UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Recommendation of the German Society for Transfusion Medicine and Immunohematology (DGTI)

Recommendations for the validation of any novel NIPT RhD assay

Acknowledgement: Working Group Members

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Topics

- Targeted antenatal anti-D prophylaxis in the German healthcare system
- Validation guidelines in the European legislation
- Recommendations: Consensus within the DGTI
- Discussion topics

German Hemotherapy Guideline
(German Medical Association 07.08.2017)

4.12.1.5 Anti-D prophylaxis in RhD-negative (D-negative) women

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Anti-D-prophylaxis in pregnant women is not required if the fetus is tested RhD-negative (D-negative) with a validated procedure.

Counselling procedure: NIPT RhD for avoiding maternal anti-D immunization (Federal Joint Committee)

18.08.2016: Counselling procedure started

22.09.2016: Institute for Quality and Efficiency in Health Care (IQWiG) recieved the mandate to summarize the state of the art

15.05.2018: IQWiG final report published

To be expected:

Call for manufacturers in the diagnostics industry to submit pre- and post-marketing documents about their NIPT RhD assay. Description, handbook, validation report, everything in German!

Common technical specifications for *in vitro*-diagnostic medical devices (2002/364/EC)

HIV, HTLV, HCV, HBV
- Screening assays
- NAT assays
- Rapid tests
- Confirmatory assays

RhD
3000 specimen

Common technical specifications for *in vitro* -diagnostic medical devices (2002/364/EG)
http://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:02002D0364-20120701&qid=1397646822109&from=DE

Common technical specifications for *in vitro*-diagnostic medical devices (2002/364/EC)

Table 9: **Blood Groups ABO, Rhesus (C, c, D, E, e) and Kell**

	1	2	3
Specificity	Number of tests per recommended method	Total number of samples to be tested for a launch product	Total number of samples to be tested for a new formulation, or use of well-characterised reagents
Anti-A, B and AB	500	3 000	1 000
Anti-D	500	3 000	1 000
Anti-C, c, E	100	1 000	200
Anti-e	100	500	200
Anti-K	100	500	200

Acceptance criteria:
all of the above reagents shall show comparable test results with established reagents with acceptable performance with regard to claimed reactivity of the device. For established reagents, where the application or use has been changed or extended, further testing should be carried out in accordance with the requirements outlined in column 1 (above).
Performance evaluation of anti-D-reagents shall include tests against a range of week RhD and partial Rh samples, depending on the intended use of the product.

Qualifications:

clinical samples:	10 % of the test population
Neonatal specimens:	> 2 % of the test population
ABO samples:	> 40 % A, B positives
'weak D':	> 2 % of Rhesus positives

Common technical specifications for *in vitro*-diagnostic medical devices (2002/364/EC)

Whereas:

(1) Directive 98/79/EC sets out the essential requirements that *in vitro* diagnostic medical devices must meet when they are placed on the market and conformity with harmonised standards provides a presumption of conformity with the relevant essential requirements.

(2) By way of exception to these general principles, the drawing up of common technical specifications takes account of a current practice in some Member States whereby for selected devices mainly used for the evaluation of the safety of blood supply and of organ donation, such specifications are adopted by the public authorities. These common technical specifications can be used for performance evaluation and re-evaluation.

3.5. **CTS for the manufacturer's release testing of reagents and reagent products for determining the blood group antigens: ABO system (A, B), Rhesus (C, c, D, E, e), and Kell (K)**

3.5.1. The manufacturer's release testing criteria shall ensure that every batch consistently identifies the relevant antigens, epitopes, and antibodies.

3.5.2. Requirements for manufacturer's batch release testing are outlined in Table 10.

Common technical specifications for *in vitro* -diagnostic medical devices (2002/364/EG)
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Regulation (EU) 2017/746 of the European Parliament and of the Council on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission decision 2010/227/EC

(21) Directive 98/79/EC allows the Commission to adopt common technical specifications for specific categories of *in vitro* diagnostic medical devices. In areas where no harmonised standards exist or where they are insufficient, the Commission should be empowered to lay down common specifications which provide a means of complying with the general safety and performance requirements and the requirements for performance studies and performance evaluation and/or post-market follow-up, laid down in this Regulation.

(22) Common specifications ('CS') should be developed after consulting the relevant stakeholders and taking account of the European and international standards.

Medical Device Coordination Group (MDCG) can release Common Specifications (CS)

Details | Additional Information | Meetings | Subgroups | Statistics | Members

Name: **Medical Device Coordination Group (X03565)** **Active**

Abbreviation: MDCG

Policy Area: Public Health

Lead DG: GROW - DG Internal Market, Industry, Entrepreneurship and SMEs

Associated DG: JRC - Joint Research Centre
SANTE - DG Health and Food Safety

Type: Formal, Permanent

Scope: Broad

Mission: MDCG provides advice to the Commission and assists the Commission and the Member States in ensuring a harmonised implementation of medical devices Regulations (EU) 2017/745 and 2017/746.

Task: Assist the Commission in relation to the implementation of existing Union legislation, programmes and policies
Coordinate with Member States, exchange of views

Contact: GROW-COSMETICS-AND-MEDICAL-DEVICES@ec.europa.eu

Publication in RegExp: 10 Jan 2018

Creating Act: Article 103(1) of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC: "A Medical Device Coordination Group ('MDCG') is hereby established"

Link to Website: https://ec.europa.eu/growth/sectors/medical-devices_en

Last updated: 05 Mar 2019

Classification according to the regulation (EU) 2017/746 of the European Parliament and of the Council: **Intended use and associated risks**

Determination of the fetal RhD-status from maternal blood for targeted anti-D prophylaxis in RhD-negative pregnancies

(Neither list A of annex II of regulation 98/79/EG nor class D of regulation 2017/746)

Recommendations für NIPT RhD (approved by DGTI)

Diagnostic sensitivity and specificity	1000 specimen for a new procedure 100 specimen for a well validated and published procedure
Requirements for validation specimen	plasma from D-negative pregnant women gw 10 - 29, documentation of transportation time and transportation temperature in the validation report for each sample
Analytical sensitivity	Dilution series (1-in-2) WHO reference material (NIBSC code 07/222) in 4 replicates, the dilution 1-in-2 must test positive in 4 of 4 replicates.
Measuring range and linearity	100 ng/ml D-positive DNA in D-negative plasma, dilution series (0.5 log) in 3 replicates, the concentration 100 pg/ml must test positive in 3 of 3 replicates.

Recommendation for validation (2)

Intra-assay variation	8 replicates from a plasmapool, obtained from D-negative pregnant women with a D-positive fetus, tested in one run
Inter-assay variation	9 replicates from a plasmapool, obtained from D-negative pregnant women with a D-positive fetus, tested in at least 3 runs on 3 different days. The tests should be performed by different technicians.
robustness	3 runs, 12 samples per run, 6 D-positive and 6 D-negative samples, respectively

Recommendations for quality assurance

Sampling week	week 20 - 27 of gestation
Transportation time	As short as possible, ≤5 days from blood sampling until plasma separation
Test for confounding factors	Visual inspection for hemolysis before nucleic acid extraction
Positive run-control	1 plasmapool from pregnant women per run
Negative run-control	1 plasma from D-negative individual/plasmapool
Extraction-/amplification control	Either a human housekeeping gene or a heterologous DNA-fragment is present during DNA-extraction and amplification/detection

Discussion topics

- Is somebody here who would like to be the first author of a similar recommendation in an international journal?
- Is somebody here who would support a submission to an international society for approval (e.g. ISBT or ESHG)?
- Is anybody here with contacts to the Medical Device Coordination Group (MDCG)?
- Is any respresentative from a diagnostic company here who is applying or will apply for IVD CE approval for a NIPT RHD assay?
- Further comments or questions?