical benefits. Leveraging such data is acceptable provided that the device in question operates on the same principles and demonstrates comparable or superior performance metrics. The manufacturer's methodical approach to assessing clinical performance data, including adherence to recognized clinical and laboratory standards, underlines their commitment to validating the kit's clinical utility. In cases the report articulates a clear rationale for the chosen study designs, sample sizes, and the inclusion criteria for the studies cited, this further strengthens the reliability of the conclusions drawn regarding the kit's performance.

The clinical performance report for the kit under PECP assessment appears to provide a solid foundation for the device's use in clinical settings, supported by both direct evidence from clinical studies and indirect evidence from a comprehensive review of the literature. High diagnostic sensitivity and specificity are particularly notable, as they directly impact the kit's primary application in preventing HDFN by facilitating targeted anti-D prophylaxis. However, the clinical utility of any diagnostic device ultimately depends on its performance across diverse populations and different stages of pregnancy. Any limitations in the data or gaps in the evidence should be clearly stated, with justifications based on the overall body of evidence supporting the device's use. Additionally, any deviations from direct clinical performance studies to reliance on secondary data sources should be rigorously justified, emphasizing the comparability of the device to those previously studied. It is noted that, as in analytical performance section, an important flaw in this section is the lack of reference to standard evaluation protocols, such as those from CLSI (see section 2 above).

In conclusion, the manufacturer's clinical performance report for the device under PECP assessment, assuming it thoroughly and accurately reflects the device's efficacy in real-world clinical settings, seems to provide sufficient data to support its clinical utility. The careful consideration of clinical performance parameters and the reliance on a robust evidence base are commendable, ensuring that the device meets the high standards necessary for clinical application.

3.4 Views on specific assessment aspects of the performance evaluation report (PER)

(IVDR, Annex XIII, Section 1.3.2, second paragraph)

Views of the expert panel on the specific aspects included in the performance evaluation report of the manufacturer (PER)
1. The justification for the approach taken to gather the clinical evidence
The manufacturer's approach to gathering clinical evidence for the device under PECP assessment, as outlined in the Performance Evaluation Report, reflects a multifaceted strategy that encompasses a comprehensive literature review, detailed analytical performance evaluation, and a focused assessment of clinical performance through direct clinical studies and the examination of relevant clinical outcomes. This methodology aims to establish not only the technical accuracy and reliability of the test but also its clinical utility and safety in the population covered by its intended use. In particular, the manufacturer conducted an extensive literature review to establish the state of the art and gather existing evidence on the clinical utility of non-invasive prenatal testing (NIPT) for determining foetal RHD status. This review included studies on diagnostic sensitivity and specificity, the clinical impact of accurate foetal RHD status determination on the management of HDFN, and the overall safety of implementing NIPT in prenatal care. The report details rigorous analytical performance evaluations, including sensitivity, specificity, precision, and stability, which are essential for ensuring the test's accuracy and reliability. Furthermore, the clinical performance evaluation, including direct clinical studies, provides evidence of the test's efficacy and safety in a real-world setting. The approach to assessing safety and clinical benefits seems to involve correlating the test's accuracy with its impact on clinical outcomes, such as reducing unnecessary anti-D prophylaxis and preventing HDFN in RhD-negative pregnancies. The combination of a thorough literature review with detailed analytical and clinical performance evaluations represents a comprehensive approach to substantiating the clinical utility and safety of the device under PECP assessment. By relying on both existing scientific evidence and direct data from performance evaluations, the manufacturer provides a solid foundation for the intended clinical benefits of the device. The justification for this approach, which integrates various sources of evidence, appears sound and well-aligned with the complexities of demonstrating the effectiveness and safety of a diagnostic test in the prenatal care context. The reliance on a broad evidence base, including direct clinical studies, enhances the credibility of the clinical evidence gathered. Assuming the clinical studies were appropriately powered and conducted in accordance with best practices for clinical research, this approach is indeed adequate for demonstrating that the device can achieve the intended clinical benefits and safety when used as intended. The evidence generated would be instrumental in showing that accurate determination of foetal RHD status leads to improved clinical outcomes by enabling targeted anti-D prophylaxis, thereby reducing the risk of HDFN without compromising patient safety. The justification for the chosen approach to gathering clinical evidence is sound and demonstrates a clear understanding of the regulatory and clinical requirements for validating a diagnostic test. By addressing both the analytical and clinical aspects of performance and emphasizing the clinical impact of the test, the manufacturer adheres to a holistic evidence generation strategy. It is noted that the manufacturer's justification is endorsed to the extent that it reflects a robust and methodologically sound approach to evidence gathering. However, ultimately the endorsement would depend on the detailed execution of this strategy, including the quality of the clinical studies conducted, the rigor of the literature review, and the transparency of reporting the findings.

In conclusion, the manufacturer's approach to gathering clinical evidence for the device under PECP assessment is comprehensive and well-justified, potentially providing a strong basis for demonstrating the device's intended clinical benefits and safety. However, the degree of agreement with the manufacturer's justification ultimately hinges on the quality of execution and robustness of evidence.

2. The literature search methodology, protocol and report

The literature search methodology, protocol, and report outlined in the manufacturer's documentation for the device under PECP assessment reveal a structured and comprehensive approach aimed at gathering relevant clinical evidence to support the device's intended use. In particular, the manufacturer has employed a thorough literature search methodology, focusing on identifying studies and reviews pertinent to the detection of foetal RHD status in maternal plasma. This includes exploring databases such as PubMed and leveraging keywords related to the Rhesus factor D, non-invasive prenatal testing (NIPT), and cell-free foetal DNA (cffDNA). The methodology appears to be systematic, aiming to encompass a wide range of relevant publications that inform the state of the art for the device's technology and intended clinical application.

The protocol specifies inclusion and exclusion criteria, with limits set for time and language, ensuring that the search is both focused and comprehensive. The use of the snowball method to avoid overlooking relevant literature is a prudent choice, demonstrating diligence in capturing as wide an evidence base as possible. Screening by title and abstract, followed by the acquisition of full texts for potentially relevant studies, aligns with standard practices for literature reviews. The management of references, including the documentation of search terms and results, indicates a structured and replicable approach. The report's presentation of findings, including the number of articles screened and the rationale for inclusion or exclusion is critical for transparency and the assessment of the literature review's comprehensiveness. Highlighting the specific contributions of selected studies to the understanding of foetal RHD detection and its clinical implications supports the device's development and intended use.

The literature review's focus on non-invasive prenatal determination of foetal RHD status, analytical and clinical performance requirements for such tests, and the clinical implications of accurate RHD status determination seems well-aligned with the device’s intended purpose. It appropriately informs the device's development in terms of technological choices, performance validation, and clinical utility. While the manufacturer's literature review appears thorough and relevant, a few potential areas might require further exploration or clarification. In particular, ensuring that the most recent studies are included could strengthen the evidence base, especially given the rapid advancements in NIPT technologies. Additionally, given the genetic variability across populations, especially concerning RHD variants, verifying that the literature review adequately addresses studies covering a diverse range of ethnicities and geographical locations would be beneficial. Also, more detailed comparisons between the device under PECP assessment and other commercially available NIPT-RHD tests, focusing on performance metrics in varied clinical settings, could provide deeper insights into the device's competitive advantages or areas for improvement. Furthermore, examination of clinical guidelines and recommendations by authoritative bodies (e.g., American College of Obstetricians and Gynaecologists, Royal College of Obstetricians and Gynaecologists) on NIPT for foetal RHD status could offer additional context on clinical practice and expectations.

In conclusion, the literature search methodology, protocol, and report as executed by the manufacturer provide a solid foundation for substantiating the development and intended clinical use of the device. However, addressing the noted potential gaps could further enhance the device's validation process, ensuring its clinical utility and safety are comprehensively demonstrated.

3. The technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety

The device under PECP assessment is based on real-time Polymerase Chain Reaction (PCR) technology for non-invasive prenatal testing (NIPT) to determine foetal Rhesus D (RhD) status in RhD-negative pregnant women. This technology leverages circulating cell-free foetal DNA (cffDNA) found in maternal plasma, offering safe and non-invasive prenatal testing. Real-time PCR is a well-established technology in molecular biology that offers high sensitivity and specificity, crucial for detecting low levels of cffDNA in maternal plasma. The choice of real-time PCR for NIPT to detect foetal RhD status is scientifically sound and aligns with the device's intended purpose. It allows for early, accurate determination of foetal RhD status, facilitating informed decisions on the need for anti-D prophylaxis in RhD-negative pregnant women to prevent haemolytic disease of the foetus and newborn (HDFN). The technology's sensitivity is particularly important in early pregnancy when the concentration of cffDNA is lower. The specificity is crucial for ensuring that the detected RhD gene sequences are indeed of foetal origin and not maternal or contaminants, thereby reducing the risk of false-positive or false-negative results.

The manufacturer's claims regarding the performance and safety of the device under PECP assessment are supported by the device's technological basis and the rigorous analytical and clinical validation processes outlined in the performance evaluation report. By demonstrating high sensitivity and specificity, the manufacturer substantiates the device's ability to accurately determine foetal RhD status, thereby contributing to the effective management of HDFN risk. The non-invasive nature of the test inherently enhances its safety profile, eliminating the risks associated with invasive prenatal diagnostic procedures. This aspect of the device's performance and safety is not only a direct consequence of the chosen technology but also a significant advantage over traditional methods.

The application of real-time PCR technology for NIPT, specifically for determining foetal RhD status, represents an innovative use of molecular diagnostics in obstetric care. This innovation lies in the ability to obtain critical genetic information about the foetal without risking the pregnancy's viability. The device exemplifies how advances in molecular biology and genomics can be applied to improve patient care in obstetrics and gynaecology. Furthermore, the development of such a kit reflects an understanding of the need for personalized medicine approaches in prenatal care, in this case tailoring interventions like anti-D prophylaxis to the specific needs of the individual patient based on foetal genotype rather than broad population-based approaches. While the device under PECP assessment represents a significant advancement in prenatal testing, it is essential to consider the broader context of its implementation, including ethical considerations around genetic testing, the management of borderline or indeterminate results, and the integration of this technology into existing prenatal care protocols. Additionally, ongoing evaluation and post-market surveillance will be crucial to ensure that the device continues to perform as intended in diverse populations and clinical settings.

In summary, the technology underlying the device is highly appropriate for its intended purpose, and the manufacturer's claims about the device's performance and safety are well-supported. The innovative application of real-time PCR for NIPT highlights the potential of molecular diagnostics to enhance prenatal care and supports the trend toward more personalized and non-invasive approaches in obstetrics.

4. Acceptability of clinical evidence (clinical data and performance evaluation results) against state of the art in medicine

The clinical evidence provided by the manufacturer for the device under PECP assessment, as detailed through a combination of literature review, analytical performance validation, and clinical performance evaluation, aligns with the current state of the art in medicine, particularly in the field of non-invasive

prenatal testing (NIPT) for foetal RhD status. This evaluation encompasses a critical examination of the test's accuracy, reliability, and clinical utility, framed within the broader context of prenatal care and maternal-foetal medicine. The approach taken by the manufacturer in leveraging real-time PCR technology for NIPT to determine foetal RhD status is consistent with current practices in prenatal diagnostics. The use of cffDNA in maternal plasma as a basis for testing reflects a significant advancement in the field, minimizing risks associated with invasive diagnostic procedures.

The reported high levels of clinical sensitivity and specificity in detecting foetal RHD status are crucial metrics that indicate the kit's ability to provide accurate results. These performance metrics are in line with expectations for NIPT and are essential for the device's intended clinical benefits, particularly in guiding the administration of anti-D prophylaxis to RhD-negative pregnant women to prevent HDFN. The inclusion of a clinical study, demonstrating the kit's diagnostic performance in a real-world setting, is a strong aspect of the clinical evidence. It not only substantiates the device's analytical accuracy but also its practical utility and reliability across diverse clinical scenarios. The study's design and outcomes should ideally allow for a broad, non-restrictive inclusion of pregnant women to ensure the device's effectiveness and safety across different patient demographics. The thorough literature review conducted by the manufacturer helps contextualize the device within the broader landscape of prenatal testing, showcasing its development against the backdrop of existing research and clinical practices. The review's comprehensiveness is critical for establishing the test's relevance and for allowing comparisons to existing methodologies.

The device under PECP assessment embodies the state of the art in prenatal care by offering a non-invasive, risk-free alternative to traditional methods for determining foetal RhD status. This aligns with the increasing demand for safer prenatal diagnostic options that do not compromise the well-being of the mother or foetus. The capability for early detection and subsequent intervention is another aspect of the kit that aligns with the state of the art in medicine. Early and accurate determination of foetal RhD status allows for timely and targeted anti-D prophylaxis, potentially reducing the incidence of HDFN. The kit's application in guiding personalized medical interventions (i.e., the need for anti-D prophylaxis) is reflective of the broader trend towards personalized medicine by acknowledging the variability in patient needs and tailoring medical care accordingly. The clinical evidence provided for the device appears sufficient and robust, supporting its intended clinical benefits and safety profile. However, the field of prenatal diagnostics is rapidly evolving, and continuous updates to clinical evidence may be necessary to keep pace with advancements in technology, shifts in clinical guidelines, or emerging insights into foetal and maternal health. Additionally, while the device aligns well with the state of the art, any innovative aspects or potential improvements over existing tests should be highlighted, ensuring the kit remains competitive and relevant in a rapidly advancing field.

In conclusion, the clinical evidence presented by the manufacturer for the device is comprehensive and adequately supports the device's clinical utility and safety. The evidence aligns with current medical standards and practices, indicating that the device can achieve its intended benefits within the context of current prenatal care.

5. Adequacy of PMPF report(s), where applicable

The adequacy of the Post-Market Performance Follow-up (PMPF) report(s) is a critical aspect of the continuous evaluation of a medical device's safety, effectiveness, and overall performance once it has been introduced to the market. Such reports are essential for ensuring that the device continues to perform as intended in the broader population and in real-world settings, beyond the controlled environments of pre-market studies. While the specifics of the PMPF report(s) for this device are not detailed here, the criteria

outlined above provide a framework for evaluating the adequacy and robustness of such reports. An adequate PMPF plan and corresponding reports are vital for maintaining high standards of patient care and safety, ensuring that the device remains a valuable tool in clinical practice. Continuous monitoring, analysis, and response to post-market data are fundamental to achieving these goals.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report

The performance evaluation report of the device under PECP assessment demonstrates a comprehensive approach to validating the device's analytical and clinical performance for the non-invasive determination of foetal RHD status in RhD-negative pregnant women. The use of real-time PCR technology to analyse circulating cell-free foetal DNA (cffDNA) in maternal plasma is both appropriate and innovative, aligning with current trends towards less invasive, more accurate prenatal testing methods. The report provides detailed insights into the technology, intended purpose, and claims about the device's performance and safety, showcasing the manufacturer's commitment to adhering to high standards of quality and regulatory compliance.

The panel's recommendations are summarised below:

- The test demonstrates robustness and reliability within Caucasian populations, a detail that should be explicitly stated in the IFU.
- It is recommended that the manufacturer incorporate references to relevant standards and guidelines, such as CLSI evaluation protocols, in their analytical and clinical performance evaluations. This would strengthen the validation framework by providing a clear benchmark for the device's performance metrics. These references must also appear in the leaflet so that it is suitable for the end user.
- Given the evolving landscape of prenatal diagnostics, ongoing post-market performance follow-up is crucial. This should include active monitoring of the device's real-world performance and adverse event reporting to ensure continued safety and effectiveness.
- Enhancing transparency regarding the device's performance evaluation processes and making this information accessible to healthcare professionals can foster greater confidence in the test's utility and application in clinical practice.
- The PER should explicitly demonstrate compliance with the relevant regulatory requirements, including those outlined in the Regulation (EU) 2017/746, to confirm that all necessary criteria for CE marking have been met.
- The IFU is missing a comment on the usage of "low ROX" and "high ROX" devices, and it should be mentioned that when using "high ROX" devices, "ROX" should be added.
- Data on the storage time of uncentrifuged EDTA blood should be added.

In summary, the performance evaluation report of the device under PECP assessment showcases a robust validation of the device's capability to improve prenatal care through non-invasive testing. Addressing the noted limitations by incorporating standardized references and adhering to established evaluation protocols will further solidify the device's place in the field of maternal-foetal medicine.

3.6 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[4]
Has the Secretariat provided information from stakeholders?
☐☒NO
If yes, please summarise the information and how it was taken into account.
N/A

3.7 Divergent positions in case no consensus can be reached

In case no consensus on the views can be achieved[5], please indicate how many of the experts of the panel had divergent positions
None
Please summarise those divergent positions, if applicable
None

[4] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.

[5] According to Article 106.12 of Regulation (EU) 2017/745, when adopting its scientific opinion, the members of the expert panels shall use their best endeavour to reach a consensus. If consensus cannot be reached, the expert panels shall decide by a majority of their members, and the scientific opinion shall mention the divergent positions and the grounds on which they are based.