Biomedical Alliance in Europe

Case studies/examples for the MDCG Task Force responsible for the guidance document on conditions for in-house devices

1. Case study presented by the European Hematology Association

By Isabel Dombrink (UKSH, Kiel, DE) and Bart Lubbers/Jacques J.M. van Dongen (LUMC, Leiden, NL).

Questions and concerns from diagnostic laboratories about the conditions for in-house devices in IVDR Article 5.5 and the general safety and performance requirements in IVDR Annex I.

Preamble 29: What is an in-house device?

In addition to CE-IVD tests used in line with their intended purpose and instructions for use, several other categories of IVDs are an essential part of the diagnostic test portfolio of diagnostic laboratories, i.e. laboratory-developed tests (LDTs), research use only (RUO) kits, and CE-IVD tests that are modified/used off-label.

According to Preamble 29, health institutions should have the possibility of manufacturing, modifying and using devices in-house (under specific conditions). It is currently not entirely clear whether all categories mentioned above (LDTs, RUOs and modified/off-label CE-IVDs) will be considered as in-house devices that are allowed under the exemption for health institutions.

- Will RUOs and modified/off-label CE-IVDs be considered in-house devices and therefore are regulated by the IVDR under the health institution exemption? If not, what will be their regulatory status?
- Which extent of modification is allowed before a CE-IVD is considered to be modified?
    - *Bank et al., Clin Chem Lab Med 2020, https://doi.org/10.1515/cclm-2020-1384 give useful suggestions*
- Are all steps of more complex multistep tests considered as LDTs? Or only the part that is directly needed for the diagnosis?
    - *E.g.: Mutation analysis via next generation sequencing. The intended purpose of the step "DNA extraction" is to extract DNA from a blood or bone marrow sample. If we would add "to examine several genes for mutations to determine gene mutation in myeloid diseases" in the intended purpose of the DNA extraction it would be considered as an LDT but it could and should also be seen as a preparation step.*

Figure 1. Determination of prognosis and disease-relevant gene mutations in myeloid diseases.

Art. 5.5a: Transfer to another legal entity

- "the devices are not transferred to another legal entity"

The quality of in-house devices, and their significance for diagnostic patient care, greatly benefit from collaborative development, standardization, validation and evaluation of diagnostic tests, as well as from sharing of knowledge and expertise. The basis for this is the sharing, either privately or publicly, of know-how, data/results, protocols/standard operating procedures (SOPs), and other documents such as guidance and templates. Furthermore, in specific situations, transfer of patient samples between laboratories (e.g. to reference laboratories) is currently common practice, yielding inter-laboratory education, specialization and better diagnostic results.

- Is the transfer between health institutions of anything that is not considered to be a device by the IVDR restricted in any way?
    - *Preferably, transfer/sharing of know-how, data/results, protocols/standard operating procedures (SOPs), and other documents such as guidance and templates, as well as patient samples, is not restricted in any way by the IVDR, to support (collaborative) innovation and to maximize the quality of diagnostic patient care.*

Art. 5.5d: Justification

- "the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market"

The fact that the IVDR regards CE-IVD tests as the "default choice" will restrict the use of in-house devices. This can be beneficial for the quality of diagnostic health care as CE-IVD tests are supported by extensive (technical) documentation which is usually reviewed by a notified body. However, an in-house device is the most appropriate test for a specific application when alternative CE-IVDs are not available or have better characteristics; this is not an infrequent situation (see for example Vermeersch et al., Clin Chem Lab Med 2020, https://doi.org/10.1515/cclm-2020-0804). Many questions have been raised by diagnostic laboratories about the justification for use of in-house devices (see also Figure 2).

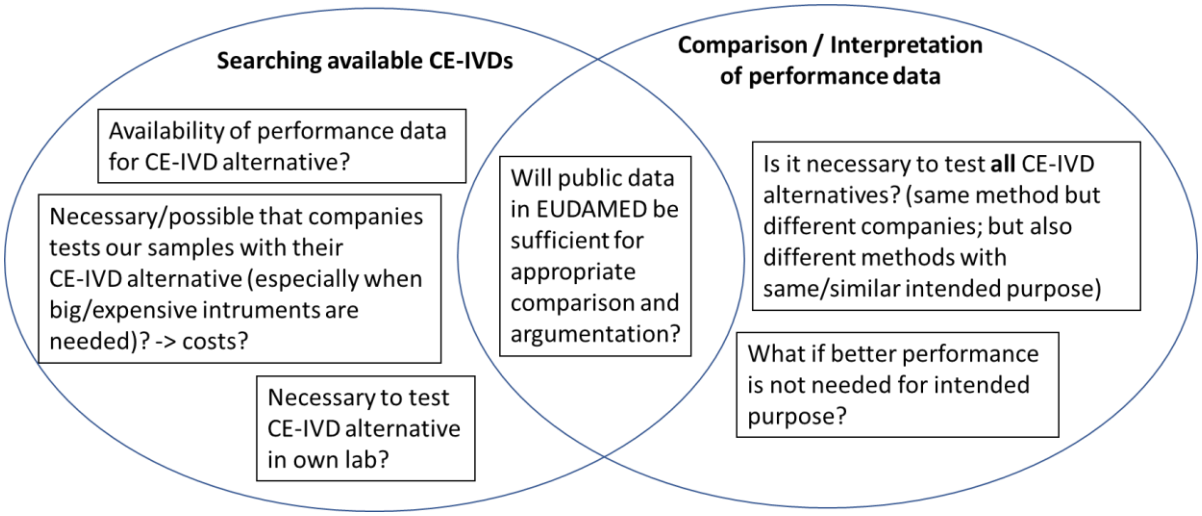

Figure 2. Questions related to the searching of CE-IVD alternatives for in-house devices and their comparison.

- What will be the definition of "equivalent"?
  - *This would preferably include that the assay measures the same (combination of) analytes using the same technology and equipment; for explanation see below.*
- What will be the definition of "appropriate level of performance"?
  - *For optimal quality of diagnostic health care, a CE-IVD does not meet the appropriate level of performance when an in-house device performs better, taking together all relevant characteristics.*
- What are relevant arguments when justifying use of an in-house device?
  - *E.g. better analytical and/or clinical performance, faster turn-around time (if relevant), broader applicability. Also practical/logistic arguments can be relevant, for example when a CE-IVD requires equipment and/or expertise that a laboratory does not own/have yet (see also Figure 3).*
  - *Which arguments count for a benefit of the target patient group's specific needs (see also Figure 3).*
  - *Bank et al., Clin Chem Lab Med 2020, https://doi.org/10.1515/cclm-2020-1384 give some further useful suggestions.*

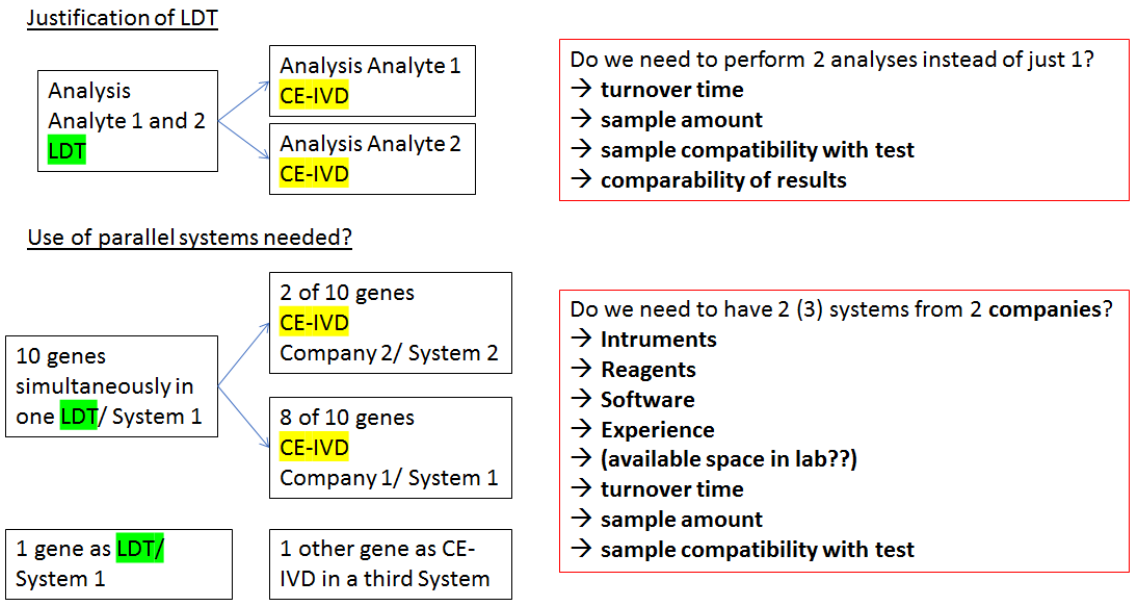

Figure 3. Illustration of some questions related to possible arguments for justification

- With which frequency should laboratories update the documentation of in-house devices and perform a comparison with equivalent CE-IVDs available on the market?
    - *Reasonable frequencies could for example be at least every year (for class D in-house devices), at least every 3 years (for class C) and when relevant (for class A, B, C and D).*
- What should be the strategy for searching for equivalent CE-IVDs available on the market, and comparing them to the in-house device?
    - *Screening should involve consulting the EUDAMED database; and comparison should include evaluation of relevant characteristics (possibly including a comparative study).*
- When it is appropriate to replace an in-house device with an equivalent CE-IVD test, within which time frame should the in-house device be replaced?
    - *This time frame should take into account the time to gain the relevant knowledge/expertise, purchase the required reagents and implement and validate the test. The exact time frame that is reasonable will depend on each unique situation.*
- Is there any mechanism in place that prevents a company from (financially) exploiting a monopoly (i.e. the most appropriate test for a specific application is a CE-IVD and there are no competitors on the market)?

Art. 5.5i: Review of experience

- "the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions"

- With which frequency should laboratories review experience with the in-house devices and update the corresponding documentation?
    - *In absence of signs that (re-)evaluation of the test is urgent, reasonable frequencies could for example be every year (for class D in-house devices) and every 3 years (for class C).*

Art. 5.5: Industrial scale

- "This paragraph shall not apply to devices that are manufactured on an industrial scale."

- How will "industrial scale" be defined?

Annex I

- "With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union"

- To what extent are the requirements of Annex I covered by a quality management system based on ISO 15189?
    - *Based on the considerable overlap between the requirements of Annex I of the IVDR and those of ISO 15189, it would be fair that, given that the requirements of ISO 15189 are met in an appropriate manner, a considerable part of the Annex I requirements are covered. Bank et al., Clin Chem Lab Med 2020, https://doi.org/10.1515/cclm-2020-1384 give useful suggestions.*

2. Case study presented by the AWMF on behalf of BioMed Alliance IVD WG

Explanations on three case studies presented by Monika Brüggeman and Michael Vogeser. *You can find the slides for the case studies here.*

Showcases of complex analytical procedures developed and carried out in specialized medical laboratories

Measurement procedure for Therapeutic Drug Monitoring of innovative pharmaceutical based on isotope dilution-mass spectrometry

Multi-step measurement procedures include products for general laboratory use (e.g. a generic mass spectrometer), medical devices (calibration samples, QC samples, potentially derivatising reagents) and complex procedural documents describing the sample preparation steps, device settings and software settings for quantification.

Cytomorpological evaluation of bone marrow smears:
This procedure consists of different steps, starting with preparation of a bone marrow smear, followed by staining of the smear using different fixation and staining reagents, finally the stained smear is evaluated by a medical doctor using a microscope.
Different types of kits are possible:

1. Kit consisting solely of staining reagents. Microscopy is done by an expert, and only the combination of staining plus medical expertise leads to a meaningful result. Different medical experts prefer different staining procedures
2. Automated platform consisting of staining plus robot microscopy and digital image analysis for operator independent cytomorphology. Such a platform might replace an integral part of medical work.

High throughput sequencing for mutation analysis in hemato-oncological malignancies:
Different kit options for this multistep procedure are possible:

1. Combination of different kits using different instruments, followed by a bioinformatic pipeline and medical interpretation of mutation pattern.
2. One automated platform that covers all steps and all instruments starting with DNA extraction and resulting in information on mutation pattern. Mutation pattern is interpreted by a medical doctor. Platform might cover e. g. genes of interest A-C but not genes of interest D-F. Other platforms might cover genes C-E, F is not covered by any commercial platform.
3. One automated platform that covers all steps mentioned in 2 but also final interpretation of mutation pattern. Such a platform might replace an integral part of medical work.

3. Case study presented by The European Society of Pathology

By Prof. Höfler Gerald.

Currently, FLT3 testing, mainly for acute myloid leukemia, is performed using the LeukoStrat® CDx FLT3 Mutation Assay for Identification of FLT3 ITD and TKD Mutations. This assay is based on European Patent number 0959132 (licensed exclusively to Invivoscribe Technologies, Inc. and owned by Takara Bio, Inc.). This assay is critical both as a prognostic and predictive test in acute myeloid leukemia.
If, for any reason, this test would not be available (e.g. due to problems in certification) a LDT could not be performed since it violate the above mentioned patent, which might lead to a critical situation.

4. Case study presented by the United European Gastroenterology

Biomedical Alliance in Europe

Comments on the IVDR regulation by Tamara Matysiak, Marcis Leja, Isabelle Cleynen on behalf of the UEG Research Committee

- the limitations of the new regulation with respect to the digital solutions, like for instance the sensor technology. This technology is increasingly used for detection of various diseases, furthermore, it has a great potential e.g. in early cancer detection. This could be used in exhaled air, urine, faeces, or from sweat from the skin.
- Computer-based model from signals obtained from sensors that are frequently cross-reactive (i.e. not specific for one substance) is used for the diagnosis.
- According to our knowledge, now with the new Regulations, in vitro diagnostic requirements apply for such devices, meaning also that particular substances have to be indicated that are measured by the device. But sensors are not measuring any substance being cross-reactive! They measure a pattern that could not be found in the chemistry tables. But a pattern detection cannot be used in a diagnostic device according to the new regulation. Currently researchers are attempting to go 'round' the requirements. They detect a substance that potentially could differentiate the two groups, and then claim that the sensors are measuring this particular substance. But this is definitely not true!
- To our understanding, this may create problems for AI in general.
- This limitation may also concern other fields of digital solutions in which we are not going to measure any particular, well defined substance, and this indicates that the current regulations are not adapted to these devices and that perhaps more specific regulations should be developed.