

DKE - Roadmap

GERMAN STANDARDIZATION ROADMAP

Mobile Diagnostic Systems

Version 1.1



Published by

VDE ASSOCIATION FOR ELECTRICAL,
ELECTRONIC & INFORMATION TECHNOLOGIES

responsible for the daily operations of the

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Electronic & Information Technologies of DIN and VDE
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May 2015 (English Edition 1.1)

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1 PRELIMINARY REMARKS

Preliminary Remarks

Mobile diagnostic systems for *in vitro* diagnostic medical devices (IVD) are becoming increasingly significant in the field of point-of-care testing (POCT). With regard to the successful placing on the market, these systems face considerable challenges in technological, economical and regulatory terms. Furthermore, the development of robust, usable systems presents a further barrier, as well as integrating them in existing technical, computerized and organizational environments and procedures.

The German Commission for Electrical, Electronic & Information Technologies of DIN and VDE (DKE) and the German Society for Biomedical Engineering within VDE (DGBMT) have set up a working group to compile a standardization roadmap for mobile diagnostic systems. This roadmap features among others an analysis of technical and legal framework conditions, as well as an overview of the status quo of currently valid standards. It also gives recommendations for further activities as an important guideline for future mobile diagnostic systems in the regulatory and normative environment.

2 ABSTRACT

2.1 Framework conditions

The possibilities offered by conducting individual sample tests as well as the discontinuation of a complex sample preparation, together with the immediate availability of test results, open up various application fields for mobile diagnostic systems that frequently go well beyond the scope of a central laboratory. This results in specific requirements for the user and also special technical solutions.

The legal requirements for mobile diagnostic systems are defined in Germany by relevant EU directives together with national legislative and subordinate regulations. European legislation is currently being reformed with additional requirements for all stakeholders.

2.2 Specifications and standards for mobile diagnostic systems

The application of harmonized standards allows mobile diagnostic systems for *in vitro* diagnostic medical devices to fulfill the essential requirements of European legislation. There exist already many standards providing important assistance for the manufacturers and operators of mobile diagnostic systems. However, gaps have emerged in the current standards collection due to the special attributes of mobile diagnostic systems, together with technical progress.

2.3 Recommendations from the first German Standardization Roadmap for mobile diagnostic systems

Normative documents are intended to provide assistance among others for the following aspects involved in development, production and application of mobile diagnostic systems:

- development and validation of analytical methods,
- consideration of regulatory requirements during development,
- interoperability,
- qualification of supplied parts,
- quality assurance of the test results,
- data security, collection and control,
- training and competence of the professional users, and
- maintenance and servicing of the mobile diagnostic systems.

Furthermore, the above mentioned reform of EU legislation will also require the elaboration or amendment of normative documents for practical implementation.

One particular challenge in the medical technology branch consists in the particularly large number of small and medium-sized enterprises (SME). On the other hand, usually such SME neither have sufficient resources to fulfill regulatory requirements, nor do they play an active role in the standardization process. One possible solution could consist in intelligent funding for knowledge transfer and ensuring that the SME become actively involved in this process.

3 INTRODUCTION AND BACKGROUND

3.1 Definition, special aspects and generic structure of mobile diagnostic systems

3.1.1 Definition of a mobile diagnostic system according to the Standardization Roadmap

Mobile diagnostic systems cover various classes of medical devices. This Standardization Roadmap addresses IVDs pursuant to the EU directive 98/79/EC in the area of POCT or “remote analysis”.

Point-of-care testing (POCT) is generally deemed to include those test methods used directly at or near the site of patient care. The Guideline of the German Medical Council for Quality Assurance of Medical Laboratory Tests (RilibÄK) refers to POCT as “immediate near patient testing”, using the following defining criteria:

- individual sample testing,
- no sample preparation (e. g. centrifugation) and
- direct conclusion of resulting treatment by the attending physician.

3.1.2 Special aspects of mobile diagnostic systems in the POCT field

The use of mobile diagnostic systems permits immediate diagnosis directly at the point-of-care (POC) and remote from the classic central laboratory in a hospital, clinic or laboratory medicine practice setting without any special operation infrastructure. POC diagnosis differs from diagnosis in the central laboratory primarily in terms of sample throughput, device size and space resources. The main differences consist in how the tests are used and conducted. In the central laboratory, IVDs are used only by specially trained staff. By contrast, a POC assay is carried out by physicians, nursing staff or paramedics who do not necessarily have to have special training. According to the RilibÄK guideline, user training by the POCT representative is sufficient. This can only work if this fact is taken into account in the basic design and application protocol of the POC assays with regard to the application safety and quality assurance.

Manufacturers can only guarantee the application safety by stipulating precise rules for conducting the tests. All additional manual work steps, such as those carried out in the application protocols by the specially trained staff in the central laboratory, would in principle be unsafe on account of their complexity and could therefore generate incorrect results.

Isolated cases of incorrect use are observed even in the central laboratories when the trained users try to shorten the test procedures.

For this reason, many POCT products are designed with a few special features compared to equivalent tests in the central laboratory, in order to rule out the risk of incorrect use as far as possible:

- the sampling procedure is specified with internal tests for verification,
- the cartridges or strips are ready for immediate use,
- test reagents are designed for unit-use and user-friendly application,
- sample preparation in the cassette/strip with all subsequent process steps,
- automated test evaluation is often integrated in the devices, and
- where rapid tests are concerned, the reagents are usually provided in the corresponding test formats.

3.1.3 Generic structure of mobile diagnostic systems

There are already many POCT systems on the market at present. An analysis of their structure reveals clearly generalized process blocks from the patient sample to the result (Fig. 1). The process begins with taking the sample from the patient. This step constitutes the start of the test application, because already at this point the IVD manufacturer has to ensure that the sampling, storage and transfer of the patient sample is simple and robust without any risk of incorrect use. After the sample has been taken, it is then processed. Having whole blood as sample material for example, the test usually involves separating the blood cells from the plasma. Processing takes place inside the cassette or strip. At this point, the sample matrix and analyte are prepared for optimal measurement. Signal amplification may be necessary (e. g. in the form of a biochemical reaction), depending on the analyte concentration in the sample and to increase sensitivity.

From the development engineer's point of view, the generic structure of mobile diagnostic systems can be visualized as follows (Fig. 1).

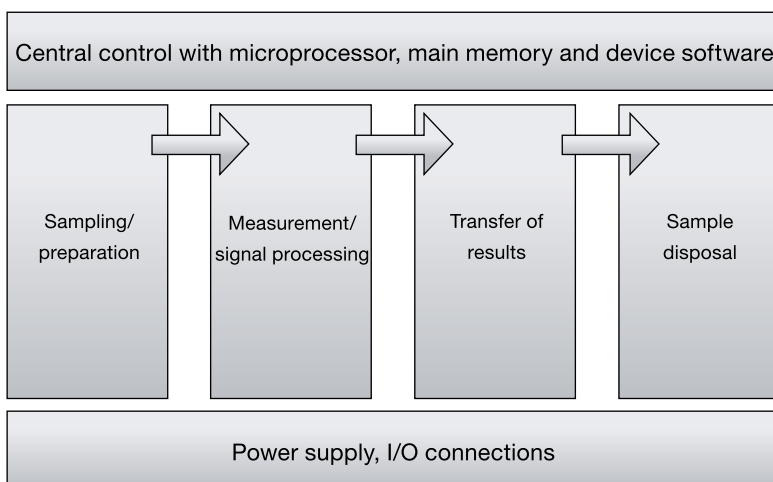


Figure 1: Generic structure of a mobile diagnostic system with its main components

3.2 Framework conditions

3.2.1 Possible application areas of mobile diagnostic systems in the context of social developments and future requirements of the healthcare system

Diagnostics plays an important role in medicine. About two thirds of all clinical diagnoses are based primarily on laboratory tests. Laboratory diagnostics permits the early detection of diseases with prompt corresponding treatment. Laboratory tests steer and monitor therapy decisions, for example when administering medication. The share of laboratory expenditure in overall expenditure by the German national health insurance funds decreased from 3.3% in 1995 to 2.9% in 2011. At the same time, there has been a clear increase in the number of laboratory tests performed. The Federal Statistical Office stated that laboratory expenditure by the national health insurance funds amounted to €5.038 billion in 2012 (outpatient tests: €2.118 billion, inpatient tests: €2.892 billion) [1].

Mobile diagnostic systems are suitable for many different uses because they are compact, the samples do not have to be transported and the test results are available immediately (Fig. 2). In this respect, the outpatient sector differs greatly from one country to the next. While many countries have community centers or outpatient clinics [2], Germany has a well developed structure of general practitioners and specialists/consultants. There are also contexts outside the classical healthcare sector, such as special fields as civil protection or the military area [3]. Applications are also conceivable in homecare and Ambient Assisted Living (AAL), for instance to optimize patient monitoring or to allow continuing an independent life in their own home. Increasing numbers of mobile diagnostic systems are also being used in the secondary healthcare market, the fitness branch and in self-monitoring.

Various economic driving forces can be identified for mobile diagnostics. Together with potential improvements in healthcare provision, these also include the pronounced pressure on costs in the healthcare sector, applying particularly to the diagnosis-related group system (DRG) in the hospital sector where payments are made in fixed amounts based on the main and secondary diagnosis/diagnoses, degree of severity and main services performed. Applying mobile diagnostics here can make sense also in purely economic terms, e. g. by reducing the time spent in hospital. It is therefore no great surprise that the greatest growth rates are anticipated for the hospital sector [4]. The situation on the outpatient sector is different. Here a uniform assessment standard (EBM) is used, where a reimbursement is allocated to the provided (diagnostic) services.

Considered individually, mobile diagnostics is frequently more expensive than laboratory diagnostics so that this reimbursement type would not appear to promote the use of mobile diagnostics [3]. However, this only applies to services billed through the national health insurance funds. When it comes to individually provided health services (IGeL), i. e. services paid by the patients, there can definitely be a greater willingness to pay for faster mobile diagnostics. Furthermore, reimbursement based on the scale of fees for physicians (GOÄ) is higher than EBM. The homecare market is therefore also seen as an important growing market [4]. Moreover, the demographic change forecast for Germany over the next few years may also increase the use of mobile diagnostic systems. The alteration in age structure will result in a large number of age-related diseases respectively multi-morbidity. The number of those aged 65 years and older will increase by a third through 2030 and amount to 22.3 million people or 29% of the total population [5].

These developments are joined by a decline in the number of physicians in private practice in some parts of Germany, presenting major problems for Germany's medical healthcare system. In the new federal states, the number of general practitioners has declined by 1041 physicians (11.4%) already since 1999 [6]. The remaining physicians will need swift diagnosis data to cope

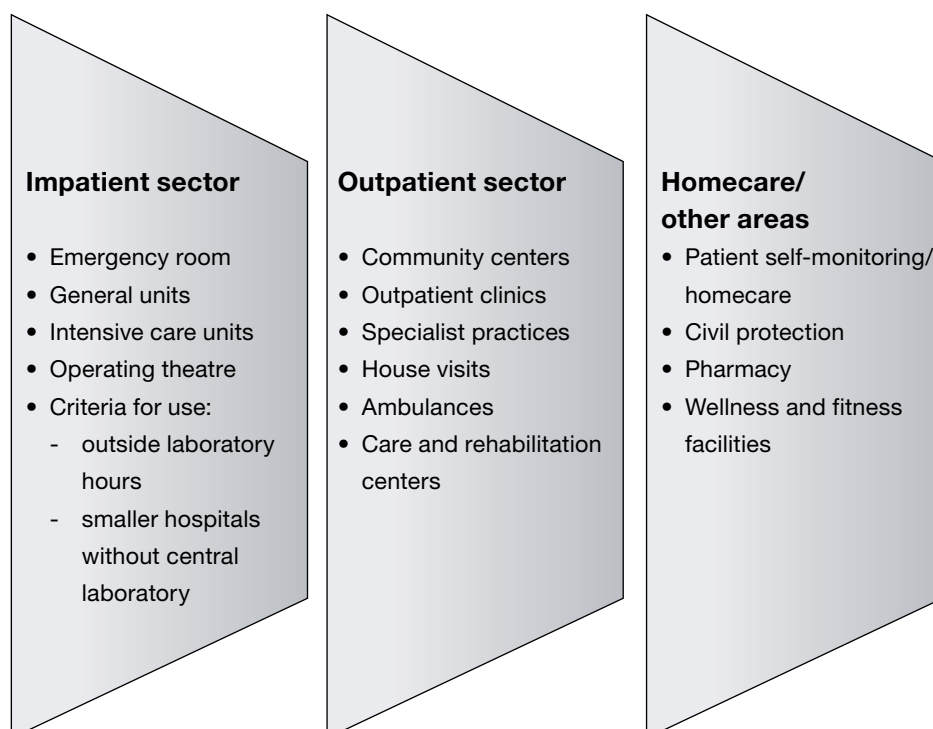


Figure 2: Applications for mobile diagnostic systems, adapted from [3]

with a larger number of patients; the data could be provided not just by the classic large laboratories but also by mobile diagnostic systems in the physicians' own practice facilities.

3.2.2 Benefits of the mobile diagnostic systems for various stakeholders

Various people and organizations have an interest in using mobile diagnostic systems, as expressed in a range of different advantages, added values and chances:

Advantages for medical laboratories

- Predictable availability of test results in emergency situations helps to avoid wasting time by repeatedly checking with the central laboratory.
- Shorter or discontinuation of sample transport reduces negative impacts on the sample and reduces pressure on internal logistics.
- Because cold storage of samples is not necessary costs will be decreased.
- Flexible use of devices is attractive for small hospitals in particular.
- Devices often are analytical systems which can be used easily.
- Tests can also be conducted by staff without any chemical laboratory training.

Advantages for the healthcare system

- Affected patients can be handled as outpatients, thus reducing the financial burden on the healthcare system.
- Hospitals can manage with smaller laboratory premises.
- Faster diagnosis with immediately available test results can reduce the patient's length of stay in hospital [7]. POCT devices have a very short turnaround time (TAT) between requesting the test and receiving the results, compared to routine laboratories. A POCT study carried out by the Charité hospital in Berlin verified a greatly reduced TAT for troponin-I assay [8]. Another study clearly revealed that POCT devices for detecting C-reactive protein (CRP) in patients with acute coughing symptoms [9] can reduce the incorrect use of antibiotics. On the other hand, a current review of 84 studies using 5 POCT instruments indicated that POCT had only a minimum impact on clinical practice [10].
- Faster availability of test results expands the possible uses, e. g. in ambulances or in civil protection.
- Individual health management and mobile home nursing services can be improved by services available outside actual medical care.

Added value for individuals and end users

- Mobile diagnostic systems can offer appropriate support in outpatient and also hospital care when a physician is not always available.

Chances for research and development

- Special requirements such as product usability give new research impetus with further improvements in other application and research areas.
- Product conformity in the entire system, e. g. in the hospital context, is a particular technical challenge.
- Interoperability and interconnectivity processes are already being supported during the product development phase.
- There is an increased transfer of innovative ideas and results to the standardization process.

Chances for the healthcare sector, SMEs and test institutes

- Additional tasks are created in certain jobs and professions.
- Additional qualification and further training possibilities are created.
- The use of innovative technology is promoted.
- New test fields are provided.

3.2.3 Key technologies

3.2.3.1 Sample types

The following sample materials are used in POCT applications:

Table 1: Sample types

Initial sample	Use/materials
Swab samples	Diagnosis of infections, taking samples with standard swab (nasal vestibule and oral cavity), vaginal swabs and brushes, nasopharyngeal and urethral swabs and swabs for gingival pockets
Arterial blood	Arterial blood gas test (ABG)
Exhaled air	Drug/medication screening, testing for diagnostic metabolites such as acetone, ammonia and NO
Sputum	Evidence of <i>Mycobacterium tuberculosis</i> and other respiratory diseases
Capillary blood	Most frequent sample material in the homecare sector, e.g. fingertip blood for glucose tests and other uses
Sudor	Drug screening
Saliva	Tests for special parameters, diagnosis of infections
Sperm	Fertility tests
Stool	Tests for occult blood in stool and diarrhea
Tear fluid	Tests for special parameters, e.g. interleukins [11]
Urine	Urine test strips (pH, protein, glucose, ketones, bilirubin, urobilinogen, nitrite, leucocytes), pregnancy test
Venous blood	Most frequent sample material in the hospital sector, e.g. blood cell tests (erythrocytes, leucocytes, thrombocytes or CD4-positive and CD8-positive lymphocytes)

3.2.3.2 Device categories

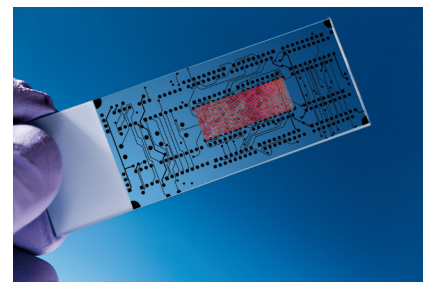
Various different devices are currently available on the diagnostic market, ranging from compact hand-held devices to bench-top systems. The POCT devices are almost completely automatic and require only very simple handling by the user from sample preparation until the test result.

A number of concepts have become successfully established in recent years such as hand-held devices, other unit-use systems, stationary bench-top devices or lab-on-a-chip systems.

POCT systems can be divided into the following categories [12]:

Test strips

Tests of this kind produce qualitative results (positive/negative responses). Lateral flow test strips (immuno-chromatography) are well-known technological applications. The read-out of these tests is frequently visual. Sample material often includes blood, urine, stool, liquor and swab samples. Tests of this type are used for urine analysis and pregnancy tests, for diagnosing infections and for emergency diagnosis (heart attacks). μ Pads (*microfluidic paper-based analytical devices*) represent a new trend in this category.



Unit-use POCT systems

Classic unit-use POCT systems have individually packed detection cartridges or strips. Whole blood is used in most of these systems. In contrast to the device-free test strips, in this case a small (portable) user device is needed to read the results from the sensors integrated in the strip. The reagents are also stored in dry state on the chip/strip.

Bench-top devices

The main difference to unit-use POCT systems consists in the size of the devices. Bench-top devices are larger systems that have a bigger platform and are mainly used on desks and laboratory benches. This group includes many devices for a wide range of applications, including blood gas analysis, clinical chemistry, immunoassays or cell counts.

Viscoelastic coagulation analyzers

The results of various tests are analyzed in combination for hemostaseology. One example here is the viscoelastic coagulation test based on three different tests (plasma coagulation, thrombocyte function and fibrinolysis).

Molecular diagnostic systems

This is a relatively recent system group; in theory, it could be allocated to the bench-top devices. However, it is appropriate to classify these systems in a separate category because they all share the attribute of performing molecular diagnostics.

Molecular diagnostics refers to using molecular biology methods for protein, RNA or DNA diagnostics associated with pathological changes or for identifying/characterizing viruses and bacteria associated with infections. Most systems currently focus on nucleic acid analysis.

New classes of mobile diagnostic systems

The category of unit-use POCT systems is currently seeing an increasing development towards smart phone applications. There are already initial systems for using smart phones for measuring blood glucose levels.

It is conceivable that these mobile diagnostic systems will become established as a market segment in their own right so that it makes sense to list them as a new category of POCT systems. The rapid growth in these applications prompted the Food and Drug Administration (FDA) to issue a guideline in September 2013 for the use of "Mobile Medical Applications".

3.2.3.3 Bioanalytical parameters

POCT laboratory parameters differ according to the specific issue. They can be listed according to application area and analyte class (see tables 2 and 3). The application areas frequently have a historical origin resulting from the various medical departments in a hospital.

Table 2: Bioanalytical parameters classified according to application areas, adapted from Luppa and Schlebusch [12].

Application area	Analytes
Coagulation analysis (hemostaseology)	Various coagulation parameters (plasma coagulation, thrombocyte function and fibrinolysis)
Diabetes mellitus care	Glucose, HbA1c, ketones
Gynecology	Hormones, sperm (fertility)
Hematology	Hemoglobin, hematocrit, blood cells (erythrocytes, leucocytes, thrombocytes)
Infectiology	Antigens, antibodies, nucleic acid [13]
Intensive care	Blood gas analysis (oxygen saturation, oxygen and CO ₂ partial pressure) and acid-base balance (pH), acute phase proteins (CRP, interleukin levels, TNF α), electrolytes
Cardiology	Cardiac markers (troponin T, NT-proBNP)

Table 3: Bioanalysis parameters categorized according to analyte classes

Application area	Analytes
Blood gas and acid-base balance	Oxygen and CO ₂ partial pressure, pH
Coagulation	Activated clotting time (ACT), thromboplastin time (quick test, INR), partial thromboplastin time (PTT), bleeding time
Drugs	Alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates
Human cells	CD4-positive and CD8-positive lymphocytes, sperm, erythrocytes, leucocytes, thrombocytes
Ions	Na ⁺ , K ⁺ , Cl ⁻ , Ca ²⁺ , Mg ²⁺ , Li ⁺
Combined tests and staining methods	Urine (measured with test strips for determining pH, protein, glucose, ketones, bilirubin, urobilinogen, nitrite, leucocytes), occult blood in stool
Lipids	Cholesterol, triglycerides
Metabolites and low-molecular compounds	Ammonia, urea, uric acid, bilirubin, creatinine, lactate, glucose
Nucleic acids	Pathogens, RNA and DNA testing with genes resistant to antibiotics, genetic predisposition testing
Pathogens	Influenza A + B, streptococci, <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , <i>Trichomonas vaginalis</i> , <i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , HIV, <i>Helicobacter pylori</i> , <i>Clostridium difficile</i> , norovirus, <i>Mycobacterium tuberculosis</i> , respiratory viruses and bacteria, gastrointestinal (GI), meningitis/encephalitis, blood culture identification (BCID), sexually transmitted infections (STI), as well as panel testing: sepsis
Peptides	Hormones (HCB, LH, FSH, TSH), interleukins
Proteins	Enzymes (amylase, alkaline phosphatase, CK, AST, ALT, γ-GT). Other proteins: alpha hemoglobin (hbA1), D-dimer troponin T + I, myoglobin, CRP, pro-calcitonin, PSA, antibodies (auto-antibodies, allergen-specific IgE, pathogen-specific antibodies)

3.2.3.4 Detection principles and determination methods

Mobile diagnostic systems can use different detection principles and determination methods. The following list shows a selection, adapted from Maier [14]:

- amperometric detection
- CO oxymetry
- pressure measurement
- electrochemical detection
- enzymatic detection
- immunochemical detection
- ion-sensitive electrodes
- conductometric detection
- optoelectronic detection
- optode fluorescence
- optical reflection
- photometric detection
- potentiometric detection
- turbidimetric detection

3.2.4 Manufacturing mobile diagnostic systems

In the medical devices sector, mobile diagnostic systems have specific attributes (see 3.1) so that the respective manufacturers have to take those into account during development and production.

3.2.4.1 Users and requirements

The handling of mobile diagnostic systems frequently needs no in-depth medical training or experience in the field of laboratory medicine, resulting in a far larger user group than for central laboratory equipment:

- professional users in the medical sector (nursing staff, physician assistants, laboratory staff and physicians),
- mobile diagnostic systems used directly by the patient (homecare),
- requirements made by the user groups:
 - o quick and easy handling,
 - o same test quality as in the central laboratory,
 - o automatic documentation of test results,
 - o simple calibration and quality control, and
 - o low usage costs throughout the entire lifecycle.

As a result of these requirements, the manufacturer has to pay special attention to device usability.

3.2.4.2 General and specific sites of use

Together with the requirements of any medical devices in terms of reliability, robustness and safety, the additional application sites for mobile diagnostic systems result in further necessary attributes. Mobile diagnostic systems are used in the emergency room, on the hospital station, in the physician's practice, in the ambulance or also in the domestic setting, including both indoor and outdoor applications under conditions that are both controlled and not controlled in terms of ambient parameters (e. g. temperature, humidity and shock resistance).

3.2.4.3 Sales channels

Large medical devices for physicians' practices, hospitals and laboratories are normally sold through the wholesale or directly by the manufacturer. Simpler mobile diagnostic systems such as blood glucose meters can also be purchased through the retail trade such as healthcare supply stores, pharmacists and online platforms. Manufacturers must therefore also presume that the devices will not always be transported and stored correctly, so that this must be taken into account already during the development phase.

3.3 Legal requirements

Market access for mobile diagnostic systems as IVDs is regulated by European and German legislation. Failure to comply results in considerable liability risks. Manufacturers, distributors and operators of medical devices must therefore become familiar with the regulatory requirements already at the beginning of the product lifecycle.

3.3.1 European legislation

As a rule, mobile diagnostic systems are covered by the EU directive on *in vitro* diagnostic medical devices 98/79/EC. In exceptional cases, the EU directive concerning medical devices 93/42/EEC may also apply, as amended by EU directive 2007/47/EC.

EU medical device legislation is currently being reformed. The consultations on the European Commission's proposal for a Regulation of the European Parliament and the Council on *in vitro* diagnostic medical devices (COM(2012) 541 final) are still in progress. The regulation will be directly applicable, so that a German implementation law is not necessary. Among others, the regulation will introduce stricter requirements for quality assurance when introducing POC diagnostic devices on the market.



3.3.2 National legislation

EU directives are legal instruments of the European Union and have to be implemented in national law within a certain period of time. As far as medical devices are concerned, the Medical Devices Act (MPG) implements applicable EU directives in national legislation. The MPG refers repeatedly to the EU directives and their annexes, for example with regard to conformity assessment and CE certification. Compliance is also required with the Medical Devices Advertising Law (HWG) which regulates advertising for medical devices and therefore has high practical significance in terms of marketing.

3.3.3 National regulations and guidelines

Numerous national regulations exist below the legislative level. They put the legislative requirements into concrete terms and are just as legally binding as laws. The following Figure 3 shows the main statutory regulations together with the general administrative regulations for implementing the MPG:

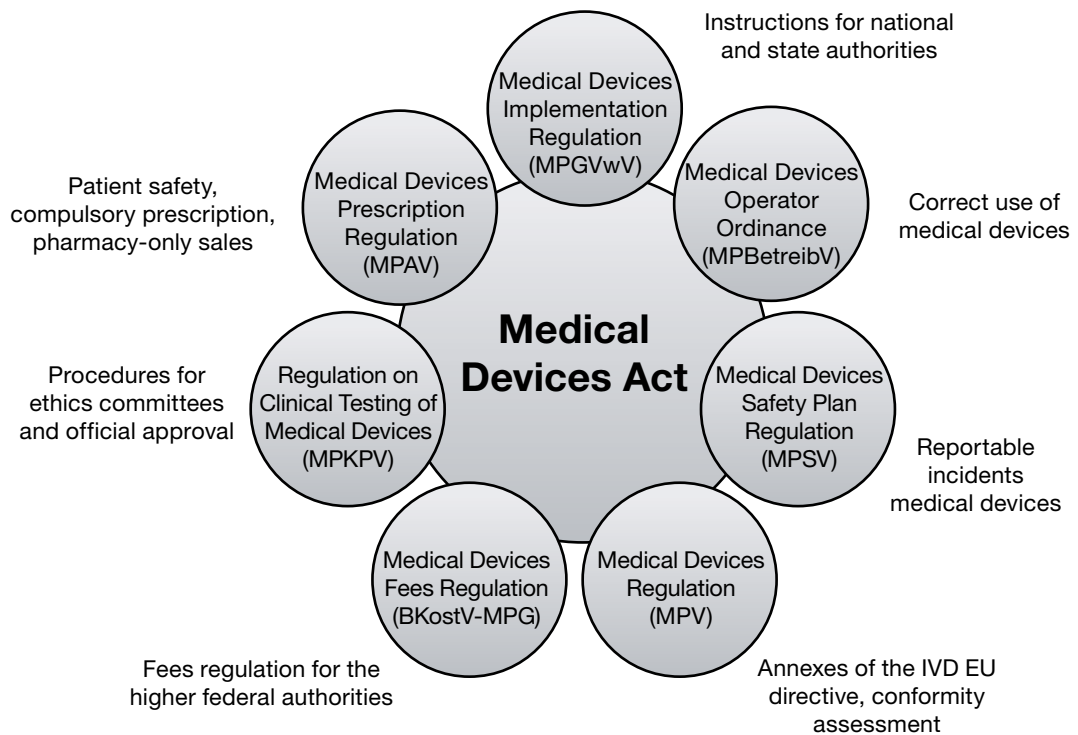


Figure 3: German legislation and subordinate regulations for medical devices

Some of the named regulations are highly significant for the manufacturers of mobile diagnostic systems. The Medical Devices Operator Ordinance (MPBetreibV), the Medical Devices Act (MPG) and the RiliBÄK guideline are addressed to the operator of the medical device and require among others the implementation of a total quality management system (QMS) for all medical laboratory tests and, thus, also for all tests carried out with a mobile diagnostic system. Even if the manufacturer is not directly affected, he should become familiar with these provisions because details given by the manufacturer regarding measuring accuracy and maintenance etc. provide important parameters and reference points for the respective QMS processes. In Germany, if a mobile diagnostic system is placed on the market as a medical device, it is presumed that the manufacturer has issued the requisite EC Declaration of Conformity and that the medical device has a corresponding CE marking. To this end, the manufacturer is responsible for carrying out a conformity assessment procedure. Article 9 of EU directive 98/79/EC stipulates that IVDs are to be classified as high-risk and risk products (Annex II, List A and B), devices for self-testing and all remaining IVDs.

3.3.4 Other legal regulations

Using mobile diagnostic systems frequently results in personal data capture which is covered by the Federal Data Protection Act (BDSG) or the respective state privacy legislation. Which law is applicable in each case depends on whether a federal or state public agency is affected or a non-public agency. The BDSG applies to German private law companies such as GmbHs, KGs, AGs or OHGs, while the respective state legislation applies to a university hospital, for example.

3.4 Guidelines, guides and other resources for developing medical devices

3.4.1 Medical Devices Guidelines (MEDDEV)

The European Commission has issued a series of MEDDEV guidelines which are to be treated as an aid for interpreting the legal requirements being frequently both vague and complicated.

MEDDEV 2.7.1 Rev.3	Clinical evaluation: a guide for manufacturers and notified bodies
MEDDEV 2.14/1 Rev.2	IVD Medical Device Borderline and Classification issues: a guide for manufacturers and notified bodies
MEDDEV 2.14/2 Rev.1	IVD Guidances: research Use Only products/A guide for manufacturers and notified bodies
MEDDEV 2.14/3 Rev.1	IVD Guidances: supply of Instructions For Use (IFU) and other information for In-Vitro-Diagnostic (IVD) Medical Devices/A guide for manufacturers and notified bodies

3.4.2 Borderline manual

This manual provides instructions from the European Commission for the classification of borderline devices in medical technology. It is difficult to differentiate clearly between the medical devices featured here and other risk products. The manual is not legally binding and only reflects case-by-case opinions of the Commission.

Borderline manual	Manual on borderline and classification in the Community Regulatory framework for medical devices
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3.4.3 International guidelines

3.4.3.1 Guideline for method validation in bioanalytical test procedures

Mobile diagnostic systems are based on the development of bioanalytical test procedures. Correct method validation for these test procedures must be heeded already in the development phase. O’Kane and colleagues examined the error rates in POC measurements and found that 2/3 of the errors occurred during the analytical measurement phase [15]. Furthermore, various publications refer to significant error prevalence in the pre- to post-analytical phase in laboratory tests [12]. In a study carried out in 2012, 7 of 34 examined blood glucose meters failed to achieve the accuracy required in ISO 15197 [16]. The Federal Institute for Drugs and Medical Devices (BfArM) also reported 1905 false-positive/negative test results between January 1, 2005 and December 31, 2013 in finally assessed risk reports.

The following documents for validating test procedures describe the parameters for the validation of analytical methods together with the necessary experimental data and corresponding statistical analysis. However, test validation is still difficult to implement in practical terms, with frequently no answer available particularly for the question which parameters are necessary for valid interpretation of the results [18].

ICH Q2(R1) for the EU, Japan and the USA	Validation of Analytical Procedures: Text and Methodology
FDA	Guidance for Industry: Bioanalytical Method Validation
EURACHEM Guide	The Fitness for Purpose of Analytical Methods: a Laboratory Guide to Method Validation and Related Topics
EMEA	Guideline on bioanalytical method validation

3.4.3.2 Guideline for conducting clinical tests of medical devices

The harmonized ICH guideline E6(R1) for the EU, Japan and the USA on Good Clinical Practice provides an international, ethical and scientific standard for planning, conducting, documenting and reporting on clinical tests on humans.

ICH E6(R1)	Good Clinical Practice
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3.4.4 Other resources

Documents interpreting the statutory regulations for medical devices can be found on the following websites.

International Medical Device Regulators Forum	http://www.imdrf.org/index.asp
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TEAM NB – The European Association for Medical devices of Notified Bodies	http://www.team-nb.org
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NBOG – Notified Body Operations Group	http://www.nbog.eu
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ZLG – Central agency of the German states for health protection with regard to drugs and medical devices	https://www.zlg.de/medizinprodukte.html
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3.5 Medical technology at the VDE: science and standardization

3.5.1 The German Society for Biomedical Engineering within VDE (DGBMT)

The German Society for Biomedical Engineering within VDE (DGBMT) currently has more than 2,700 members, making it the largest scientific technical association of the medical technology sector in Germany. It was founded 1961 in Frankfurt/Main. As one of the five technical societies of the VDE, the DGBMT promotes the cooperation between scientists, engineers and physicians in research, development, application and teaching in the sphere of medical technology. To this end, the DGBMT organizes numerous events such as expert talks, workshops and conferences. The focus is spread across the full range of topics involved in innovative medical technology from research through to clinical application. The DGBMT office handles certain priority themes in various projects. In particular, this includes supporting research and network projects to accelerate the transfer of ideas from research into patient care. The DGBMT experts are organized in 20 different technical committees where they look at central research and innovation topics in biomedical engineering.

3.5.2 The German Commission for Electrical, Electronic & Information Technologies of DIN and VDE (DKE)

The DKE German Commission for Electrical, Electronic & Information Technologies of DIN and VDE is a modern, non-profit service organization which ensures that electricity is generated, distributed and used in a safe and rational manner, thereby serving the good of the community at large. The DKE is the national organization responsible for the creation and maintenance of standards and safety specifications covering the areas of electrical engineering, electronics and information technology in Germany. DKE work results are published as DIN standards in the German standards collection or as DIN SPEC (prestandards) or accompanying sheets by DIN. DKE electrotechnical safety standards receive a VDE classification number in addition to the DIN number and are included in the VDE Specifications Code of safety standards under the VDE number. The DKE supports its partners in standardization activities. Working on the basis of research and development in innovative areas of technology, it is important to detect and take up new trends in medical technology and healthcare for forwarding to the corresponding technical bodies. With its networks, the DKE facilitates the sharing of information for and with experts together with prompt implementation of obtained findings, using among others VDE application guidelines to promote the transfer of knowledge and technology among the participating organizations, also accelerating this process by making effective use of resources (e. g. information, workflows). The DKE represents the interests of the electrical/electronic engineering and information technology sectors in international and regional electrotechnical standardization. It is an organization of DIN German Institute for Standardization and the VDE Association for Electrical, Electronic & Information Technologies.

3.6 Standardization

3.6.1 Structure of the standardization landscape

Standards and specifications are developed on various levels (National, European, International) in different organizations. So-called interested circles (companies, the retail sector, universities, consumers, skilled trades, testing institutes, authorities, etc.) delegate their experts to working groups and technical bodies of a standardization organization. This is where the standardization work is organized and carried out. For a better understanding, the following section presents an overview of the standardization organizations and their relationships. The major standardization organizations on the international level are ISO (International Organization for Standardization), IEC (International Electrotechnical Commission) and ITU (International Telecommunication Union).

The responsible standardization organizations on a European and national level are CEN European Committee for Standardization and DIN German Institute for Standardization together with CENELEC European Committee for Electrotechnical Standardization, ETSI European Telecommunications Standards Institute and DKE German Commission for Electrical, Electronic & Information Technologies of DIN and VDE (see Figure 4). The respective national standardization organizations are also members of ISO, IEC, CEN and CENELEC.

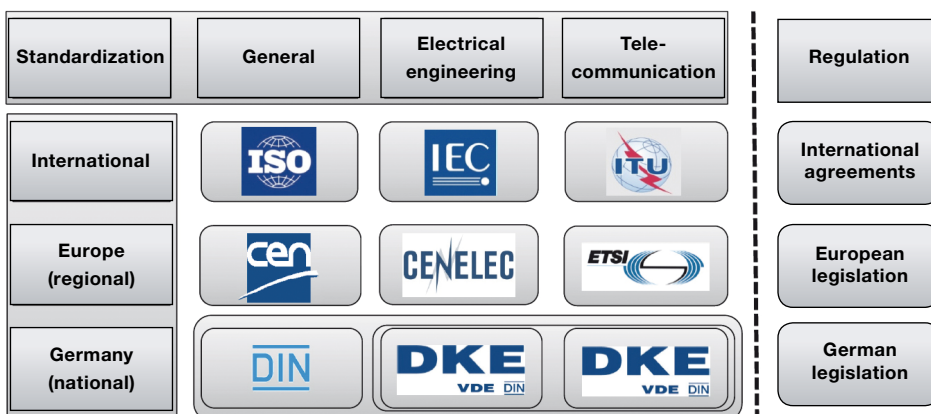


Figure 4: Main elements of the national and international standardization landscape in relation to regulation

3.6.2 DIN, CEN and ISO

DIN offers stakeholders a platform for the development of standards and specifications as a service to industry, the state and society as a whole. DIN is a private organization with the legal status of a non-profit association. Its members include businesses, associations, authorities and other institutions from industry, commerce, trade and science.

DIN's primary task is to work closely with its stakeholders to develop consensus-based standards that meet market requirements and the particular timeframe. By agreement with the German Federal Government, DIN is the acknowledged national standards body that represents German interests in the European and international standardization organizations.

Today almost 90% of the standards work carried out by DIN is European and/or international in nature. The members of staff at DIN organize the whole process of non-electrotechnical standardization on the national level, with the corresponding national bodies safeguarding German participation on the European and international level. DIN represents Germany's standardization interests as a member of CEN and as a member of ISO.

3.6.3 DKE, CENELEC and IEC

The DKE is responsible for the standardization work that is dealt with in the corresponding international and regional organizations (IEC, CENELEC). It therefore represents German interests in CENELEC and in IEC. For more details, please refer to section 3.5.2.

3.6.4 Producing standards

Certain principles have to be fulfilled in order to produce a standard. If the principles have been heeded and the standard compiled, the proposal for standards work is submitted for review by the respective committee. Once approval is given, a draft proposal is compiled and adopted on completion. It then acts as the basis for producing, reviewing and publishing a manuscript for the draft standard. This is followed by an objection period during which anyone can submit comments on the draft.

The body then discusses the submitted opinions; under certain circumstances, extensive objections may make it necessary to produce a second draft standard. Otherwise the comments are processed accordingly so that a final version of the standard can then be adopted.

The manuscript goes through another review before producing a control proof, after which the standard becomes part of the German standards collection and is published.

Specifications differ from standards and do not have the de jure status of a standard. Specifications are developed and published by many different bodies. The word "standard" is frequently used with different meanings. This is because the English "standard" is the direct equivalent to the German word "Norm", while the German word "Standard" or "Specification" means a de facto standard in English. In contrast to standardization, specifications do not have to take account of all ten principles. As long as a specification does not go through a public objection process, aspects such as the "everyman principle", for example, and public consensus building have limited relevance (see Figure 5).

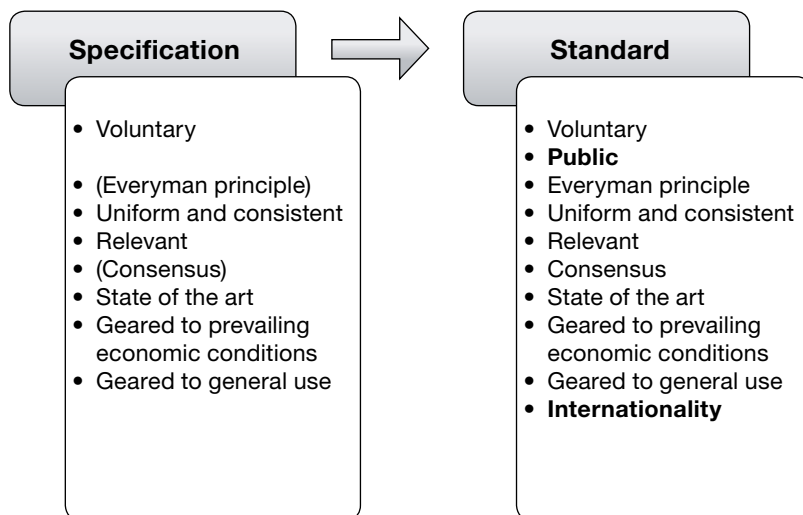


Figure 5: Attributes of specifications and standards in comparison

3.6.5 Benefits of standardization

3.6.5.1 Prejudices on standardization

Standards and specifications are taken for granted on an everyday basis and frequently used without knowing what they actually entail. There are also many prejudices on standardization. It is generally presumed that standardization "only affects big business", resulting in ignorance about the rules for producing standards so that many claim that the regulations and formal approach are too complicated.

One frequent criticism is that standardization takes too long on account of the many stakeholders involved and the resulting consensus process. However, specifications can be used as a pre-standardization document, providing a tool for accelerating the process.

3.6.5.2 Standards and specifications prepare markets

Broad-based implementation of mobile diagnostic systems needs to take account of individual requirements as well as providing the necessary flexibility. The costs of system components play a crucial role in acceptance among both manufacturers and final customers, thus also affecting marketability. These costs can be reduced not just through innovations but to a major extent through quantity effects as well. Standardization can help to remove trade barriers and open up global markets for products, innovations and services [19].

Standardization work is of major importance particularly for the following tasks:

- The many different requirements made by the heterogeneous users demand high system compatibility and a high level of interoperability. The required interoperability of components expects a detailed gap analysis in the regulations together with explicit standardization work.
- The comprehensive safety of electronic products and systems must be safeguarded by generally accepted rules and test procedures, with objective verification.
- Every effort must be made to accelerate the dissemination of technical innovations through top quality consulting and a professional approach to mobile diagnostic systems by developing new job profiles. Knowledge transfer can only be assured through qualified staff.

4 STANDARDS, SPECIFICATIONS AND GUIDELINES

Standards exist for practically all technical areas and are frequently also taken into consideration for contractual agreements. Standards can be categorized according to their particular task areas as follows:

- Terminology standards,
- Quality standards (e. g. DIN ISO 9000 et seq. and DIN EN ISO 13485),
- Dimensional and requirement standards,
- Safety standards, e. g. DIN EN 61010-1 (VDE 0411-1) and
- Test standards.

Some general standards (e. g. DIN EN 61010-1) with general stipulations are accompanied by collateral standards (e. g. DIN EN 61010-2-101/VDE 0411-2-101) with additional general requirements and tests for many products in medical use. There are also particular standards that reference to the general standard and its collateral standards. They supplement or replace the requirements and tests stipulated in the general standard, with the corresponding changes taking priority over the general stipulations. This roadmap only refers to standards down to the level of collateral standards, which means that additional particular standards may apply to certain medical devices. The scope of standards may be limited in both professional and regional terms.

As a basic principle, standards are applied on a voluntary basis. But the application of standards for medical devices leads to the presumption that the corresponding legal provisions are fulfilled.

The following section gives an overview of standards and specifications applying to mobile diagnostic systems as featured in this roadmap. They are classified according to standards for specific devices and standards that are relevant for the manufacturer and operator. A complete list of the valid standards for every single kind of mobile diagnostic system is beyond the objective of this standardization roadmap. A comprehensive list of harmonized standards can be found in the Official Journal of the European Union "Commission communication in the framework of the implementation of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices".

4.1 Standards applying to devices

4.1.1 Safety and ergonomics

The following standards describe the requirements for sterility, biological risk assessment, electrical/mechanical safety, electromagnetic compatibility and usability.

DIN EN 556-1	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices
DIN EN 556-2	Sterilization of medical devices - Requirements for medical devices to be designated, "STERILE" - Part 2: Requirements for aseptically processed medical devices
DIN EN ISO 10993	Biological evaluation of medical devices
DIN EN 60601-1-6 / VDE 0750-1-6	Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance
DIN EN 61010-1 / VDE 0411-1	Safety requirements for electrical equipment for measurement, control and laboratory use - Part 1: General requirement - Collateral standard: Usability
DIN EN 61010-2-101 / VDE 0411-2-101	Safety requirements for electrical equipment for measurement, control and laboratory use - Part 2-101: Particular requirements for <i>in vitro</i> diagnostic (IVD) medical equipment
DIN EN 61326-2-6 / VDE 0843-20-2-6	Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 2-6: Particular requirements - <i>in vitro</i> diagnostic (IVD) medical equipment

4.1.2 Software

DIN EN 62304 describes the requirements applying to the development and maintenance of medical software.

DIN EN 62304 / VDE 0750-101	Medical device software - Software life cycle processes
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4.2 Standards applying to manufacturers

4.2.1 Blood glucose

DIN EN ISO 15197 specifies the requirements for *in vitro* glucose monitoring systems in terms of the specific design together with performance validation by the intended users.

DIN EN ISO 15197	<i>In vitro</i> diagnostic testing systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus
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4.2.2 Provision of information by the manufacturer

This standard series defines requirements made of the manufacturer for supplying information about diagnostic reagents and equipment and for use by professional staff and also for self-testing.

DIN EN ISO 18113 Part 1 to 5	<i>In vitro</i> diagnostic medical devices - Information supplied by the manufacturer (labelling)
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4.2.3 Clinical tests

DIN EN ISO 14155 aims to safeguard the protection of test persons together with scientifically correct implementation of clinical testing for medical devices along the lines of Good Clinical Practice.

DIN EN ISO 14155	Clinical investigation of medical devices for human subjects - Good clinical practice
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4.2.4 Performance evaluation study

The suitability of IVD for the intended use is proven by a performance evaluation. If literature data are not sufficient a performance evaluation study has to be conducted.

DIN EN 13612	Performance evaluation of <i>in vitro</i> diagnostic medical devices
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4.2.5 Quality management

DIN EN ISO 13485 describes a specified quality management pursuant to DIN EN ISO 9000 et seq. for the manufacturers of medical devices. The standard basically contains chapters on the quality management system, management responsibility, resource management and product realization, together with measurement, analysis and improvement. The standard addresses the implementation of critical processes such as recall processes and preventing contamination.

DIN EN ISO 14971 describes risk management for medical devices and encompasses the analysis, assessment and management of the risk by means of action management, risk reassessment after implementing the action and market observation after the medical device has been supplied. The risk management results form an integral part in the technical documentation of a medical device.

DIN EN ISO 13485	Medical devices - Quality management systems - Requirements for regulatory purposes
CEN ISO/TR 14969	Medical devices - Quality management systems - Guidance on the application of ISO 13485
DIN EN ISO 14971	Medical devices - Application of risk management to medical devices

4.3 Standards applying to users

4.3.1 IT infrastructure

Mobile diagnostic systems are frequently integrated into existing IT systems, referring to hospital information systems and also laboratory information systems in the (central) laboratory.

DIN EN 80001-1 applies if no medical device manufacturer takes overall responsibility for complying with the key properties of the IT network. The standard describes the necessary risk management for IT networks with medical devices; it addresses the user initially but also the manufacturer of medical devices and providers of other IT technology.

DIN EN 80001-1 / VDE 0756-1	Application of risk management for IT-networks incorporating medical devices - Part 1: Roles, responsibilities and activities
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4.3.2 Data communication

Mobile diagnostic systems can be used in a wide range of differing environments. Special consideration therefore has to be given to the interfaces of these devices. Networking the components of a diagnostic system can be realized with a point-to-point connection (usually bit-serial) or using wired or wireless networks. The most important standards for data and communication cables are featured in the standard series DIN EN 50288 (VDE 0819) "Multi-element metallic cables used in analogue and digital communication and control", E DIN IEC 61156 (VDE 0819) "Multicore and symmetrical pair/quad cables for digital communications" and DIN EN 50173 (VDE 0800) "Information technology - Generic cabling systems".

The following standards and industrial standards for example are currently of practical relevance for point-to-point connections:

- Universal Serial Bus Revision 1.0 specification (USB)
- Universal Serial Bus Revision 2.0 specification (USB) as the further development of the Universal Serial Bus Revision 1.0
- Universal Serial Bus Revision 3.0 specification (USB) as the further development of the Universal Serial Bus Revision 2.0
- Universal Serial Bus Revision 3.1 specification (USB) as the further development of the Universal Serial Bus Revision 3.0

The following standards and industrial standards for wireless networks are relevant for networking systems on the local scale:

- IEEE Std. 802.11 Information technology – Telecommunications and information exchange between systems – Local and metropolitan area networks-Specific requirements – Part 11: Wireless LAN Medium Access Control (MAC) and Physical Layer (PHY) Specifications (WLAN)
- IEEE Std. 802.15.4 Information Technology – Telecommunications and Information Exchange Between Systems – Local and Metropolitan Area Networks Specific Requirements – Part 15.4: Wireless Medium Access Control (MAC) and Physical Layer (PHY) Specifications for Low-Rate Wireless Personal Area
- Networks (LR-WPANs) and for example the corresponding ZigBee Specification (ZigBee) or ANT+
- IEEE Std. 802.15.1 Information Technology – Telecommunications and Information Exchange Between Systems – Local and Metropolitan Area Networks – Specific Requirements – Part 15.1: Wireless Medium Access Control (MAC) and Physical Layer (PHY) Specifications for Wireless Personal Area Networks (WPANs) ("Bluetooth")
- Near Field Communication (NFC) is a contactless interface technology standardized according to ISO/IEC 18092 and 21481

The mobile diagnostic systems featured in this roadmap also have interfaces for connection to the hospital information system on the inpatient level and for connecting to information systems on the outpatient level. Interface standards in the xDT family, Health Level 7 (HL7) and POCT1-A apply in this context. Where physicians in general practice are concerned, the xDT family covers the interfaces for treatment data transfer, device data transfer and laboratory data carriers. HL7 is an industrial standard for data transfer in the clinical setting. The POCT1-A standard describes and simplifies communication channels between POCT devices, the data manager device and the hospital information system. This standard also facilitates total quality assurance in accordance with the legal requirements.

Two interfaces are defined: a device interface is responsible for information transfer between devices and what are known as "observation reviewers" (POC data managers); an "observation reporting" (EDI) interface is used for communication between an observation reviewer and an observation recipient, typically a laboratory information system or a clinical data repository. Short XML messages (eXtensible Markup Language) are exchanged via the device interface. POCT1-A has emerged from the cooperation between various manufacturers; in its current version it is an IEEE and NCCLS standard.

4.3.3 Data security

The ISO/IEC working groups have produced a series of international specifications on data security. In detail, these specifications describe the definition of privacy requirements when personal data are processed in the information systems, together with best practice for consistent technical implementation of privacy principles and a framework for secure, reliable privacy conformity management of the identity information.

ISO/IEC 29100	Information technology – Security techniques – Privacy framework
ISO/IEC 29101	Information technology – Security techniques – Privacy architecture framework
ISO/IEC 24760-1	Information technology – Security techniques – A framework for identity management – Part 1: Terminology and concepts

The use and disclosure of security and risk management standards and specifications is also important. The ISO/IEC 2700 standards series is relevant in this context. In addition, the BSI standards on IT baseline protection are of particular significance.

4.3.4 Privacy

Special requirements apply to IT infrastructures in terms of privacy [20], with corresponding discussions referring to aspects that define life-long privacy infrastructures:

- Resilient planning and assurance of personal and financial resources,
- Operating models and procedures for operation transfer,
- Warranty of privacy and data security for future developments and also for past periods,
- Verifiability of privacy and data security measures including definition of the anticipated incidents,
- Regular review of the privacy and data security measures,
- Use of current and/or development of new certification measures and
- Establishing a process for on-going risk analysis.



4.3.5 Measurements with *in vitro* diagnostic medical devices

The mobile diagnostic systems featured in this roadmap are usually subject to the EU directive on *in vitro* diagnostic medical devices (see 3.3.1). The technical committee "ISO/TC 212 Clinical laboratory testing and in-vitro diagnostic test systems" has compiled a series of standards for measuring analytes in biological samples which make statements on reference measurement procedures and material as well as reagents. A selection is presented below (no claim to completeness):

DIN EN ISO 15193	<i>In vitro</i> diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for content and presentation of reference measurement procedures
DIN EN ISO 15194	<i>In vitro</i> diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for certified reference materials and the content of supporting documentation
DIN EN ISO 17511	<i>In vitro</i> diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials
DIN EN ISO 23640	<i>In vitro</i> diagnostic medical devices - Evaluation of stability of <i>in vitro</i> diagnostic reagents

4.3.6 Quality assurance/control

In the context of quality assurance and quality control, part A of the RiliBÄK guideline in Germany regulates the basic requirements for all medical laboratory tests and contains the obligation to set up a quality management system. Since January 1, 2002, the RiliBÄK also requires hospitals to safeguard the quality of diagnostic systems used for POCT.

DIN EN ISO 15189 and DIN EN ISO 22870 define the requirements made of quality and competence as well as setting up a state-of-the-art quality management system. Both standards form the basis for the accreditation of an analytical laboratory.

DIN EN ISO 15189	Medical laboratories - Requirements for quality and competence
DIN EN ISO 22870	Point-of-care testing (POCT) - Requirements for quality and competence

Other standards for medical laboratories can be obtained from the technical committee "ISO/TC 212 Clinical laboratory testing and *in vitro* diagnostic test systems".

5 RECOMMENDATIONS

The Office of Technology Assessment at the German Bundestag has issued a report on "Medical technology innovations - challenges for research, economic and health policy" with recommendations for further development of the regulatory framework for medical devices along the lines of greater standardization and a regulatory perspective on new fields of technology [21]. Furthermore, the application of harmonized standards is expected to lead to compliance by the Member States with the essential requirements according to Article 5 of EU directive 98/79/EC for *in vitro* diagnostic medical devices. This in turn is continued in the proposals for the new EU regulations. The following section contains the recommendations of the German Standardization Roadmap for mobile diagnostic systems.

5.1 Standards to be revised for mobile diagnostic systems

This section of the standardization roadmap analyses and detects possible gaps in the current standards collection. It also gives recommendations for revising existing standards.

5.1.1 Definitions in the field of mobile diagnostic systems

Many specific definitions are used in POCT application areas for mobile diagnostic systems, including in some cases also inconsistent definitions of POCT itself. There is therefore an urgent need to set up an application guideline with definitions for the compilation of future standards and for sharing and exchange in the professional world.

5.1.2 Analytical method development and validation

Every mobile diagnostic system covered by this roadmap is based on an analytical test procedure. The corresponding test methods such as lateral flow assay must be adequately validated in order to guarantee reliable results. In POCT devices, measurement validity is often inadequate or at least capable of improvement (see 3.4.3.1). This can also be derived from the statistical evaluation of 2367 risk reports received by the BfArM in the period between January 1, 2005 and December 31, 2013 [17].

The following error types were defined, among others

- 25 interactions/interference with other substances, cross-reactivity and matrix effects, together with
- 285 deviations in performance parameters (e. g. sensitivity, specificity, precision, reproducibility, linearity).

A closer examination of the reasons results in the demand for whole-blood standards, harmonized test methods and improved quality controls [22]. Results from tests with different diagnostic systems can only be used for clinical diagnosis and patient management if the measured values are comparable within meaningful clinical limits. For certain analytes neither certified reference materials are available, nor pure substances in a suitable matrix, nor reference test systems (see DIN EN ISO 17511). International experts therefore demand a roadmap for the harmonization of clinical laboratory measurement procedures [23], which would make it easier in particular to compare mobile and stationary diagnostic systems.

The field of pharmaceutical analysis has documents that stipulate how to validate the respective test methods (see 3.4.3.1). By contrast, there are only few documents pertaining to IVD, such as the guidelines issued by the FDA in the USA [24]. Europe does not have any detailed stipulations for validating an analytical test method. In principle, it is important to distinguish between qualitative and quantitative test methods, as this also has further implications for the validation scope. By featuring various application cases, normative documents can enhance the performance and safety of mobile diagnostic systems for this field.

The development of analytical methods has to take account of the pre- and post-analytical phases particularly in application areas outside the clinic. Normative documents can provide assistance in developing robust methods.

5.1.3 Development of mobile diagnostic systems

Important parameters and test results should be documented already during the development of mobile diagnostic systems, so that all necessary information is available for certification of the medical device. Here it is advisable to draw up a standard for a structured approach, e. g. based on flow charts or checklists.

5.1.4 Interoperability

Interoperability is important in many aspects of medical technology. Particularly, in the clinical setting, many different devices have to be able to communicate with the hospital information system. The type of existing interfaces depends in some cases on the specific location; furthermore, the mobility of the devices gives preference to wireless solutions. The trend to an open POCT data management system grew out of the need to be able to use the device data from different manufacturers. On the other hand, these efforts must not be detrimental to the attributes and properties of the specific device.

Although the xDT, HL7 and POCT1-A interface standards are established for devices in outpatient and clinical use (see 4.3.2), the large number of interfaces and other proprietary solutions hampers interoperability. The POCT industry must standardize the device interfaces and corresponding data management systems to make it easier for the health institutions to integrate new products in existing solutions [25]. A corresponding standard would facilitate market access particularly for smaller businesses, and enhance communication security in general.

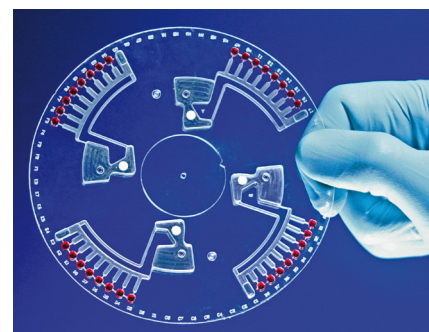
5.1.5 Qualification of vendor parts for the production of mobile diagnostic systems

Mobile diagnostic systems in the POCT environment frequently use vendor parts e. g. from the microfluidic sector. Assuring appropriate quality of the vendor parts is of crucial importance for production of the devices. The following requirements therefore refer to the need for normative documents [26]:

- Development of a general approach to the development of vendor parts, requirements for durability and resistance to external influences and standardized connections,
- Development of a general approach to testing the vendor parts in terms of part-specific characteristics,
- Description of a process for quality control throughout the entire life cycle of the vendor part, assuring among others the quality of the raw materials.

5.1.6 Quality assurance of the test results

In principle, the quality assurance of test results from analytical devices is regulated by both the MPBetreibV and the RiliBÄK. The procedure involved here includes among others saving and storing of quality data. However, inadequate consideration is given to the special requirements applying to POCT devices. Furthermore, the interlaboratory comparisons required by the RiliBÄK can be difficult to be implemented for POCT devices, so that a corresponding standard would facilitate a legally compliant, safe approach.



Picture source: HSG-IMIT Freiburg

5.1.7 Data security, collection and control

Modern mobile diagnostic systems are integrated via device interfaces into the medical networks of hospitals and physicians' practices. Furthermore, when used in the domestic setting it is also possible for test data to be forwarded to medical control centers or care units. As a result, mobile diagnostic systems face special challenges in terms of data security, which has to be assured equally by the manufacturer of mobile diagnostic systems and also by the operators.

The mobility of the devices offers one main advantage, that only wireless connections can be used for data communication. The Federal Office for Information Security (BSI) advises encoding Wi-Fi communication with WPA2 and to proceed with authentication as per IEEE 802.1X [27]. Encoding the data would also guarantee additional security. A standard taking account of the special circumstances applying to mobile diagnostic systems could provide important assistance in this respect. Here attention is also drawn to the Standardization Roadmap on "IT Security", which reveals the need for action among others in medical technology [28].

The growing collection of analytical test data in electronic patient records makes it necessary to ensure that any transfer involving both mobile and also stationary test systems must always be total and complete, and that different device classes do not use different systems. In this respect, normative documents can define the type and quantity of transferred data.

At the moment, only proprietary solutions are available for operating POCT devices from larger companies which offer possibilities for user/patient management, device control and the release of analysis results. Various different solutions for the above mentioned areas complicate integrated management for the operator and may be inadequate in the case of liability. Normative provisions are therefore recommended for the following topics:

- Management of automated user ID,
- Logging user activities based on centrally stored logs in compliance with the privacy regulations,
- Recording the device data with the possibility of automatically blocking a device in the event of a malfunction,
- Workflow for technical release of the analysis results and
- Data consolidation for interpretation by the physician in charge.

5.1.8 Training and competence of users in the professional setting

The use of mobile diagnostic systems for POC diagnostics entails carrying out "medical laboratory tests only by persons qualified according to the national legislation" (RiliBÄK, see 5.2). Qualified persons according to the law on technical assistants in medicine (MTAG, Sections 1, 9 and 10) are as follows:

1. Medical laboratory assistants,
2. Physicians and scientists with the necessary know-how on account of their university degrees,
3. Homeopathic practitioners,
4. Trainee medical technicians,
5. Persons having completed another form of medical training without being entitled under Section 10 (1) 1-5 MTAG, under the supervision and responsibility of a person named under 1.

Furthermore, section 5.2 of the RiliBÄK guideline demands "regular initial and advanced training" with corresponding records being kept. But the word "regular" gives no further indication how often training has to take place to fulfill the legal requirements. Other requirements for training and for maintaining competence are stipulated in the MPBetreibV and in DIN EN ISO 28870 for senior executives in medical laboratories. It is up to the individual medical laboratory department or POCT manager to develop, implement and monitor an adequate training concept. Large medical technology vendors have developed proprietary solutions in this context to assure regular training for those operating the particular devices.

But this results in two problems for daily implementation. On the one hand, when using devices from different manufacturers, a medical laboratory department has to coordinate the contents of individual proprietary training solutions. On the other hand, there must also be a standard level of safety and security for access to the device with corresponding training events together with on-going monitoring. Moreover, such manufacturer solutions are often not available from smaller companies. What is needed here is a standard to illustrate a general approach to establishing a training concept that also takes account of the legal framework conditions (privacy) and operational framework conditions (in Germany participation of staff/works council). Finally, it would also be desirable to have a normative document that describes the procedure for monitoring the training activities of users with the possibility of blocking the use of a device if necessary competence is not available.

However, to avoid over-regulation, this standard should take account of device complexity and the type of use.

5.1.9 Maintenance and servicing of mobile diagnostic systems

Every hospital with a quality management system also has regulations for the maintenance and servicing of its medical devices. As a rule, here the manufacturers provide maintenance plans indicating the time intervals and technical workflow. Some devices also have automatic reporting systems that keep records of implemented maintenance work and also monitor the intervals. Mobile diagnostic systems are also used for outpatient care where there are frequently neither established quality management systems nor automatic reporting procedures. Test and measurement quality depend on the perfect technical functioning of the devices. It is therefore advisable to have a standard that addresses all aspects of maintenance and servicing for mobile diagnostic systems.

5.1.10 Reforming the EU legislation

The currently valid EU directive for IVD breaks the devices down into four groups (List A pursuant to Annex II (high risk), List B pursuant to Annex II (risk), products for own use and all other IVDs). The proposal by the European Commission for an IVD regulation features a new break-down into the classes A, B, C and D (lowest risk/highest risk) based on the particular intended purpose and the associated risks. This change in classification together with the other proposed changes will present IVD manufacturers with many challenges. In this situation, informative documents (e. g. application guides) can make an important contribution to fulfilling these requirements.

5.2 Internationality of standardization

Many countries have developed their own standards and guidelines for analytical laboratory practice and POCT [29]. The establishment and implementation of internationally valid standards is urgently recommended so that products can be sold on an international scale despite development and trading barriers.

5.3 Further recommendations for stronger integration of standardization in the development and production of mobile diagnostic systems

5.3.1 Intelligent funding for overcoming barriers when launching mobile diagnostic systems and with standardization

Public funding plays a major role for both SME businesses and also for institutes and universities in providing major assistance for implementing research and development (R&D) projects. This also applies to the development of new innovative technologies particularly also in the field of mobile diagnostic systems. As a rule, public funding projects tend to omit any prospective integration of regulatory matters both for knowledge generation and also for future standardization work. The discussions in the working group have generated the following recommendations with regard to future funding:

- The economic benefit of standardization is undisputed [19]. To achieve the greatest possible social consensus, funding measures should consider and support the involvement of collaborative projects in national standardization. This suggestion is also featured in the report on “Medical technology innovations - challenges for research, economic and health policy” issued by the Office of Technology Assessment at the German Bundestag [21].
- An annual forum on mobile diagnostic systems should offer a possibility for the various stakeholders in politics, healthcare, industry, public research and patient representatives for sharing and exchanging. This would be especially beneficial for enhancing social consensus on standardization with greater involvement of all interested stakeholders. The usability of mobile diagnostic systems in particular would benefit from this.
- Individual, modular and consistent funding programs should allow for funding to be adapted flexibly to the needs of the respective applicants. This could entail creating capacities for smaller companies, institutes and universities in particular with regard to training events on regulatory contents and for standardization work.
- An external, independent team of experts to accompany the particular project by dealing with knowledge gaps (e.g. applicable standards and legislation) and providing planning advice about regulatory requirements would help to facilitate the procedures involved in introducing mobile diagnostic systems to the market.

As the basis for recommending further activities, more detailed investigations should be carried out by a group of experts. The aim is to ascertain which social and regulatory barriers are currently detrimental to using mobile diagnostic systems in the outpatient and homecare sectors of the healthcare system. The experts in the DKE working group suggest that a survey of persons in all main interest groups for mobile diagnostic systems could be a suitable instrument.

6 ABBREVIATIONS

Abbreviation/ acronym	Meaning
AAL	Ambient Assisted Living
BDSG	Federal Data Protection Act (German: Bundesdatenschutzgesetz)
BDT	treatment data transfer (German: Behandlungsdatentransfer)
BfArM	Federal Institute for Drugs and Medical Devices (German: Bundesinstitut für Arzneimittel und Medizinprodukte)
BSI	Federal Institute for Drugs and Medical Devices (German: Bundesinstitut für Arzneimittel und Medizinprodukte)
CDR	Clinical Data Repository
CEN	Comité Européen de Normalisation (English: European Committee for Standardization)
CENELEC	Comité Européen de Normalisation Électrotechnique (English: European Committee for Electrotechnical Standardization)
DGBMT	German Society for Biomedical Engineering within VDE (German: Deutsche Gesellschaft für Biomedizinische Technik im VDE)
DIN	German Institute for Standardization (German: Deutsches Institut für Normung e. V.)
DKE	German Commission for Electrical, Electronic & Information Technologies of DIN and VDE (German: Deutsche Kommission Elektrotechnik Elektronik Informationstechnik in DIN und VDE)
DRG	diagnosis related groups
E DIN	draft standard (German: Entwurf DIN)
EBM	uniform assessment standard (German: Einheitlicher Bewertungsmaßstab)
EC	European Community
EDI	Electronic Data Interchange
EMC	electromagnetic compatibility

Abbreviation/ acronym	Meaning
EN	European Standard (German: Europäische Norm)
ETSI	European Telecommunications Standards Institute
EU	European Union
EEC	European Economic Community
FDA	Food and Drug Administration (USA)
GDT	device data transfer (German: Gerätedatentransfer)
GKV	National health insurance funds in Germany (German: Gesetzliche Krankenversicherung)
GOÄ	scale of fees for physicians (German: Gebührenordnung für Ärzte)
Hb	hemoglobin
HL7	Health Level 7
HWG	Medical Devices Advertising Law (German: Heilmittelwerbe-gesetz)
I/O	Input/Output
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
IEEE	Institute of Electrical and Electronics Engineers
IFU	Instructions For Use
IGeL	individually provided health services (German: Individuell erbrachte Gesundheitsleistungen)
ISO	International Organization for Standardization
IT	Information Technology
ITU	International Telecommunication Union

Abbreviation/ acronym	Meaning
IVD	<i>in vitro</i> diagnostic medical devices
KIS	hospital information system (German: Krankenhausinformationssystem)
LAN	Local Area Network
LDT	laboratory data carrier (German: Labordatenträger)
LIS	laboratory information system (German: Laborinformationssystem)
LR-WPAN	Low-Rate Wireless Personal Area Network
MAC	Medium Access Control
MEDDEV	Medical Devices Guidelines of the European Commission
MPBetreibV	Medical Devices Operator Ordinance (German: Medizinprodukte-Betreiberverordnung)
MPG	Medical Devices Act (German: Medizinproduktegesetz)
MTAG	Law on Technical Assistants in Medicine (German: Gesetz über technische Assistenten in der Medizin)
NBOG	Notified Body Operations Group
NCCLS	National Committee for Clinical Laboratory Standards
NFC	Near Field Communication
PHY	Physical Layer
POCT	Point-Of-Care Testing
QMS	Quality Management System
R&D	Research and Development

Abbreviation/ acronym	Meaning
RiliBÄK	Guideline of the German Medical Council for Quality Assurance of Medical Laboratory Tests (German: Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen Standard)
SME	Small and Medium-sized Enterprises
Std.	Standard
TAT	Turnaround Time
TEAM NB	The European Association for Medical devices of Notified Bodies
USA	United States of America
USB	Universal Serial Bus
VDE	Association for Electrical, Electronic and Information Technologies (German: Verband der Elektrotechnik Elektronik Informationstechnik e. V.)
WLAN	Wireless Local Area Network
WPAN	Wireless Personal Area Network
XML	Extensible Markup Language
ZLG	Central agency of the German states for health protection with regard to drugs and medical devices (German: Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten)

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8 ANNEX

8.1 Standardization bodies

The following list of standardization bodies relevant to mobile diagnostic systems does not claim to be complete and can vary according to the device type.

The following standardization bodies exist on the national level in Germany:

DIN Standards Committees

- NA 023 Ergonomie
- NA 043 Informationstechnik und Anwendungen
- NA 053 Rettungsdienst und Krankenhaus
- NA 063 Medizin
- NA 063-03-11 AA Patientennahe Sofortdiagnostik (POCT)

DKE Committees

- DKE/K 111 Terminologie
- DKE/K 767 Elektromagnetische Verträglichkeit (EMV)
- DKE/K 810 Elektrische Geräte in medizinischer Anwendung
- DKE/K 811 Allgemeine Bestimmungen für elektrische Einrichtungen in medizinischer Anwendung
- DKE/UK 811.2 Elektromagnetische Verträglichkeit medizinischer elektrischer Geräte und/oder Systeme
- DKE/UK 811.3 Sicherheit von medizinisch genutzten Geräten/Systemen/Einrichtungen in der vernetzten Anwendung
- DKE/K 812 Elektromedizinische Geräte
- DKE/K 911 Sicherheitsanforderungen an elektrische einschließlich elektronische Geräte für das Messen, Steuern und Regeln
- DKE/K 913 Sicherheitsanforderungen an typische Geräte, Einrichtungen und Systeme für Labor und Unterricht
- DKE/AK STD_1811.0.5 Mobile Endgeräte / mobile Applikationen für AAL

The following bodies exist on the European level:

CEN

- Technical Committee CEN/TC 140 In vitro diagnostic medical devices

ETSI

- ETSI/TC Digital Enhanced Cordless Telecommunications
- ETSI/TC Machine to Machine Communication

Finally, the following bodies are relevant on the international level:

ISO

- ISO/IEC JTC 1/SC 6 Telecommunications and information exchange between systems
- ISO/IEC JTC 1/SC 7 Software and systems engineering
- ISO/IEC JTC 1/SC 25 Interconnection of information technology equipment
- ISO/IEC JTC 1/SC 27 IT Security techniques
- ISO/IEC JTC 1/SC 32 Data management and interchange
- ISO/IEC JTC 1/SC 35 User interfaces
- ISO/IEC JTC 1/SC 37 Biometrics
- ISO/IEC JTC 1/SC 38 Distributed application platforms and services
- ISO/IEC JTC 1/SWG 1 Accessibility
- ISO/IEC JTC 1/WG 7 Sensor networks
- ISO/TC 210 Quality management and corresponding general aspects for medical devices
- ISO/TC 212 Clinical laboratory testing and in vitro diagnostic test systems
- ISO/TC 215 Health informatics

IEC

- IEC/SC 62A Common aspects of electrical equipment used in medical practice
- IEC/SC 62D Electromedical equipment
- IEC/TC 1 Terminology
- IEC/TC 62 Electrical equipment in medical practice
- IEC/TC 64 Electrical installations and protection against electric shock
- IEC/TC 77 Electromagnetic compatibility

IEEE Standards Association

- IEEE 802 LAN/MAN Standards Committee

Other Standardization Bodies

- CLSI Clinical and Laboratory Standards Institute
- Continua Health Alliance
- Health Level 7
- Organization for the Advancement of Structured Information Standards (OASIS)
- OSGi Alliance
- UPhP Forum
- USB Implementers Forum, Inc.

8.2 DGBMT bodies

The DGBMT is borne by the professional, scientific work in its technical committees and working groups. Here physicians, engineers and natural scientists from hospitals, research institutes and companies work together on an inter- and transdisciplinary basis. Their work contents range from sharing knowledge and networking via planning and holding events through to producing studies and position papers.

DGBMT technical committees relevant to mobile diagnostic systems

- Medical engineering in the hospital
- Micro- and nanosystems
- Mobile diagnostic and therapeutic systems
- Usability for medical engineering



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