Editorial

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Editorial to the revision of the "Guideline of the German Medical Association on quality assurance in medical laboratory examinations – Rili-BAEK"

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Quality assurance in laboratory medicine started in the Federal Republic of Germany in 1971 with the publication of the "Guidelines of the German Medical Association for the implementation of a statistical quality control and round robin tests in the field of medicine". Since then quality assurance in general has developed further and the "Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations" (abbreviated Rili-BAEK) has been refined in numerous revisions to date. In 2008, the foundation stone for the current structure of the Rili-BAEK was laid [1]:

- A: Basic requirements for quality assurance in medical laboratory examinations
- B: Special Parts
- B 1: Quantitative medical laboratory examinations
- B 2: Qualitative medical laboratory examinations
- B 3: Direct detection and characterisation of infectious agents
- B 4: Examinations of ejaculate
- B 5: Molecular genetic and cytogenetic medical laboratory examinations
- C: Advisory board
- D: Expert groups
- E: Reference institutions
- E 1: General requirements for reference institutions conducting external quality assurance programmes
- E 2: Special requirements for reference institutions
- F: Temporary regulations
- G: Entry into force

The great importance of the Rili-BAEK is reflected in its explicit mention in Section 10 (1) of the Medical Devices Operator Ordinance (MPBetreibV) from 2024, which passed the resolution by the upper house of the German parliament on July 5th 2024 and states that [2]: "Anyone who carries out laboratory medical examinations must establish a quality assurance system in accordance with the state of the art in medical science and technology to maintain the necessary quality, safety and performance in the use of *in vitro* diagnostics and to ensure the reliability of the results obtained prior incepting this activity. Proper quality assurance in accordance with sentence 1 is assumed if the 'Guideline of the German Medical Association on Quality Assurance of Laboratory Medical Examinations' in the version of 30 May 2023 (Deutsches Ärzteblatt of 30 May 2023, DOI: 10.3238/arztebl.2023.rili_baek_Labor) is observed."

When the Rili-BAEK was revised in 2019, Part A was modernised with regard to quality management. Contents of the general quality management standard of the Federal Joint Committee (G-BA) were incorporated (i.e. structure and process quality, continuous improvement, high level on patient safety, effort in reasonable proportion to the equipment) [3] and important elements from the DIN EN ISO 9001:2015 were adopted (i.e. documented information, documentation on the quality management instead of the quality management manual) [4]. The way was paved for using process-orientated quality management systems in the future and the concept of risk-based quality assurance was introduced. Furthermore, the peer review was anchored in the Rili-BAEK as an important element of medical quality assurance. The peer review contains a professional dialogue in multiprofessional cooperation on the same level not only involving doctors and scientists but also technicians. The German Medical Association provides a curriculum for this that can be employed for advanced training to become a peer. Reactions on the introduction of the peer reviews in laboratory medicine were positive throughout [5].

Within the revision of the Rili-BAEK 2019 the increased medical demands on measurement quality – on the example of HbA_{1c} – were incorporated [6]. Since HbA_{1c} according to the guidelines not only is a measurand for patient follow-up but can also be used for the diagnosis of diabetes mellitus

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medical demands on measurement quality have tightened. In this context the demands on the internal quality assurance decreased from ±10 % via ±5 % to ±3 % with a transition period of four years. This adaptation was necessary, because in the case of a deviation of measurement of ±4 % with a true HbA_{1c} value of 44 mol/mol Hb the results are both in the range of no risk for diabetes mellitus (<39 mmol/mol Hb) and in the range of a risk for diabetes mellitus (>47 mmol/mol Hb). Therefore, with the former demands on measurement quality it was impossible to guarantee a reliable diagnosis of diabetes mellitus. Later on in 2023 the American Association for Clinical Chemistry and the American Diabetes Association recommended in a joint publication an intralaboratory CV for HbA_{1c} of 1.5 % [7]. In the Rili-BAEK 2023 the demands on the external quality assurance (round robin tests) decreased from ±18 % to ±8 %. Furthermore, demands on the internal quality assurance for further 30 measurands were defined, quality criteria for the diagnostic in cerebrospinal fluid were revised and the specimen dried blood for Newborn Screening was added. In the Parts B 2 and B 3 the number of measurands with external quality assurance was increased by 10 and the risk-based quality assurance was established. Actualisations and the elimination of redundancies, which arose due to the sequential formulation of the different B-parts, were made in the subsequent parts.

The proposals for changes to a new Rili-BAEK drawn up by the Expert Groups and the Advisory Board are presented to the Executive Board of the German Medical Association that accept or reject them. From the minutes of the meeting of the Executive Board of the German Medical Association on 17/18 October 2019, two points were given to the Rili-BAEK committees for future work:

- Board members express the wish that the greater consideration given to the medical requirements for measurement quality in the case of the HbA_{1c} should also be extended to other measurands in the next revision of the guideline.
- Furthermore, in addition to the actual laboratory medical examination, the requirements for pre-analytics, which also includes, for example, the dispatch of the materials to be examined, should also be revised in future, as this has a significant influence on the quality of the measurement results [8].

With regard to the first aspect, the specifications for the measurand glucose were revised in the Rili-BAEK 2023 [9]. In the Rili-BAEK of 2019, a value of ±11 % applies to glucose for internal quality assurance, which will be reduced to ±5 % in the Rili-BAEK 2023 – with a three-year transition period. This defines the quality criteria for glucose determination that were already valid for internal quality assurance in 2003. In the Rili-BAEK, there is only ever one quality specification for each measurand. The high value of ±11 % came about 20 years ago, because, in addition to analyses in medical laboratories, patient near immediate laboratory examinations were also covered by the Rili-BAEK. The Rili-BAEK thrives on its educational character, which at the time led to the analytical hurdles for patient near immediate laboratory examinations being kept low so that this important area could also be covered by the Rili-BAEK. In the field of patient near immediate laboratory examinations, analytical quality has improved considerably over the last two decades, so that it was time for the originally defined medical demands to become valid again – in terms of patient safety. There are currently around 9 million people with diabetes mellitus in Germany, meaning that the determination of glucose is likely to remain by far the most frequent and most important laboratory examination in the future [10].

The aspect of pre-analytics has led to a new Table B 1-1 being created for the first time in the Special Part B 1, which contains two measurands that are analysed very frequently and present us with pre-analytical challenges: glucose and potassium.

Glucose is an important source of energy for blood cells, so that in blood samples that do not contain glycolysis inhibitors, the blood glucose concentration falls continuously until the glucose values have reached zero mmol/L or mg/dL. This process of blood glucose degradation in the sample begins immediately after the blood withdrawal, so that for decades plasma and not serum has been specified as the specimen by the relevant professional associations in order to avoid the loss of time due to coagulation during the formation of serum [11]. Within the first hour, the glucose concentration decreases by approx. 7 %, which proceeds continuously [12]. This process can be stopped or minimised if

- the examination is done very quickly,
- the plasma is quickly separated from the cells, e.g. by immediate centrifugation with gel tubes, or
- by using tubes containing suitable glycolysis inhibitors.

Inhibition with fluoride and simultaneous acidification of the sample with citrate is currently considered state of the art for glycolysis inhibition [13]. Glycolysis is thus inhibited immediately and is guaranteed for at least 24 h. This means that different methods are available to ensure a valid glucose determination, taking into account the pre-analytical requirements. This aspect has already been taken into account in the German Maternity Guidelines since 2011, which recommends for the screening of pregnancy diabetes

that suitable measures must be taken to avoid falsification of the measured glucose values by glycolysis [14]. In the field of patient near immediate laboratory examinations, the pre-analytical requirements with regard to glycolysis are lower, as both glucose determination on a patient near immediate laboratory examinations device and blood gas analysis, which today often includes glucose determination, can be carried out very quickly from whole blood. Glycolysis therefore plays a negligible role in these samples.

The objectives of the Rili-BAEK state [9]: "The objective of this guideline is to ensure, and constantly improve the quality of medical laboratory examinations, and to keep risks for patients and users to a minimum. It aims to ensure, in particular, that:

- influencing and confounding factors are minimised during the pre-analytical phase,
- medical laboratory examinations are conducted properly and factors influencing and confounding the results are identified and minimised and
- results are correctly assigned and documented, and a report is generated in compliance with information security and data protection regulations."

The topic of pre-analytics is closely linked to the measurand potassium. Important works on the subject of pre-analytics were published, for example, by the DGKC's Pre-analytics Working Group in 1998 [15]. An even older publication from 1974 is cited in the package insert for potassium from an important diagnostic company [16]. The book "Samples: From the Patient to the Laboratory" by Guder, Narayanan, Wisser and Zawta from 2008 is also recommended [17]. The analysis of potassium from heparin plasma is clearly favoured and justified here, as intracellular potassium is released from the thrombocytes to a considerable extent during the coagulation process that precedes serum formation. The potassium concentrations in serum are generally approx. 0.3 mmol/L higher than in plasma [18]. At higher platelet counts, this effect can increase to up to 2.0 mmol/L. This shows that the serum potassium values are artificially altered. The interfering factor – intracellular potassium from platelets – cannot be corrected by different reference ranges for plasma and serum, as these are individual characteristics. Potassium is a very frequently requested measurand. The clinical significance of altered potassium concentrations is evident in the field of cardiology and nephrology, so that the avoidance of interfering factors is necessary from the point of view of patient safety in order to fulfil the requirements of precision medicine in the field of laboratory medicine. The entitlement to treatment that meets the generally recognized professional standards is also set out in the German Social Code (SGB) Fifth Book (V) [19]. This aspect of pre-analytical procedures is mentioned in the DIN EN ISO 15189 as well [20].

Since the publication of Rili-BAEK 2023, the topic of pre-analytics has taken on a new significance within German laboratory medicine, which has led to public discussions, numerous talks and lectures. After professional associations initially called for the "orientating glucose determination from serum" to be retained at all costs, large sections of the community have now set out to implement these important pre-analytical guidelines in practice. Tubes with glycolysis inhibition for glucose determination were already being used by numerous laboratories before Rili-BAEK 2023. The number of laboratories has increased further since the introduction of Table B 1-1, thus achieving an important improvement in the quality of laboratory medical examinations. The fact that these special tubes are not economically covered by the EBM is the subject of critical discussion. However, this economic aspect should not be mixed up with the medical aspects explained above, but addressed in a separate discussion.

In the pre-analytics of potassium, the professional associations repeatedly talk about having to take an additional heparin plasma tube for potassium. It would be simpler to switch from serum to plasma for most clinical chemistry measurands, which is easily possible today and has been standard in many hospital laboratories for decades. In such a scenario, serum would be the additional tube required for serum electrophoresis and other specialised examinations, for example.

In the meantime, proposals for the other B parts are also being developed in the ongoing discussions on pre-analytics in the German Medical Association, so that the requirements of the Executive Board of the German Medical Association from 2019 are gradually being implemented – to improve patient safety.

Part B 5 was completely revised in the Rili-BAEK 2023. Numerous new technologies that have found their way into healthcare in recent years are now taken into account. The specifications for internal and external quality assurance are defined in various tables:

- specific molecular genetic examinations (already available)
- molecular genetic ctDNA examinations of solid tumours
- targeted molecular genetic, quantitative examinations for haemato-oncological diseases
- targeted molecular genetic examinations for haemato-oncological diseases in initial and relapse diagnostics
- molecular genetic cffDNA tests for the nominal determination of fetal sex and aneuploidy (non-invasive prenatal test – NIPT)

– high-throughput sequencing (molecular genetic examinations using next-generation sequencing – NGS)
– cytogenetic examinations (already available).

The criteria for validation were specified, and the aspects of post-analytics were expanded and concretised.

At the Advisory Board meeting on 15 April 2024, the decision was made together with the pathology representatives to expand the Rili-BAEK to include tissue-based pathology diagnostics. As a result, two further B parts will probably be created and the name of the Rili-BAEK will – once again – change after many decades.

This fundamental further development of the Rili-BAEK will be decided by all participating representatives of the Rili-BAEK Advisory Board and will be an important step towards increasing the quality of patient care through quality assurance in tissue-based diagnostics.

The following article is a translation of the current Rili-BAEK from 2023 [21]. It is the second translation after 2015 and enables international dialogue on quality assurance of laboratory medical examinations in Germany.

I would like to take this opportunity to mention the achievements of Dr Karl-Heinz Pick, who unfortunately passed away recently. He was heavily involved in the further development of the Rili-BAEK from 2002 to 2023 with great personal commitment. He was appreciated by all committee members for his objective work and his judgements carried a great deal of weight. I will greatly miss him and his advice as I continue my work for the German Medical Association.

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