REVIEW 10.1111/1469-0691.12052

European quality clearance of new microbiological diagnostics

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Abstract

Laboratory-based diagnosis of infectious diseases is evolving quickly. New technologies and new tests are frequently commercialized, and although guidelines for their proper clinical validation do exist, these are often at the national or regional level. Therefore, the guidelines remain open to interpretation, and are not always applied properly. One of the main questions is how a high level of test quality can be maintained by European legislation. How can product quality be reliably and independently assessed and how can the penetration of sub-standard assays in the European market be managed and hopefully prevented? We here propose that local initiatives, including external quality assessment, public health initiatives, and close multidisciplinary collaborations between manufacturers and academic research institutes, may accelerate decision-making. Vigilance in test quality assessment and legal simplification are important key concepts warranting selective use of those diagnostic tests that comply with the highest quality standards.

Keywords: Conformité Européene marking, clinical microbiology, molecular diagnostics, point-of-care tests, quality control
Article published online: 24 September 2012
Clin Microbiol Infect 2013; **19**: 29–38

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Introduction

Fifty years ago, many of the infectious pathogens currently described in humans were not even discovered. Agents such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) were unknown, as were several bacterial species [1–4]. To date, the variety and complexity of *in vitro* diagnostic (IVD) tests have expanded and evolved to such an extent that these previously unknown pathogens can also be detected and identified to an adequate taxonomic level. Hence, IVD research has been dynamic and innovative [5,6]. The current tests are fast and timely, and provide information beyond simple detection and determination. The required clinical samples are smaller than was required in the past, and many samples are taken with minimal trauma. The current generation of tests is also increasingly user-friendly. This has led to the availability of point-of-care (PoC) and near-patient testing formats that are easy to use for medical personnel and, in some cases, allow self-sampling [7]. Innovative (molecular) technologies, including next-generation sequencing, microelectronics and microfluidics, allow for continuous miniaturization of tests, and DNA or protein 'arrays', 'biochips' or 'lab-on-a-chip' devices are going to be (widely) used [8,9]. The application of nanotechnology will further improve the quality and broad-spectrum applicability of novel generations of IVD tests for infectious and other diseases [10]. IVD testing should facilitate personalized medicine, whereby diagnostics and therapy are directly coupled. These 'theranostic' devices are currently being introduced into clinical laboratories [11,12]. Within the framework of this Theme Section, we will discuss the European governance of quality clearance of such novel and innovative tests in the domain of infectious diseases. This will highlight the general regulatory aspects, mainly from a technology perspective, but exemplified by several viral and (atypical) bacterial business cases.

Molecular IVD testing is the fastest-growing segment, with an explosive growth of nucleic acid diagnostics for infectious

diseases. These tests provide high economic value, both commercially and medically. Their most prominent features are sensitivity, specificity, timeliness, speed, and the fact that they generate critical therapeutic information for the infectious disease specialist when clinical intervention is still possible. To date, the initiation of antibiotic therapy or its refinement have increasingly depended on the outcome of a molecular laboratory test [13]. It may be the molecular PoC or rapid laboratory-based tests that have the greatest potential to facilitate clinical decision-making. Tests that play such an important role will have to be subjected to rigorous quality control. This has led to the introduction of common regulatory requirements dealing with the safety, quality and performance of IVD medical devices: EU Directive 98/79/EC, describing the quality criteria and their management, was published on 7 December 1998 [14]. The first publication initiated a transition period that ended on 7 December 2003. From that moment onwards, IVD devices placed on the European market had to comply with the Directive. This meant that only 'Conformité Européene' (CE)-marked devices could be offered to diagnostic laboratories. This should ensure that only safe and functional products would be placed on the European market and it should facilitate the free flow of goods, persons, services and capital in this market segment.

Summary of EU Directive 98/79/EC

EU Directive 98/79/EC of the European Parliament applies to IVD medical devices and their accessories. The following technical definitions were applied:

1. 'Medical device' refers to any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software necessary for its proper application, intended to be used for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of human disease.
2. '*In vitro* diagnostic medical device' refers to a reagent, a reagent product, a calibrator, control material, a kit, an instrument, apparatus, equipment, or a system, used alone or in combination, intended to be used for the examination of human specimens for the purpose of providing information concerning a physiological or pathological state, or concerning a congenital abnormality, for determining the safety and compatibility with recipients, or for monitoring therapeutic measures.
3. 'Device for self-testing' refers to any device to be used by lay persons at home.
4. 'Device for performance evaluation' refers to any device that will be subject to performance evaluation studies in medical laboratories or in other environments.
5. 'Manufacturer' refers to the natural or legal entity with responsibility for the design, manufacture, packaging and labelling of a device.
6. 'Authorized representative' refers to any natural or legal entity designated by the manufacturer who may be addressed by authorities in the EU instead of the manufacturer with regard to the latter's obligations.
7. 'Intended purpose' refers to the use for which the device is intended
8. 'Placing on the market' refers to the first availability in return for payment or free-of-charge use of a device other than when a device is distributed for performance evaluation purposes only.
9. 'Putting into service' refers to the stage at which a device has been made available to the final user as being ready for use.

For the purposes of EU Directive 98/79/EC, the collection of human tissues, cells and substances shall be ethically governed by the Convention of the Council of Europe for the protection of human rights and dignity. Member states will not create obstacles to the placing on the market or the putting into service within their territory of devices bearing the CE marking if these devices have undergone conformity assessment. Neither shall member states create obstacles to devices intended for performance evaluation in the laboratories using such tools.

Manufacturers are required to comply with the common technical specifications (CTSs): if manufacturers do not comply with those specifications, then they must adopt solutions of an equivalent level. Where reference is made to harmonized standards, this is also meant to refer to the CTSs. During the conformity assessment procedure for a device, the manufacturer shall take account of the results of any assessment and verification operations that have been carried out at an intermediate state of manufacture.

Devices considered to meet the essential requirements must bear the CE mark of conformity when they are placed on the market. The CE mark shall be accompanied by the identification number of the notified body responsible for implementation of the procedures [15].

The manufacturer must prepare technical documentation to qualify for certification of the IVD product, and ensure that the manufacturing process follows the principles of accepted quality assurance. The technical documentation must allow assessment of the conformity of the product, and it must include the following: