Review

Reference, Calibration and Referral Laboratories - A Look at Current European Provisions and Beyond

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Article

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Abstract: European Union (EU) regulations on *in vitro* diagnostics (IVD) and on serious cross-border threats to health provide for the establishment of European Reference Laboratories (EURLs) and their harmonisation and cooperation with National Reference Laboratories (NRLs). While the EURLs under the IVD Regulation will be operational by 1 October 2024, the EURLs under the Regulation on serious cross-border threats to health will be operational by January 2025. Although NRLs may have been operating for a long time on the basis of national legislation, they should now cooperate with each other and with EURLs in a network of centres of excellence for the authorisation and post-market surveillance of IVDs and for the epidemiological surveillance and control of communicable diseases. The term "reference laboratory" has long been used colloquially to refer to many kinds of laboratories, regardless of their tasks, competencies, responsibilities and designation. To clarify the roles and functioning of EURLs and NRLs, we evaluated the relevant current EU provisions and compared the findings with those of reference laboratories designated by other organisations, calibration (reference) laboratories and referral laboratories, which are simply referred to as "reference laboratories".

Keywords: reference laboratory; referral laboratory; European Union reference laboratory; national reference laboratory; calibration laboratory

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Introduction

Stakeholders in the laboratory community and in the IVD industry are currently facing substantial changes in European legislation on *in vitro* diagnostic medical devices (IVDs). One of the fundamental changes brought about by Regulation (EU) 2017/746 (*In vitro* Diagnostics Regulation (IVDR)) concerns the establishment of European Union Reference Laboratories (EURLs) and their crucial role in the authorisation and postmarket surveillance of IVDs [1]. Moreover, the first EURLs for public health under Regulation (EU) 2022/2371 have been established [2]. Cooperation between them and National Reference Laboratories (NRLs), designated by the national competent ministries, is encouraged in order to make progress in the further development of the existing network for epidemiological surveillance and control of communicable diseases [3–5].

It appears that the term "reference laboratory" is used arbitrarily due to the different types of laboratories that could fall under such a definition. These may be laboratories that have been officially designated by (i) the European Commission (EC) or by (ii) national authorities or (iii) international organisations; or are (iv) reference measurement service providers (calibration (reference) laboratories) listed in the Joint Committee on Traceability in Laboratory Medicine (JCTLM) database; or (v) *referral* laboratories that offer, for example, a broader array of analyses, operating hours that go beyond those of the referring laboratories or provide staff with extraordinary skills, experience and expertise for consultations.

To provide guidance in view of the current changes and of the newly established EURLs, we analysed and compared the characteristics and tasks of both designated and merely so-called "reference laboratories".

Materials and Methods

The current EU legal framework for the establishment, assigned tasks, and foreseen networks of EURLs and NRLs was analysed and their tasks and characteristics were compared with those of laboratories designated as “reference" by other competent organisations, calibration (reference) laboratories and with those of referral laboratories that are casually also referred to as “reference laboratories”.

PubMed was used to search for articles published between 01.01.2024 and 29.07.2024 that included the terms “reference_laboratory”, “reference_laboratories”, “referral_laboratory”, or “referral_laboratories” in the title or abstract. Publications identified as eligible for this article were evaluated for their understanding and use of the abovementioned terms.

Results

The results of the evaluation for the individual laboratory categories are presented in the sections below and summarised in Table 1.

Designated Reference Laboratories

The European Union, as a supranational organisation, national authorities and competent organisations such as national or international professional associations are entitled to designate reference laboratories. These laboratories are entrusted with contractually defined tasks, which they fulfil either for the remunerating contracting authority or on its behalf for a third party. They must fulfil certain technical requirements relating primarily to the performance of the testing methods offered (in case of operations under private law) or used (in case of official acts) and to their methodological or diagnostic expertise. These laboratories may then be called EURLs, NRLs, or reference laboratories to the respective organisation (e.g. World Health Organisation (WHO) reference laboratories). Depending on the focus and tasks assigned to them by the applicable EU framework, the reference activities of EURLs may focus on methodological excellence and

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performance evaluation of pathogens relevant to patient diagnostics and public health. (Tables 1 and 2). It should be noted that this review does not cover other networks of EURLs such as those under Regulation (EU) 2017/625 established for animal health, food and feed and plant health [6,7].

Table 1. Laboratories that are designated or referred to as "reference laboratories".

Type of laboratory	**Designated reference laboratories**					**Referral laboratories**
Name	**European Union Reference Laboratories for**		**National Reference Laboratories [3]**	**Reference laboratories designated by other organisations**	**Calibration (reference) laboratories**	**Medical laboratories**
	IVD assessment [1]	**public health [2]**				
designated by	European Commission	European Commission	National government	Competent organisation	Endorsement by IFCC, listing by the JCTLM	n/a
current number	5 (as of 5 December 2023) [8]	6 (as of 22 March 2024) [19]	(not collected)	(not collected)	27 (listed by JCTLM) [65]	(not collected)
Service						
area	Performance evaluation of class D IVDs	Public health surveillance and epidemiology	Public health surveillance and epidemiology	As agreed with designator	Operation of RMPs compliant to ISO 15195 and ISO 17025	Routine laboratory diagnostics, area of expertise
aim	Only IVDs compliant with IVDR on the market	Provision of continuous, robust monitoring and early warning and response mechanisms	Provision of continuous, robust monitoring and early warning and response mechanisms;	As agreed with designator	Metrological traceability and harmonisation of measurement results	Support of referring laboratory

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			routine diagnostics			
applicable standard	ISO 17025	ISO 17025	ISO 17025 (in addition ISO 15189 if analyses also for patient diagnostics are carried out)	As agreed with designator	ISO 17025	ISO 15189
prerequisites	Designation by European Commission	Designation by European Commission	Designation by national government	As specified by designator	Accreditation according to ISO 17025	Operating licence under national law
examination procedures used	Methods according to common specifications and harmonised in the subnetworks of the EURLs	Methods according to common specifications and harmonised in the subnetworks of the EURLs	Methods selected by the NRL	As agreed with designator	RMPs	Routine examination procedures
materials analysed	Harmonised between the EURLs and according to the common specifications	Clinical specimens, specimens of non-human origin	Clinical specimens, specimens of non-human origin	As agreed with designator	Materials intended to become RMs or CRMs, but also quality control materials	Clinical specimens
report type provided and recipient	Evaluation report to NB	???	Medical or micro-biological report to referrer	As agreed with designator	Calibration certificates	Medical report to referrer

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in operation from	October 1, 2024	January 2025	Individually different	n/a	1998	as long as laboratory diagnostics
costs for services borne by	customer (NB)	EU4Health programme	Regulated differently from state to state	to be determined by the designator	customer (IVD manufacturer, EQA provider)	Patients, their health insurance company or the referrer
non-financial benefit from service	none recognisable	Epidemiological surveillance data	Epidemiological surveillance data	none recognisable	standardisation of clinical measurements	none recognisable
Referral laboratory according to ISO 15189:2022	no	no	can be	can be	no	yes
Referrer / customer / user of services						
is / are	NBs	???	Referring diagnostic laboratory, national and European public health authorities	Designator or their eligible organisations	Manufacturers of IVD and CRM, EQA providers	Patient and physician
may select laboratory	yes	???	no	yes	yes	yes
selects measurands to be determined	no	???	no	As agreed with designator	yes	yes

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receives result/report	yes	yes	yes	As agreed with designator	yes	yes

Legend: n/a - not applicable.

Table 2. Tasks and responsibilities of EURLs.

regarding IVD compliance assessment [1,8]	**regarding public health surveillance [2,19]**
• to verify the performance claimed by the manufacturer and the compliance of class D devices with the applicable common specifications, when available, or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent, as provided for in the third subparagraph of Article 48(3) • to carry out appropriate tests on samples of manufactured class D devices or batches of class D devices, as provided for in the Section 4.12 of Annex IX and in Section 5.1 of Annex XI • to provide scientific and technical assistance to the Commission, the MDCG, the Member States and notified bodies in relation to the implementation of this Regulation • to provide scientific advice regarding the state of the art in relation to specific devices, or a category or group of devices • to set up and manage a network of NRLs after consulting with the national authorities and publish a list of the participating national reference laboratories and their respective tasks • to contribute to the development of appropriate testing and analysis methods to be applied for conformity assessment procedures and market surveillance • to collaborate with notified bodies in the development of best practices for the performance of conformity assessment procedures • to provide recommendations on suitable reference materials and	• reference diagnostics, including test protocols • reference material resources • external quality assessments • scientific advice and technical assistance • collaboration and research; • monitoring, alert notifications and support in outbreak response, including to emerging communicable diseases and pathogenic bacteria and viruses • training (tasks and responsibilities are defined in detail for each EURL in Annexes I - VI of Regulation (EU) 2024/892 [19]

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reference measurement procedures of higher metrological order ● to contribute to the development of CS and of international standards ● to provide scientific opinions in response to consultations by notified bodies in accordance with this Regulation and publish them by electronic means having considered national provisions on confidentiality

EURLs for IVD Assessment under Regulation (EU) 2017/746 (IVDR), Art. 100

The European Parliament and the Council are in the process of setting up a system of EURLs for serious cross-border threats to health [2] and supporting conformity assessment of IVD medical devices by notified sodies (NB) [1,8]. For the latter, the IVDR aims to *establish a robust, transparent, predictable and sustainable regulatory framework for in vitro diagnostic medical devices that ensures a high level of safety and health while promoting innovation*. Conformity assessment must be thorough and objective, considering both favourable and unfavourable data. Importantly, its depth and extent must be proportionate and appropriate to the characteristics of the device including the risks, risk class, performance, and its intended purpose [1]. The IVDR states that EURLs are involved in conformity assessments for class D IVDs and have an advisory role in this process. However, class D only applies to approximately 1.5 to 4% of all IVDs [9]. As the new type of classification requires explanations, the Medical Device Coordination Group (MDCG) and their subgroup Borderline and Classification Working Group (BCWG) provide examples for the classification of IVDs that explain the implementation of risk-based classification rules for IVDs [10,11]. For definitions of class D IVDs, see Table 3.

Table 3. Class D IVDs according to IVDR.

Devices intended to be used for the following purposes are classified as class D [(1)]: ● detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration; ● detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation; ● determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management. Devices intended to be used for blood grouping, or to determine feto-maternal blood group incompatibility, or for tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration, are classified as class C, except when intended to determine any of the following markers: ● ABO system [A (ABO1), B (ABO2), AB (ABO3)]; ● Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)]; ● Kell system [Kel1 (K)]; ● Kidd system [JK1 (Jka), JK2 (Jkb)]; ● Duffy system [FY1 (Fya), FY2 (Fyb)] in which case they are classified as class D[(2)].

Legend: [(1)] IVDR, Article 47(I) & Annex VIII Section 2 Rule 1; [(2)] IVDR, Annex VIII Section 2 Rule 2.

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The harmonised standard EN ISO/IEC 17025 can be used for proof of conformity in the designation of the EURLs [12,13]. The requirements for performance evaluation are laid down in the "Common Specifications" (CS) drawn up by the EU, which are available to the manufacturers and EURLs for verification of compliance of the performance of IVDs [14]. They are a set of technical and/or clinical requirements that provide a means by which a product can fulfil the legal obligations applicable to it. The tasks of the EURLs in the conformity assessment process of IVDs, include (i) verification prior to certification that the performance of the IVDs actually meets the manufacturer's specifications and the CS (if any), (ii) performing batch testing for the release of class D devices (Art 48 paragraph 5 of the IVDR), and (iii), outside of the context of conformity assessment procedures, providing recommendations on suitable reference materials and reference measurement procedures (RMPs) of higher metrological order [15,16]. For these tasks, a contract between the NBs and the EU reference laboratories is required to ensure clarity, certainty and transparency. The EURLs may charge fees to cover the costs of carrying out the requested tasks, which are invoiced to the NBs. By the COMMISSION IMPLEMENTING REGULATION (EU) 2023/2713, a total of five EURLs were designated for class D devices in 2023 [8]: one from Germany, three from Spain (including one consortium consisting of one lead and three member laboratories) and one from Sweden. Different devices intended for the detection or quantitation of markers of (i) hepatitis or retrovirus infection (Germany, Spain), (ii) infection with bacterial agents (three EURLs from Spain), (iii) herpesvirus (three EURLs from Spain), and (iv) respiratory viruses that cause life-threatening diseases (Germany, Sweden) were assigned to these EURLs. As of August 2024, for the remaining categories of class D devices (arboviruses, haemorrhagic fever and other biosafety level 4 viruses, parasites, blood grouping), no EURLs have been designated yet. Article 100 of the IVDR requires that the EURLs form networks and scope-specific subnetworks to coordinate and harmonise their processes, in particular the examination procedures used for performance verification and batch testing of IVDs (e.g. reagents, controls, calibrators) using standardised and harmonised evaluation methods [1,12]. The NRLs appointed by the respective Member States are intended to support the capacities of the EURLs by outsourcing. The EURLs must then (per scope) establish and manage a network of NRLs and publish a list of network members and their respective tasks. The appointment of the NRLs will follow that of the EURLs, and a network with the NRLs will have to be established. As of August 2024, such a network of NRLs has not yet been established. (Table 2)

In the coming years, NBs will also be involved in the performance evaluation for the first certification of IVDs of classes A - C and for IVDs of all classes that were first authorised before 26 May 2022 and are still on the market then ("legacy devices"). From today's perspective, this will occur from 2028 for class D, from 2029 for class C and from 2030 for classes B and A (those placed on the market in a sterile condition); otherwise they may no longer be placed on the market or put into service [17]. While the involvement of EURLs is not foreseen for the assessment of class B and A IVDs, the EU may, at the request of a Member State, also designate EURLs for class C IVDs [1]. The introduction of the new categorisation rules A - D by IVDR means an increase in the proportion of IVDs to be assessed by NBs from less than 10% under the previous IVD Directive 98/79/EC (IVDD) to approximately 80% under the IVDR [18]. It is therefore foreseeable that NBs will be confronted with an enormous workload [16].

EURLs for Public Health under Regulation (EU) 2022/2371

Regulation (EU) 2022/2371 was implemented *in light of the lessons learnt during the ongoing COVID-19 pandemic and in order to facilitate adequate Union-wide preparedness for and response to all cross-border threats to health, the legal framework for epidemiological surveillance, monitoring, early warning of, and combating serious cross-border threats to health, including zoonotic-related threats* [2].

As stated in Article 2, *this regulation shall apply to public health measures in relation to the following categories of serious cross-border threats to health: (a) threats of biological origin, consisting of (i) communicable diseases, including those of zoonotic origin, (ii) antimicrobial resistance and healthcare-associated infections related to communicable diseases ("related special health issues") and (iii) biotoxins or other harmful biological agents not related to communicable diseases; (b) threats of chemical origin; (c) threats of environmental origin,*

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including those due to the climate; (d) threats of unknown origin; and (e) events which may constitute public health emergencies of international concern under the International Health Regulations (IHR) ("public health emergencies of international concern"), provided that they fall under one of the categories of threats set out in points (a) to (d). In addition, this Regulation shall also apply to the epidemiological surveillance of communicable diseases and of related special health issues and establishes a network of EURLs for public health; a network for substances of human origin; and an advisory committee for the occurrence and recognition of a public health emergency at Union level [2].

Article 15 states that *the EURLs shall be responsible for coordinating the network of national reference laboratories, in particular, in the areas shown in Table 2. The network of EURLs shall be operated and coordinated by the ECDC (European Centre for Disease Prevention and Control), in cooperation with the WHO reference laboratories. The governance structure of that network shall cover cooperation and coordination with existing national and regional reference laboratories and networks* [2].

EURLs with tasks in public health [2] may, but do not have to be the same EURLs that have tasks in the conformity assessment for IVDs [1]. As published in the COMMISSION IMPLEMENTING REGULATION (EU) 2024/892 in March 2024, the first six EURLs were designated for public health according to Regulation (EU) 2022/2371 [2,19]. These laboratories are in fact consortia, each consisting of one lead and two to four member laboratories, located in Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Italy, The Netherlands, Portugal, Slovenia and Sweden. EURLs have been designated for (i) antimicrobial resistance (AMR) in bacteria, (ii) vector-borne viral pathogens, (iii) emerging, rodent-borne and zoonotic viral pathogens, (iv) high-risk, emerging and zoonotic bacterial pathogens, (v) legionella, and (vi) diphtheria and pertussis [20]. EURLs for public health are designated for seven years and will start their activities in January 2025. In contrast to the EURLs under IVDR, which are paid for their services by the contracting NBs, the EURLs under Regulation (EU) 2022/2371 will be funded by the EU4Health programme [21]. The networks will be operated and coordinated by the ECDC to avoid administrative burden and duplication of effort, as well as overlap in reporting and reviewing activities with existing structures and mechanisms for planning and implementing prevention, preparedness and response to serious cross-border health threats at a national level [2,22]. The next EURLs to be designated will focus on (i) food- and water-borne bacteria, (ii) food-, water-, and vector-borne helminths and protozoa, and (iii) food- and water-borne viruses [23].

NRLs under Regulation (EU) 2022/2371

In some countries, national reference centres and advisory laboratories for a number of infectious agents were designated by public institutions years ago and before they were foreseen at the EU level [3]. These public health microbiological laboratories play a central role in detecting infectious diseases, monitoring disease outbreaks and providing scientific evidence for disease prevention and control with a similar scope to that of the EURLs under Regulation (EU) 2022/2371 e.g. [24–28]. In 2010, the ECDC found that the organisation, selection and assessment procedures for microbiological NRLs were remarkably heterogeneous in the EU and thus recognised the need to develop common and harmonised standards for them [29]. In 2013, the foundation was laid for a network of microbiological public health laboratories [4,30,31]. The terms "National Reference Laboratory" and "National Reference Centre" are commonly used, but their use is often country specific, and they have different interpretations [32]. The current legal basis for NRLs is Regulation (EU) 2022/2371, which statesin Article 15 that "*EU reference laboratories are designated to provide support to NRLs to promote good practice and alignment by Member States on a voluntary basis on diagnostics, testing methods, use of certain tests for the uniform surveillance, notification and reporting of diseases by Member States"* [2]. As established in all EU Member States, NRLs under Regulation (EU) 2022/2371 are operating as public health microbiology laboratories with national responsibility and appropriate tools and skills to support national surveillance and the capacity to address emergency situations [33]. The core functions of NRLs are shown in Table 4 and include testing for viruses, bacteria, fungi, parasites and prions, thus providing continuous robust monitoring, early warning and response mechanisms [34].

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Table 4. Core functions of microbiology NRLs.

Function	Description	Activities
Reference diagnostics	The reference laboratory has state-of-the-art validated laboratory methods in operation and the ability to deliver accurate confirmation of diagnostic results within its field of expertise. This may include the analysis of samples in a variety of areas, such as the verification of results (e.g. detection or confirmation) reported by external laboratories, the detection of specific microbial markers and the investigation of atypical samples.	• Have up-to-date reference methods in operation for specific pathogen/disease characterisation. • For selected pathogens: offer diagnostic confirmation services (i.e. validate diagnostic test results, provide advice and support). • Investigate atypical samples.
Reference material resources	If necessary, the reference laboratory develops and maintains - in accordance with international standards and procedures - a collection of relevant reference material that is to be shared with laboratories and organisations that request such materials. These materials can include reference laboratory strains and cultures, clinical isolates, sera, genetic materials, etc. These resources are important for the varied purposes of quality assurance systems, method evaluation and validation.	• Develop, maintain and/or have access to relevant source reference materials. • Provide and/or facilitate access to reference material for relevant laboratories and organisations.
Scientific advice	The reference laboratory is a resource and coordination point for expertise within its specific area and shares information and advice with relevant stakeholders. This can include technical advice on methods and procedures, scientific support and advice on the interpretation and relevance of laboratory findings on pathogens to relevant public health authorities (policy makers and public health professionals).	• Provide scientific advice and recommendations to public health authorities. • Provide technical support for policy development, e.g. vaccine issues, outbreak response management and preparedness planning. • Provide advice and support to laboratories (i.e. including activities such as conducting workshops and other training activities based on needs but

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		also for the implementation of new methods and policies).
Collaboration and research	The reference laboratory is at the forefront of technological and scientific development in its field of expertise, particularly in areas relevant to public health action. Contacts with regional and international laboratory networks as well as related initiatives should be established and maintained. Examples of collaboration are involvement in EU and other international disease-specific networks, network activities of regional laboratories, or global initiatives via WHO or the US CDC.	• Participation in regional/international public health microbiology laboratory networks. • Participation in other regionally or internationally relevant projects and initiatives, including research and development activities to underpin the quality, scope and development of core reference laboratory activities; participation in, and contribution to, international surveillance.
Monitoring, alert and response	The reference laboratory performs or contributes to surveillance activities, or has established channels of communication with the national surveillance body to regularly report incidence data and provide an 'alert function' for unusual occurrences. These can include failure of a diagnostic test, detection of changes in incidence, virulence, drug resistance, emergence of a possibly infectious disease of unknown aetiology, etc. In the case of an outbreak, the reference laboratory supports outbreak investigations, e.g. by offering diagnostic services, advice and technical expertise, and, upon request, provides surge capacity for diagnostics.	• Provide data to national surveillance institutes or, if part of a national surveillance institute, to other appropriate bodies. • Provide surge capacity as part of a national preparedness plan. • Provide advice and technical support in outbreak investigations. 5d. Provide early warnings in case of unusual occurrences.

Legend: adapted from [29].

Approximately 50 diseases and "special health issues", such as antimicrobial resistance, are listed in the Implementing Decision (EU) 2018/945 for monitoring through the EU's epidemiological surveillance network [35]. In the case of a clinically suspected case (supported by medical history) or if a listed pathogen is detected in a medical laboratory, patient specimens should be forwarded to the competent NRL for diagnostic testing or for confirmation, further typing, registration and reporting to the ECDC. The referring laboratories receive a result or a report from the NRL. While the results of *diagnostic* examinations carried out by NRLs are directly relevant for patients and their treatment,

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examinations carried out for *confirmation* purposes or for *epidemiological reasons* have clinical impact only in exceptional cases (e.g. the identified subtype of pathogen requires a specific therapy or the suspected pathogen has not been confirmed). While the NRLs operate for epidemiological purposes on behalf of the authorities, the referring laboratory cannot assume responsibility for the services of the NRL, as required by ISO 15189. However, if an NRL is selected from several providers of certain tests to forward a patient's specimen for diagnostic purposes, the NRL is, in this case, a referral laboratory for whose performance the referring laboratory assumes responsibility towards the patient or clinician. The assumption of costs for the epidemiological and diagnostic services of the NRL is not uniformly regulated in the Member States and ranges from the billing of each individual service to the public purse or the patient's health insurance fund to the granting of a regular lump sum that covers all services.

Reference Laboratories Designated by Other Competent Organisations

Various organisations have recognised laboratories that carry out relevant tests and refer to them as “reference", “accredited”, or simply “designated” laboratories. Although these three terms are neither clearly defined nor used in a standardised and unambiguous way, it can be assumed that they are used interchangeably and with the same meaning. The organisations mentioned below as examples are internationally operating and perceived by the public as having a high level of expertise and integrity, high moral standards and/or a humanistic mission. However, there is no generally accepted and recognised definition of or requirements for “competent organisations” that may designate reference laboratories. What they all have in common is just that they have reviewed the performance of the applicant or selected laboratories and, if recognised, awarded them the mostly temporary but renewable designation "reference laboratory" or similar. It is at the discretion of the designator to determine who bears the costs of the examination services. (Table 5)

Table 5. Examples of reference laboratories tdesignated by organisations other than the EU.

WHO reference, accredited, or merely designated laboratories	
H5 Reference Laboratories (Influenza A(H5N1))	[36]
Global HIV, hepatitis and sexually transmitted infections (STIs) and resistance programmes	[37]
measles and rubella laboratory network	[38]
for poliomyelitis	[39]
for tuberculosis	[40]
for prequalification of medical products (IVDs, medicines, vaccines and immunisation devices, vector control)	[41]
ECDC reference laboratory networks	
European COVID-19 reference laboratory network (ECOVID-LabNet)	[43]
European Reference Laboratory Network for TB (ERLTB-Net)	[44]
European Reference Laboratory Network for Human Influenza (ERLI-Net)	[45]
WADA accredited laboratories	

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for doping control analysis	[48]
ETRL reference laboratory	
EPT provider for histocompatibility related assays for laboratories accredited or not accredited by the European Federation for Immunogenetics (EFI)	[49]
EFI accredited laboratories	
for immunogenetics, tissue typing and transplantation	[50]
Immunohematology Reference Laboratories	
Organisations designating immunohematology Reference Laboratories:	
Association for the Advancement of Blood & Biotherapies (formerly American Association of Blood Banks) (AABB)	[54]
College of American Pathologists (CAP)	[55]
according to the standard ISO 15189, if required by accreditation organisations with authorization according to the Clinical Laboratory Improvement Amendments (CLIA)	[56,68]

The WHO has designated laboratories as "reference", "accredited" or merely "designated" laboratories for infectious diseases and for quality controls of medicinal products [36–41]. It should be noted here that one of the prerequisites for the “accreditation” of a laboratory by the WHO is valid accreditation in accordance with ISO 17025 by an accreditation body.

The ECDC has established a comprehensive set of disease and laboratory networks, whereby some of them act also as reference laboratories [42–45].

The World Anti-Doping Agency (WADA) requires that laboratories that analyse doping control samples must achieve and maintain accreditation according to the WADA International Standard for Laboratories (ISL) [46,47]. Here, valid accreditation in accordance with ISO 17025 by an accreditation body is also a prerequisite for “accreditation” by WADA. In August 2024, a total of 30 laboratories were accredited for doping control analysis [48].

The Eurotransplant Reference Laboratory (ETRL) provides specialised monitoring, training, quality assurance and external proficiency testing (EPT) for laboratories accredited by the private noncommercial organisation European Federation for Immunogenetics (EFI), but also EPT for histocompatibility testing for non-accredited laboratories [49–52]. The EFI accredits laboratories according to established standards for immunogenetics, tissue typing and transplantation. Such accreditation is required by a number of organisations active in the field of stem cell transplantation for the Foundation for the Accreditation of Cellular Therapy (FACT), the Joint Accreditation Committee of the International Society for Cell and Gene Therapy (JACIE, ISCT), and the European Society for Blood and Marrow Transplantation (EBMT), and organ transplantation for Eurotransplant (ET). In August 2024, a total of 274 laboratories were accredited by the EFI [53].

The vast majority of "reference laboratories" are likely to be found in the field of immunohaematology. Many of them are accredited as immunohematology reference laboratories (IRLs), but by different organisations, such as the Association for the Advancement of Blood &

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Biotherapies (AABB), the College of American Pathologists (CAP), or the U.S. Food and Drug Administration (FDA) [54–57]. In August 2024, a total of 1038 laboratories worldwide were accredited by the AABB alone.

Calibration (Reference) Laboratories

Calibration (reference) laboratories serve to support traceability in laboratory medicine, a cornerstone of quality assurance not only in medical laboratory diagnostics. Their goal and that of their network, organised in the intergovernmental Bureau International des Poids et Mesures (BIPM), is to achieve accurate and comparable test results, regardless of the procedure and the IVD used or the laboratory in which the test is performed [58,59]. Calibration laboratories determine the concentrations of measurands, e.g. in materials intended as secondary reference materials for commercial test standardisation or for target value assignment of trueness verifiers intended to be used in external quality assessment (EQA) [60]. The provision of calibration services is an important mission of National Metrology Institutes (NMIs) but other calibration laboratories exist. These can operate as independent organisations, or as part of an academic laboratory, for example, which operates a department for reference measurements in addition to a diagnostic laboratory. The services of the calibration laboratories are invoiced to the customer.

The term "reference laboratory" was used in metrology guidelines before ISO 15195:2018 came into force, and the term "calibration laboratory" was introduced [61]; ISO 17511:2020 [62] mentions "reference/calibration laboratories". These laboratories are currently referred to as "calibration laboratories", "reference laboratories" or "reference measurement service providers".

RMPs are costly and time-consuming complex chemical analysis methods that are unsuitable for routine clinical analyses. RMPs, reference measurement services (RMS) and materials intended to become reference material (RM) or certified reference material (CRM) are listed in the JCTLM database. After reviewing the evidence of compliance with the standards ISO 15193 [63], ISO 15194 [64] and ISO 15195 [61], compliant RMPs, CRMs and reference measurement service providers are listed in the freely accessible database of the JCTLM [65,66]. In August 2024, a total of 238 RMPs were listed for 112 clinical measurands, 290 RMs, and 285 RMS, these RMS are provided by a total of 27 laboratories located in six countries, namely Belgium (1), China (19), France (1), Germany (4), Japan (1), and the United Kingdom (1), and their analysis spectra comprised two to 34 analyses [66]. (Table 6) Further prerequisites for the endorsement of laboratories are (i) accreditation according to the International Standard ISO 17025 [13], (ii) the use of an RMP listed by the JCTLM, and (iii) participation in international interlaboratory comparisons such as RELA, the EQA program of the IFCC for reference laboratories in laboratory medicine [67,68].

Table 6. RMPs, RMSs and RMs as listed by the JCTLM.

Analyte category	Reference measurement procedures (RMP)	Reference measurement services[(4)] (RMS)	Reference materials (RM)
Blood cell counting	3[(1)]	0	0
Blood grouping	0	0	3
Coagulation factors	0	0	1
Drugs	29	5	23
Electrolytes	46	40	36
Enzymes	7	111	10ju

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Metabolites and substrates	52	72	80
Non-electrolyte metals	15	0	41
Non-peptide hormones	40	41	32
Nucleic acids	9(2)	0	24
Proteins	27(3)	14	38
Vitamins and micronutrients	10	2	2
total	**238**	**285**	**290**

Footnotes: (1) - including thrombocytes, thrombocytes for lower particle concentration, erythrocytes. (2) - including human cytomegalovirus quantification by PCR, SARS-CoV-2 N, E, and ORF1ab gene measurement, KRAS G12D/WT by digital PCR, EGFR L858R, T790M, and 19 DEL mutation fraction abundance, BRAF V600E (1799 T>A fractional abundance. (3) - Note that although there are RMPs for total IgG, IgM and IgA, there are no RMPs for specific antibodies as used in infection diagnostics. (4) - A total of 27 reference service providers are located in six countries ((Belgium (1), China (19), France (1), Germany (4), Japan (1), United Kingdom (1)), and their analysis spectra comprise two to 34 analyses. **Legend:** adapted from [65].

Referral Laboratories

In common parlance, laboratories are sometimes referred to as "reference laboratories" although they are in fact *referral* laboratories. The International Standard ISO 15189:2022 defines a referral laboratory as an "*external laboratory to which a sample or data is submitted for examination*" [69]. According to this definition, reference laboratories are a subset of referral laboratories, and if a laboratory that receives referred samples does not fall under the definition of a "reference laboratory", it is still a "referral laboratory".

With the exception of the officially designated reference laboratories, which cannot be selected, the management of a referring laboratory selects referral laboratories and decides for which tests (e.g. rare tests) and, if applicable, at what time of day (e.g. night) or day(s) of the week (e.g. weekend) samples or data for analysis or interpretation are forwarded to them. ISO 15189:2022 requires the laboratory to take responsibility for externally provided products and services, including the services of referral laboratories and consultants [69]. As a part of the selection procedure, the laboratory must define its requirements for (potential) referral laboratories and consultants and specify how it will manage the initial and recurrent review and approval of externally provided products and services. Depending on the agreement, the patients or their health insurance providers are charged with the analytical services. (Table 1)

A subset of referral laboratories may be "eminence" laboratories. These laboratories have specific unique competences but no mandate from a competent organisation. This also applies to recognised experts who may be consulted. The opinions of such experts are jokingly referred to as "eminence-based", and their laboratories are referred to as "eminence laboratories" [70]. Nevertheless, "eminences" are important and indispensable contacts also in laboratory diagnostics. Without them and their advice, clinicians could be left in doubt about unclear cases and patients would be at risk of inappropriate treatment due to a diagnostic error or a missed diagnosis. The inability to objectively assess the competence of an "eminence" can pose a major challenge for documenting the rationale for appointing consultants and in assessing their competence on an ongoing basis in accordance with ISO 15189:2022.

"Reference" and "Referral" Laboratories in Recent Scientific Publications

A literature search for publications that included the terms "reference" or "referral" laboratory and laboratories identified a total of 212 citations; three duplicates and 22 articles that either did not

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refer to reference or referral laboratories or were not freely accessible (and the meaning of the search terms could not be interpreted from the title or abstract) were excluded. The remaining 187 (100%) articles comprised a total of 104 (56%) that referred to EURLs or NRLs or reference laboratories designated by other competent organisations, 11 (6%) that correctly referred to referral laboratories, and 72 (39%) that used the term "reference laboratory", but the content clearly indicated that these were referral laboratories, mostly clinical or expert laboratories. (Figure 1)

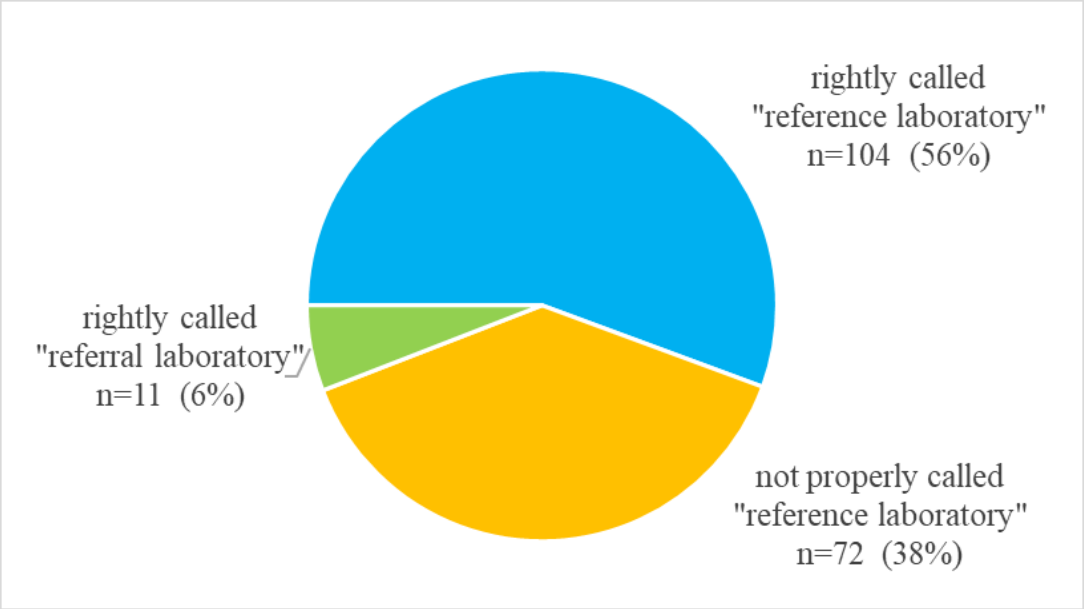

Figure 1. "Reference" and "referral" laboratories in recent scientific publications.

Discussion

Neither EURLs nor other designated reference laboratories are newly established laboratories for the sole purpose of carrying out the reference tests expected of them. They are rather highly specialised laboratories that have been well established for a long time and are often part of universities, university hospitals or other competence clusters. They have the appropriate technical equipment and human resources and by being designated as a "reference laboratory", merely take on an additional task and function at a certain point in time. It can therefore be assumed that such laboratories continue to perform other tasks in addition to their reference activities, namely those they they already performed before their designation, such as research and teaching or carrying out analyses for patient diagnostic or public health purposes.

Great efforts are currently undertaken to implement the regulations for the establishment of EURLs regarding the performance verification and monitoring of class D IVDs and on serious cross-border threats to health. The tasks of these nascent institutions are broadly defined, and it is up to them to determine the technical details of their activities. This applies both to the activities of the EURLs in relation to IVDs and to public health. The required and promoted networking and cross-border cooperation on the one hand, and the freedom to determine the details of their activities themselves on the other, lead us to expect that the achievements of the individual groups involved will not only add up but will multiply through the exchange and complementarity of knowledge and capacities.

The risk-based classification of IVDs according to IVDR leaves room for interpretation when categorising individual devices. Although guidance is provided on the application of the classification rules for IVDs, discussions on their actual classification between manufacturers applying for authorisation of their devices and NBs are to be expected. The opinions of the EURLs or other experts can be helpful in such discussions.

The impacts of IVDR implementation on the manufacturing, release, and distribution of IVDs and their postmarket surveillance are expected. The approval of IVDs will no longer be carried out

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by self-declaration of conformity by the manufacturer, but rather by an NB as a competent third party, and the EURLs will have an additional gatekeeper function for high-risk IVDs. However, it remains to be seen whether the designation of EURLs for IVDs of class D will progress as intended. It seems that either the interest in this responsible task is moderate or the requirements of the EU for applicants are high, since only five EURLs have been designated after the first call and a new call may be started [71]. However, precautionary measures for conformity assessment in the absence of EURLs were taken in the IVDR. Devices may still be certified by NBs and placed on the EU market, as EURL-related elements of the conformity assessment do not apply to them until a EURL is designated.

The areas of animal health, food and feed, and plant health appear to be much more comprehensive and have been regulated in the EU for much longer than infection control in humans. This could be because the healthcare system is considered to be under the national sovereignty of the respective Member States and the EU has only little influence. Although EURLs for public health are also intended to carry out reference diagnostics, the focus of EURLs is not in the area of medical laboratory diagnostics. Apart from the fact that in some countries the preparation of medical reports is reserved for physicians, the analysis services for infection diagnostics provided by medical diagnostic laboratories are indistinguishable from those provided by microbiological laboratories, except that the latter not only analyse specimens obtained from humans, but also samples from other areas, such as animals, water or food. EURLs and NRLs can and often function as medical and microbiological laboratories simultaneously, offering their services without differences in analytical procedures depending on the origin of the samples.

The JCTLM was founded in 1998 by the IFCC, the BIPM [59] and the International Laboratory Accreditation Cooperation (ILAC) [72]. The initial involvement of the IFCC may have contributed to the fact that most of the 238 measurands currently listed in the JCTLM database can be assigned to the discipline of clinical chemistry. Other professional associations, such as those for haematology, coagulation, immunology, microbiology, virology and immunohaematology are only at the beginning of the path towards RMPs, which clinical chemistry has been following for several decades.

The unexpectedly high proportion of more than a third of recent scientific publications reporting contributions from supposed reference laboratories to their studies, actually meaning *referral* laboratories, shows that this ambiguity exists not only in the general population and in primary care facilities, but also extends to the entire spectrum of medicine. The term “reference" emphasises a product or service and identifies it as being of outstanding quality, just as scientists may refer to groundbreaking publications as “reference papers”, or audiophiles like to call excellent recordings of music “reference recordings”. It is curious that reviewers and editors take care to italicise "*in vitro*" in the scientific literature and avoid excessively long sentences that make it difficult to understand the content, but are less strict in regard to the use of imprecise connotations, such as “reference laboratory.” Such terms are widely used as if they have an agreed-upon definition when no such agreement exists. Because various industry sectors also inconsistently use the term “reference laboratories” rather than describing the functions of such laboratories, the inappropriateness of its use is apparently tolerated or deliberately accepted.

Our investigations revealed another terminological weakness in this context, namely the ambiguity of the term “competent organisations”, which are supposed to designate reference laboratories. Since the conditions for the establishment of such organisations can range from an international treaty, an association of several states, EU legislation, private associations, or supranational subjects of international law to informal cooperation at the civil servant/ministerial level, this point is circumvented - from a legal point of view - by speaking of “competent organisations” in order to avoid having to go into how they were founded and on what legal basis (law, private law, decisions of international organisations, etc.) they appoint reference laboratories. Seeking business advantages by pretending to be superior to competitors is particularly inappropriate in the healthcare sector. As such practices cannot be prevented, attention should be

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paid to the indication whether a reference laboratory has been designated by a competent organisation and by which one.

The newly regulated classification of IVDs and their risk-based approach, the use of EURLs for conformity assessment in IVD authorisation and postmarket surveillance procedures and for cross-border public health matters represent fundamental changes in development, production, verification, assessment, release, trade, use and postmarket surveillance of IVDs in the EU. New competent bodies will be established later or simultaneously to address antimicrobial resistance and healthcare-associated infections related to communicable diseases, biotoxins or other harmful biological agents not related to communicable diseases, threats of chemical or environmental origin, including those related to climate, and threats of unknown origin. These are important, but also ambitious, extensive and challenging projects in the EU.

Conclusion

The EU is only at the beginning of a journey towards the implementation of new regulations for IVDs and public health, which will take time and require effort, commitment, seriousness and courage from several interested parties. With these EU regulations, at least the objectives of providing safe and high-quality IVDs and adequate public health surveillance for communicable diseases appear to be achievable.

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