

**Vigilance experience for high risk in vitro diagnostics:  
Risk assessment by the German competent authority  
and possible implications for the parties involved in the  
European medical devices system**

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## List of Abbreviations

Ab	antibody
BfArM	Federal Institute for Drugs and Medical Devices
CA	Competent authority
CE	<i>fr.: conformité européenne</i>
CEN	<i>fr. Comité Européen de normalisation</i>
CENELEC	<i>fr. Comité Européen de Normalisation Electrotechnique</i>
CMV	cytomegalovirus
CTS	Common technical specifications
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
EC	European Community
EEA	European Economic Area
EN	European standard
EQAS	external quality assessment scheme
EU	European Union
EUDAMED	European database on medical devices
GHTF	Global Harmonization Task Force
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-cell leukemia virus
IEC	International electrotechnical committee
ISO	International Organisation of Standardization
IVD	in vitro diagnostic medical device
IVDD	Directive 98/79/EC on in vitro diagnostic medical devices
MPG	Medizinproduktegesetz
MPSV	Medizinproduktesicherheitsplanverordnung
MS	Member State
OEM	original equipment manufacturer
PES	Performance evaluation study
PMCF	post market clinical follow-up
POCT	point-of-care-testing
PEI	Paul-Ehrlich-Institut
PEI-IVD	Testing laboratory for IVD, Paul-Ehrlich-Institut
VR	Vigilance report
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten

## 1. Introduction

### **1.1 Statutory framework for in vitro diagnostic medical devices in the European Union**

The regulation of medical devices including in vitro diagnostics within the European Union (EU) is based on a regulatory strategy originally laid down by a Council Resolution of the year 1985 (1) and presenting a formerly new concept of legal harmonisation for a variety of products called the New Approach.

This approach was implemented for the accelerated realization of the free movement of goods as a cornerstone of the single market within the EU and is based on the following principles: Firstly, European legislative harmonisation is limited to essential or minimum requirements that products placed on the Community market must meet in observance of health and environmental protection requirements. Secondly, the technical specifications and manufacturing processes meeting the essential requirements set out in the European directives are laid down in harmonised standards. Although these standards are not legislative in nature and their application therefore remains voluntary, the compliance with harmonised standards benefits from a presumption of conformity with the corresponding essential requirements. Thirdly, the New Approach is based on the reciprocal recognition of conformity assessments generally carried out in the responsibility of the manufacturer and supported by competent bodies all over Europe that are involved in those cases where product failure can cause a serious risk to health. The conformity assessment procedures result in certificates of conformity accepted by all Member States. Finally, the CE-marking of a product indicates the conformity with European legal requirements (CE = *fr. "conformité européenne"*)

The New Approach was supplemented by the Global Approach (2, 3, 4) that implemented a harmonized concept of product conformity assessment. According to this approach, a manufacturer can choose among several conformity assessment procedures, that are composed by different modules for the design and the production phase of the product. The New Approach directives provide the information which modules may principally be applied for conformity assessment of the respective products.

In vitro diagnostics are regulated by the Directive 98/79/EC on in vitro diagnostic medical devices (IVDD) (5) that, together with the Directive 90/385/EEC relating to active implantable medical devices (6) and the Directive 93/42/EEC concerning medical devices (7) is part of the basic European medical device law<sup>1</sup>. According to the IVDD, in vitro diagnostic medical device means "any medical device which is a reagent, reagent product, calibrator, control

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<sup>1</sup> Further directives so far published and amending the basic European legislation on medical devices are: Directive 2001/104/EC, Directive 2003/12/EC, Directive 2003/32/EC and Directive 2005/50/EC.

material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information concerning a physiological or pathological state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures”.

Such as active implantables, but in contrast to the other medical devices, in vitro diagnostics are not assigned to different product classes. However, and in contrast to active implantables, the IVDD differentiates four product categories that, - depending from the potential health risk related to the malfunction of the device -, are subjected to different conformity assessment procedures.

Devices covered by Annex II, List A are so called “high risk” devices. Malfunction of these devices may cause serious health risks. Among them are reagents for the detection of HIV and HTLV infection, hepatitis B, C and D and several systems for determining blood groups. Devices covered by Annex II, List B are categorized as “risk” devices. Examples for List B devices are reagents for the detection of rubella infection, toxoplasmosis, cytomegalovirus, chlamydia, but also a number of systems for determining blood groups. Self-diagnosis devices for the measurement of blood sugar also belong to the List B devices. The main criticism concerning the List B devices refers to a certain lack of risk systematics for the analytic parameters enumerated in List B (8). Devices for self-diagnosis are part of the third category of in vitro diagnostics except for those devices covered by List B. All the rest of devices are assessed as products with the slightest risk potential. According to the list principle of the IVDD, all the devices neither covered by Annex II nor classified as devices for self-diagnosis belong to the group of “other” devices without any further categorisation.

According to the directive, the EU Member States should have implemented the national laws to comply with the IVDD not later than 7 December 1999 and were supposed to apply the IVDD provisions with effect from 7 June 2000. Many Member States including Germany did not transform the IVDD provisions into national law at time<sup>2</sup>. A transitional period of five years following the entry into force of the Directive was provided to accept the placing on the market (for the first time) of devices which conformed to the formerly established national rules. This period ended on December 7<sup>th</sup>, 2003 and was added by two more years, during which these devices could be put into service. This period ended on December 7<sup>th</sup>, 2005. Consequently, since December 8<sup>th</sup>, 2003, any in vitro diagnostic medical device was placed on the market according to the new provisions of the IVDD.

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<sup>2</sup> In Germany, the IVDD provisions were transformed into national law by the Zweite Medizinprodukteänderungsgesetz effective from January 1st, 2002.

## ***1.2 Conformity assessment of in vitro diagnostics: Premarket requirements and involved parties***

### **1.2.1 Essential requirements for in vitro diagnostic medical devices**

In vitro diagnostics “must meet the essential requirements set out in Annex I (of the directive) which apply to them, taking account of the intended purpose of the devices concerned” (Article 3, IVDD).

According to the central demand of the essential requirements, the manufacturer must specify the intended purpose of a device and take the guarantee that the product performances are in accordance with the stated purpose. Among the main device performance characteristics are the sensitivity and specificity (analytical and diagnostic), the accuracy, the repeatability, the reproducibility, the relevant interferences, the limits of detection, and the traceability of the control/calibration material.

Furthermore, the essential requirements refer to the safety of users and patients, the stability of the device during its shelf life, and the specific characteristics concerning the chemical, physical, infection, radiation and energy properties of the device. General demands also exist for devices with measuring function and for self-testing. Finally, the provisions laid down in Annex I include detailed product requirements concerning the labelling and the instructions for use to ensure the correct and safe device use.

Apart from those mentioned in Annex I, further requirements are raised for all categories of in vitro diagnostics. Without consideration of the conformity assessment procedure, a technical documentation for each device is required that must not only include a description of the design and manufacturing process, but also - as key data of the device - a documentation of the quality system established by the manufacturer, the performance evaluation data and the results of the risk analysis. The installation of a postmarket surveillance system is also generally required (IVDD, Annex III, section 3, indents 3-13; Annex IV, section 4.2; Annex V, section 3).

Devices for performance evaluation must be identified and characterized by the manufacturer's statement according to Annex VIII. Since performance evaluation data should originate from studies in a clinical or other appropriate environment (if they do not result from relevant biographical references), and a “device for performance evaluation” means “any device intended by the manufacturer to be subject to ... performance evaluation studies in laboratories for medical analyses ... outside his own premises” (Article 1, paragraph 2e, IVDD), medical laboratories play an important role in the premarket conformity assessment of in vitro diagnostics. The testing competence of these laboratories is a decisive precondition for the generation of correct performance evaluation data (9).



Risk analysis is understood as the implementation of a complex risk management system, where risk analysis is one step of a sequence followed by risk assessment, risk control and risk surveillance for a given device (10). Since performance evaluation and postmarket experience data may be relevant for the manufacturer's risk management, medical laboratories as conformity assessment bodies (premarket phase) and users (postmarket phase) are involved in this process. As far as devices for self-testing are concerned, lay persons as users are among the parties involved.

Among the so far over thirty harmonised standards mandated by the European Commission in the context of the IVDD and created by the European standardization organisations CEN (CEN = *fr.* Comité Européen de normalisation) and CENELEC (CENELEC = *fr.* Comité Européen de Normalisation Electrotechnique), EN 13612 (9) and EN 14971 (10) refer to performance evaluation and risk management of in vitro diagnostics, respectively.

### **1.2.2 Modular concept and conformity assessment procedures according to directive 98/79/EC**

Among the total of eight different modules for conformity assessment provided by the Global approach, six are applicable for medical devices including in vitro diagnostics. In comparison with the directives 90/385/EEC and 93/42/EEC, new elements were added to the modules by the IVDD: Apart from the obligatory implementation of a quality management system for all product categories, advanced quality assurance is required for devices covered by Annex II, List A, which is performed by a "verification of the manufactured products" as batch testing. Furthermore, a new kind of "standard" was introduced as so called "common technical specifications" (CTS) (11). The CTS comprise performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials for Annex II, List A devices. When applied by the manufacturer, the CTS give presumption of conformity with the essential requirements of the directive. In terms of their binding force, the CTS are superior to harmonized standards but inferior to the directive.

For devices that are not covered by Annex II and that are not devices for self-testing, manufacturers may choose a conformity assessment procedure according to Annex III (module A, EC declaration). In sole responsibility – without any participation of third parties in the design or production phase – they will perform the conformity assessment and CE-marking of the device.

Manufacturers of devices for self-testing that are not covered by Annex II may also choose the conformity assessment procedure according to Annex III, but are obliged to involve an independent, competent testing body in the examination of the device design.

The testing bodies are conformity assessment bodies and must comply with the criteria set in Annex IX. These criteria refer to the impartiality of the bodies and their inspection staff, the

material and human resourcing including the scientific and technical competence of the bodies, the professional secrecy and liability aspects. In Germany, as in most other Member States, the compliance of the testing bodies is assessed and confirmed by accreditation. Accreditation and the following designation of the bodies are performed in the responsibility of the Member States to ensure the compliance of the bodies with the legal requirements. In Germany, the designating authority in the field of in vitro diagnostics is the Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG). Following the accreditation and designation procedure, the Member States inform the European Commission and the other Member States of the designation of these bodies. Since this procedure is called “notification”, the bodies are also called “notified bodies”. Subcontractors of the notified bodies, for example testing laboratories, must fully comply with the criteria set in Annex IX. Their compliance may also be confirmed by accreditation (4, 5, 12).

For devices covered by Annex II, the participation of the notified body in the conformity assessment procedure increases. Manufacturers of List A devices may choose between the procedure according to Annex IV (module H, full quality assurance system) or a combination of Annex V (module B, EC type-examination) and VII (module D, quality assurance production). Both options require therefore the involvement of a notified body for both the design and production phase. The verification of the manufactured products is obligatory for List A devices and performed by the notified body. However, the required extent of batch testing is dependent from pre-agreed conditions between the manufacturer and the notified body and therefore not harmonized for all notified bodies in the European Union. For List B devices, the same conformity assessment procedures may be applied as for List A devices except for the verification of the manufactured products which is not obligatory for List B devices. In addition, when choosing the EC type-examination in the design phase, the manufacturer of List B devices is free to choose the EC product verification in the production phase (module E, Annex VI).

### **1.2.3 Exceptional provisions for national marketing authorization of medical devices**

Under exceptional conditions, for example in cases of risk to public health, the Member States may allow the temporary placing on their national market and putting into service of medical devices without premarket conformity assessment according to the New approach directives. In Germany, the competent authority may provide restricted marketing authorization of medical devices including in vitro diagnostics according to § 11 (1) of the Medical Device Act (12).

## ***1.3 European market surveillance activities and information exchange systems for medical devices***

### **1.3.1 Market surveillance by public authorities**

The obligation for market surveillance is complementary to the provisions of the New Approach directives that require Member States to allow free movement of products without any premarket approval by competent authorities under the condition that the products are in compliance with the essential requirements set in the directives.

Market surveillance involves the monitoring of products placed on the market and, in cases of non-compliance with the legal requirements, appropriate action to establish conformity. To guarantee the impartiality of market surveillance, these activities are primarily understood as the responsibility of the public authorities(13).

To be able to monitor products placed on the market, surveillance authorities shall have the competence to visit the premises of the manufacturers and the work places where products are put into service, to examine products and to require all necessary information on the products in question. New Approach directives provide two different tools that enable authorities to get this information: the EC declaration of conformity and the technical documentation. Whereas the EC declaration of conformity must be made available for the authority immediately upon request and therefore should be kept inside the European Community (even if only the authorised representative and not the manufacturer is established within the Community), the technical documentation can only be requested by the authority when there are substantiated doubts about the conformity of the product or an obvious risk to health and safety of persons must be prevented (13). For new products, that means products that were not available on the EU market for a specific parameter during the last three years or that use new technology in connection with a given parameter, the surveillance authority may request a safety report relating to the experience gained with the device at any time during the first two years following its placing on the market.

### **1.3.2 Vigilance system for in vitro diagnostic medical devices**

According to the above mentioned provisions, market surveillance in the field of medical devices including in vitro diagnostics comprises the usually proactive collection of information on the quality, safety or performance of medical devices placed on the European market. Due to the special risks posed by medical devices, the European directives also require the application of a reactive system for the notification and evaluation of adverse incidents known as vigilance system. This system applies for active implantables, medical devices and in vitro diagnostics.

For in vitro diagnostics, the vigilance procedure is based on Article 11, IVDD. It requires that “Member States shall take the necessary steps to ensure that any information brought to their knowledge regarding incidents involving devices bearing the CE marking is recorded and evaluated centrally”. Incidents are defined as “any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health”. Furthermore, incidents are understood as “any technical or medical reason in relation to the characteristics or performance of a device..., leading to systematic recall of devices of the same type by the manufacturer” (5).

Usually, the manufacturer<sup>3</sup> is responsible for activating the vigilance system and must inform the surveillance authority about incidents and near (= potential) incidents within a maximum of 10 or 30 days, respectively (14). The report should generally be made to the competent authority in the country of occurrence of the incident. Incidents resulting in corrective action concerning in vitro diagnostics listed in Annex II or for self-testing and occurring outside the European Economic Area (EEA) should be reported to the competent authority of the Member State where the corresponding notified body is situated. In the aforementioned case, but for devices not covered by Annex II or for self-testing, the incident should be reported to the competent authority of the Member State where the manufacturer (or authorized representative) is situated.

After the notification which is followed by further investigations, the competent authority performs a risk assessment, often together with the manufacturer. Actions performed by the authority may include a consultation with the notified body on matters relating to the conformity assessment. The notified body or the authority may also consult with testing laboratories involved in premarket performance evaluation of a device. Consequently, the parties involved in the premarket conformity assessment procedure may also be involved in the vigilance procedure.

Under certain conditions, the authority must inform the other Member States and the Commission of the incidents and of relevant actions that have been taken or should be taken. This dissemination of information as so called “Competent Authority Report” or „Vigilance Report“ (14) should only be performed, when corrective actions including recalls are to be taken or when a serious risk to health and safety appears, but corrective actions have not yet been undertaken due to ongoing assessment and examination.

At the international level, the Global Harmonization Task Force (GHTF) has established criteria as guidance for the exchange of reports concerning medical devices including in vitro

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<sup>3</sup> When the manufacturer is not established within the EU, the responsibilities concerning vigilance reporting refer to the authorized representative.

diagnostics (15). Exchange of vigilance reports therefore takes place not only within the EU, but also between EU and Australia, Canada, Japan and United States, if a “high” degree of public health threat is determined by the authority (on the basis of the criteria seriousness, unexpectedness of the incident, concerned population (pediatric/elderly), preventability, public concern, benefit/risk - state of the art, lack of scientific data, repeated device problems, written notifications by the authority to the public).

To guarantee efficient information exchange among the Member States, the IVDD requires the construction of a European database (EUDAMED) which contains, among others, the data obtained in accordance with the vigilance procedure (Article 12, IVDD).

According to the IVDD provisions, the vigilance system established in the Member States may also include a user reporting system activated by medical practitioners including medical institutions and organisers of proficiency testing schemes (Article 11, paragraph 2, IVDD; 16). After having received the incident information, the authority will contact the manufacturer and undertake the steps mentioned above. In contrast to the obligatory notification system activated by the manufacturer, the setting of a user reporting system in the Member States is optional.

In comparison with other medical devices, vigilance reporting for in vitro diagnostics is specific and may be more difficult since these devices do not generally come into contact with patients. Harm or risk to patients is more likely to be indirect, for example a result of action taken on the basis of an incorrect result obtained with an in vitro diagnostic device like misdiagnosis, delayed diagnosis, delayed or inappropriate treatment, and transfusion of inappropriate materials.

Incorrect results may arise from a faulty designed IVD, for example, the device does not achieve the claimed sensitivity or specificity or gives rise to user/device interface problems. However, it may be difficult to determine if a serious deterioration in the state of a patient’s health was or could be the consequence of an erroneous IVD result, or if the harm was the consequence of an error by the user or third party. In particular, it can be difficult to judge near incidents in which no harm was caused, but where harm could result if the incident was to occur again elsewhere.

### **1.3.3 Safeguard clause procedure**

A special and so far rarely used procedure within the European market surveillance activities is set by the safeguard clause procedure applicable for all products covered by New Approach directives. For in vitro diagnostic devices, the procedure is described according to Article 8, IVDD. The safeguard clause enables a Member State to restrict or forbid the placing on the market of in vitro diagnostics on the national level when there is substantial evidence that a device may compromise the health and safety of persons due to non-

compliance with the essential requirements, wrongly applied standards or a shortcomings in standards themselves. According to the safeguard clause procedure, the Member State will at first inform the European Commission. The safeguard clause notification can be withdrawn during the procedure, where the apparent risks originally observed are eliminated on the basis of adequate corrective actions by the manufacturer. Following the notification, the Commission will start as soon as possible a consultation of all involved parties and take an opinion on the justification of the national measure. On the basis of this opinion, the Commission will either inform the other Member States to take measures to protect the European Community against health/safety risks in their territories or will ask the originally notifying Member State to re-establish the free movement of the device in question on its territory. In the first case, the matter will within two months either be brought before the committee on standards and technical regulations (17), when a shortcoming of a standard might be related to the case, or before the committee on medical devices (6), when problems related to the content or to the application of the CTS occurred. Usually, a consensus opinion on further actions will then be adopted by the respective committee and the Commission.

Another special kind of “particular health monitoring measures” is provided by Article 13, IVDD. Following this procedure, a Member State may restrict the placing on the market of devices on the national level by the same reasons as mentioned in Article 8. However, there are some differences: Notification is not only necessary towards the Commission but also to all other Member States, assumptions related to standards or to the CTS are not explicitly mentioned, no time-scales are indicated for the procedure conducted by the Commission and usually only the committee on medical devices (not the committee on standards and technical regulations) will be consulted.

The safeguard clause procedure is different from the vigilance procedure, since the latter requires notification even if the manufacturer takes the necessary measures on a voluntary basis. The application of the vigilance system does not exclude the use of the safeguard clause procedure, if the conditions for the safeguard clause notification apply. This may become apparent during the risk assessment of the surveillance authority. It is therefore suggested to indicate on a Competent Authority Report whether the safeguard clause was also used or not (14). However, application of the vigilance procedure is not a necessary condition for invoking the safeguard clause.

#### **1.3.4 Post market surveillance**

While the wording "market surveillance" within the EU is generally used to indicate the tasks carried out by the authorities, "post market surveillance" primarily refers to activities carried out by the manufacturer.

According to the IVDD requirements, the manufacturer “shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product”. Post market surveillance activities by the manufacturer are required, since the technical and performance data that can be gathered in the premarket phase for conformity assessment are limited and do not always enable the manufacturer to detect infrequent complications or problems only apparent after widespread or long term use. Post market surveillance may include active supervision by customer surveys, inquiries of users and patients, literature reviews and post market clinical follow up (14, 18). In the case of in vitro diagnostics, it may include the consideration of extended performance evaluation studies. The notification procedure for the activation of the vigilance system is also part of post market surveillance.

The involved notified body must review the appropriateness of the manufacturer's general post market surveillance procedures under consideration of the innovation of the device, the related health risk in case of malfunction, and the data from premarket performance evaluation.

#### **1.4 The vigilance system in Germany according to the Medical Device Act and further regulations**

In Germany, European legislation on medical devices is transformed into national law by the Medical Device Act (deutsch: Medizinproduktegesetz, MPG<sup>4</sup>, 12) from August, 2<sup>nd</sup>, 1994 (valid from January, 1<sup>st</sup>, 1995). Directive 98/79/EC was implemented in 2002 by the Zweite Medizinprodukteänderungsgesetz. As in the case of the earlier transformed directives, the IVDD provisions were converted to almost 100% into national legislation by extensive referencing to the original IVDD wording. In addition to the MPG, further regulations specify certain aspects in relationship with the placing on the market and putting into service of the devices (19, 20, 21, 22, 23, 24, 25, 26, 27).

The medical devices vigilance system is described in the fifth section of the MPG and the Medizinproduktesicherheitsplanverordnung (MPSV, 20). The definition of incidents and near incidents is directly adapted from the wording of the European directives. The MPSV (§ 3) not only requires the (near) incident notification by the manufacturer (compare footnote 3), but also by users and medical practitioners. The timescale for the initial reporting corresponds to the provisions of the European guidance document (14) with the exception of an explicit requirement of *immediate* notification in case of danger ahead. To ensure an efficient complaint management system, MPG requires the notification of a qualified person

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<sup>4</sup> In the following text, only the German expressions are used for the terms concerning national legislation in Germany.

for vigilance by the manufacturer (MPG § 30). This qualified person shall collect, evaluate and coordinate all measures that are related to vigilance and that shall be reported to the authority. The minimum qualification for the qualified person is proven by a technical, scientific or medical university degree or an education that enables to fulfill the qualified persons' responsibilities.

In Germany, there are two competent authorities that record and evaluate incident and recall notifications for IVDs: The Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich-Institute (PEI). PEI is responsible for high-risk products, namely those listed in Annex II of the IVD Directive, that are related to infectious diseases or those that will be used for safety or compatibility testing of blood or tissue donations. All other IVDs (as all other medical devices) are within the responsibility of the BfArM.

The risk assessment by the competent authority is mainly performed in cooperation with the manufacturer and shall determine the degree of risk associated with an incident and the extent of necessary corrective actions. The manufacturer is obliged to cooperate by providing technical, clinical/performance data and results from the risk analysis on demand of the authority (MPSV § 12). However, the legal provisions do not directly impose a fine on the manufacturer in case of non-compliance with these requirements. Scientific examination may be initiated by the authority in order to clarify an incident (MPSV § 11). Following the risk assessment, the competent authority will deliver its evaluation to all involved parties at the international and national level. Thereby informed competent authorities of the Länder may perform further surveillance activities<sup>5</sup>. In case of an incident related to a device assessed by a German notified body during the premarket conformity assessment, the designating authority ZLG (in case of IVDs) will also be informed. The risk assessment usually ends with a final report delivered to all involved parties. BfArM and PEI shall periodically and scientifically review their risk assessments and publish the obtained results (MPSV § 23).

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<sup>5</sup> According to its federal structure, Germany is subdivided into 16 Länder where competent authorities are responsible for market surveillance in each of the Länder.



## ***1.5 Issues under examination***

Since December 2003, any in vitro diagnostic medical devices are placed on the European market according to the new IVDD provisions. Due to safety reasons, especially high risk in vitro diagnostics covered by Annex II are the focus of public and regulatory attention. In order to ensure a high level of public health protection, the installation of a complex postmarket information system is required that constitutes a safety network with interfaces between the parties involved in premarket conformity assessment and in postmarket surveillance activities.

By review of the incident notification data registered by PEI during the year 2004, this thesis aims at the evaluation of the European and German vigilance system for high risk in vitro diagnostics and at the discussion of possible implications for the bodies related to the European medical devices system.

The study differentiates between a statistical analysis of the incidents reported to PEI in 2004, a detailed presentation of exemplary cases, a critical evaluation of the notification practice in Germany and the discussion of consequences resulting for manufacturers, notified bodies, laboratories and public authorities.

## 2. Tools and Methods

The case reports and incident notifications recorded by PEI during the years 2002 to 2005, with special emphasis on the year 2004, were statistically evaluated. Data were obtained by initial and follow-up reports of the notifying parties. For notifications initiated in Germany, the documents provided by Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) were mostly used (<http://www.dimdi.de/dynamic/de/mpg/download/index.htm>). Intense consultation with notifying and other involved parties took place. For the storage and management of the PEI data, the software Optimal AS, version OS: 4.x (Optimal Systems, Gesellschaft für innovative Computertechnologien mbH, Berlin) was used.

To provide an overview of the notification system, the following evaluation criteria were used: number of (near) incident notifications, sources of incident notification, kind of product category, involved notified body, number of corrective actions, number of vigilance reports.

For the detailed characterization of the risk assessments performed by PEI, the following criteria were applied: incident origin (for example product defect including the determination of the critical performance parameter, user problem, sample status, regulatory shortcoming, unknown), effects and possible effects of the incident, results of the device design examination, performance evaluation data, kind of premarket conformity assessment procedure, kind of corrective and/or preventive actions, parties involved in the risk assessment.

To provide information about the functioning and efficacy of the information exchange inside the European medical devices system, the conduct of investigation for the different cases was analysed. Among the criteria used were the notification time-scale, the cooperation attitude between the involved parties, the progress and outcome of investigation and the provision and use of regulatory tools according to the directive 98/79/EC.

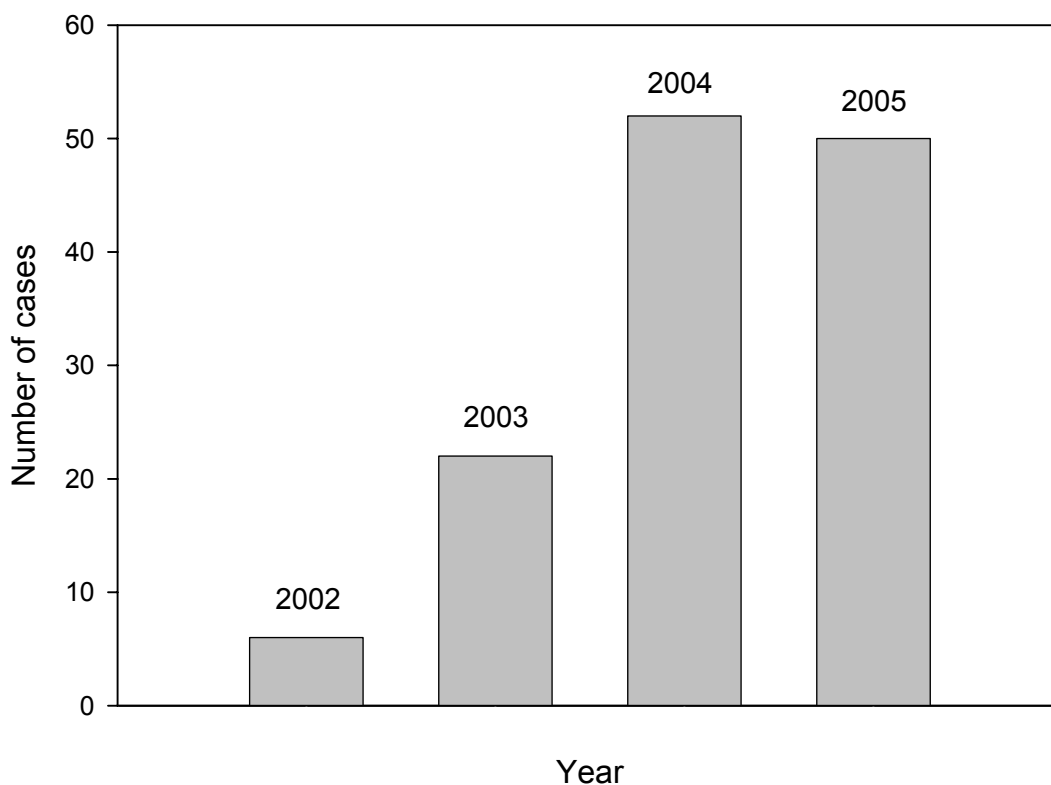
## 3. Results

### 3.1 Overview of the vigilance data 2004

#### 3.1.1 Quantification of notifications

In Germany, the competent authorities that record and evaluate incident notifications for in vitro diagnostics are BfArM and PEI. PEI is responsible for high-risk products that are related to infectious diseases and those that will be used for safety testing of blood or tissue donations. All other in vitro diagnostics are within the responsibility of BfArM. These products are not included in the following analysis.

From 2002 to 2005, a total of 130 notifications have been recorded by PEI. In the beginning of this period, many of the reports were not related to CE marked devices, as CE marking was not possible until June 2000 and there was a transitional period for manufacturers until December 2003. The number of reports has been rapidly increasing in 2003 and again has been doubled in 2004. In 2005, the number of reports was comparable to that of the year 2004 (Fig. 1).

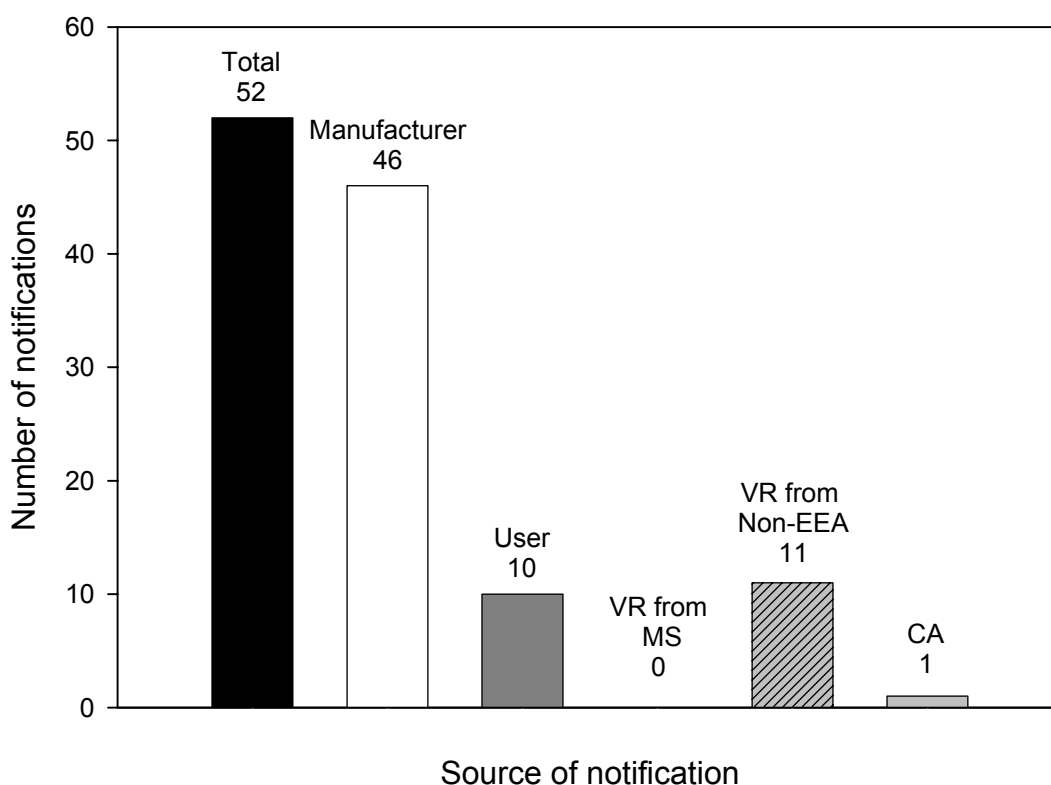


**Fig. 1. Quantification of the notifications during the years 2002 to 2005.** Reports of incidents and near incidents obtained by PEI without differentiation between notifications and vigilance reports.

### 3.1.2 Sources of (near) incident notification

The data recorded in 2004 represent the first year, where placing on the market of in vitro diagnostics was solely possible according to the IVDD requirements. The further analysis therefore confines to this period.

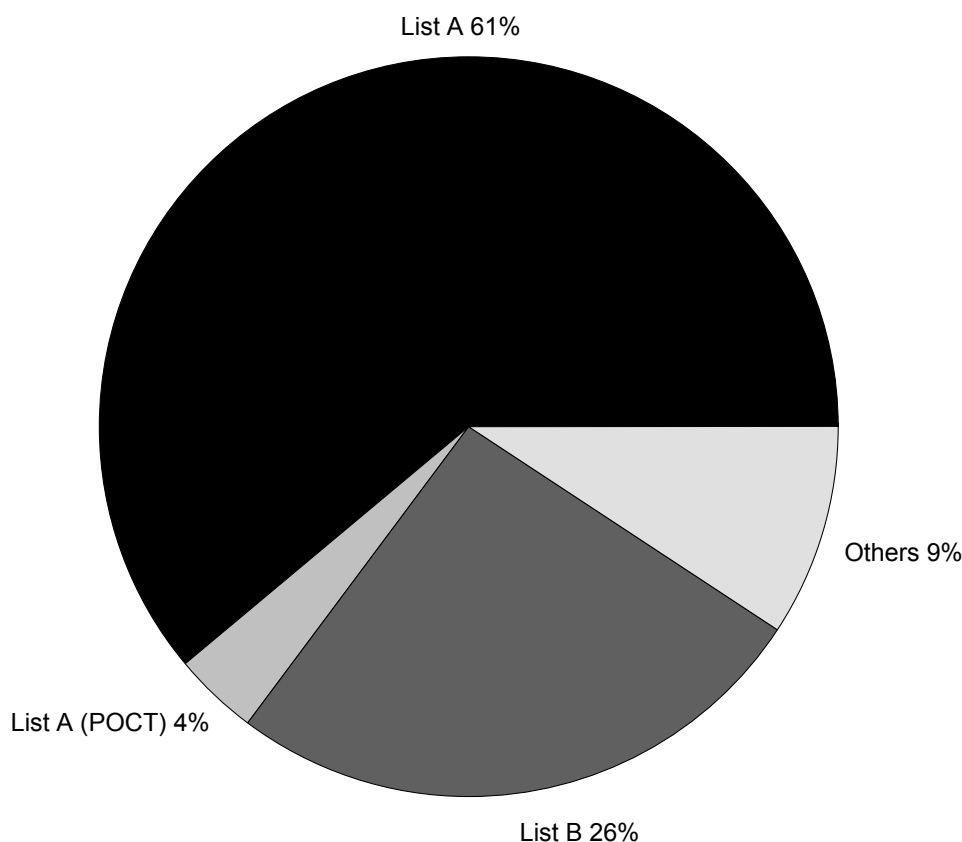
From the total of 52 cases registered by PEI in 2004, the vast majority of notifications was sent in by manufacturers. About 20% of initial reports referred to the same cases, but were performed at the same time by different sources. Less than 20% of the notifications were sent in by users, who, - due to the nature of the devices registered by PEI -, are professional users without exception. Competent authorities of other Member states did not send any vigilance report and only 1 notification report (which was referring to a near incident of unknown reason sent rather for information than for vigilance purposes). A considerable number of vigilance reports was obtained from Switzerland as part of the Non-European economic area (Non-EEA). Notably, none of the reports were sent in by proficiency testing organisations. Any notification was neither obtained by national competent authorities (Fig. 2).



**Fig. 2. Determination of the sources of (near) incident notification.** 46 notifications were obtained by manufacturers, 10 by users, 11 by the Non-EEA and one by a competent authority inside the European Union (CA).

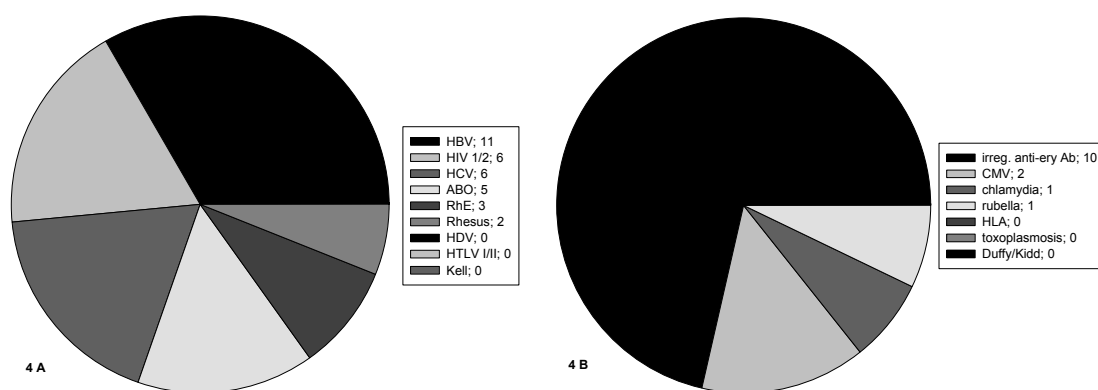
### 3.1.3 Product categories

Notifications recorded by PEI concern all devices covered by Annex II, List A and a selection of devices enumerated in Annex II, List B. In detail, List A devices are reagents (including related calibrators and control materials) for determining the blood groups ABO system, rhesus (C, c, D, E, e) and anti-Kell and reagents for the detection, confirmation and quantification of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D. List B devices related to infectious diseases and to use for safety testing of blood or tissue donations are reagents for determining the blood groups anti-Duffy and anti-Kidd, reagents for determining irregular anti-erythrocytic antibodies, reagents for the detection and quantification of rubella, toxoplasmosis, cytomegalovirus and chlamydia infection and reagents for determining the HLA tissue groups DR, A, and B. Almost two thirds of the reports received were related to List A devices. Interestingly, devices used for point-of-care-testing (POCT) were among them. Less than one third of notifications counted for List B devices. The small remainder referred to devices usually registered by BfArM but transferred for information purposes to PEI. Those cases for example were related to software defects or product information mistakes for instruments that are used in connection with high risk in vitro diagnostics (Fig. 3).



**Fig. 3. Determination of the product categories related to (near) incident notification.** The figure differentiates between devices covered by List A and List B of Annex II, POCT devices and “other” devices initially recorded and assessed by BfArM.

Among the list A devices, about one third of the reports was related to reagents used for the detection of hepatitis B infection. Notifications related to HIV and HCV detection and to the determination of blood groups of the ABO and Rhesus system appeared in comparable frequency. A slightly increased number of inadequately determined anti-E samples in blood group serology was recorded. No reports were obtained in connection with the detection and determination of hepatitis D, HTLV and blood groups of the Kell system, respectively (Fig. 4 A). As for the List B devices, the clear majority of reports related to in vitro diagnostics used for the determination of irregular anti-erythrocytic antibodies, while only occasional or even no reports were reported for the remaining devices (Fig. 4 B).



**Fig. 4. Numbers of notifications related to Annex II, List A (Fig. 4A) and List B (Fig. 4B) devices.** Incident and near incident notifications are not differentiated.

The distribution of product categories related to PEI notifications correlate with their relevance and frequency of use mainly in the fields of transfusion medicine and immune haematology. Since, for example, safety testing of blood or tissue donations mainly includes the determination of parameters related to List A devices, it is not surprising that the part of notifications related to these devices is higher than for List B devices. The same is true for the contribution of devices used for determining irregular anti-erythrocytic antibodies to the number of notifications among the List B devices.

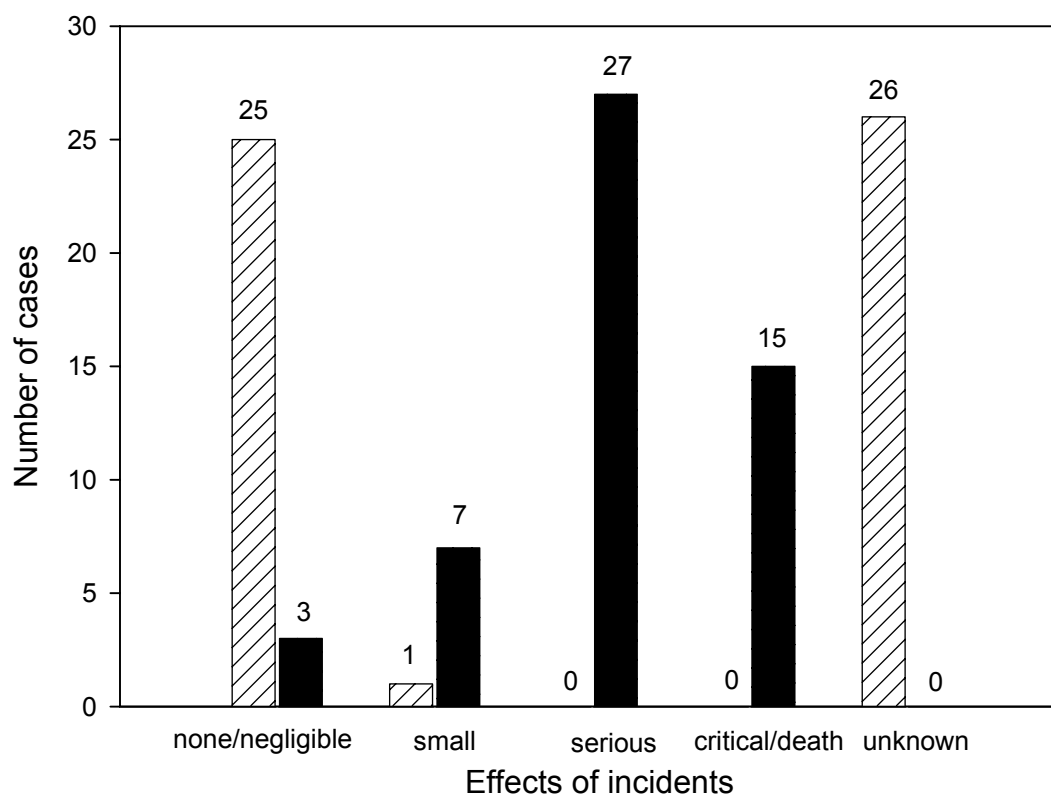
### **3.2 Incident analysis and risk assessment by the competent authority PEI**

#### **3.2.1 Incidents and near incidents**

Incident analysis is mainly characterized by the evaluation and assessment of the risk to public health which may be related to deficits reported to the competent authority PEI. In accordance with the IVDD provisions, PEI not only differentiates between the confirmed effects that occurred in connection with a vigilance case (= incident) and the potential effects

that might occur in case of recurrence (= near incident), but also between the degrees of seriousness related to the reports.

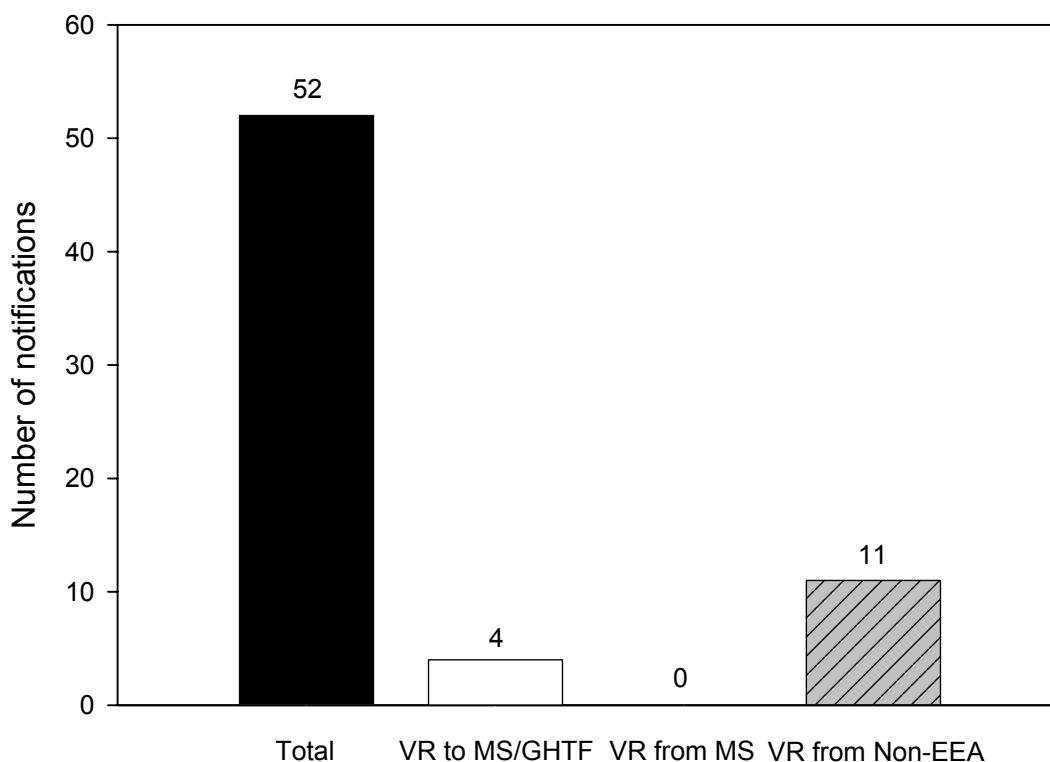
For the cases assessed by PEI in 2004, no incident consequences with serious health or safety impairment could be *verified*. However, only about half of the notifications were *confirmed* to show no or only small effects related to public health impairment (Fig. 5). These data demonstrate the difficulties specifically related to vigilance reporting for in vitro diagnostics. Since harm or risk to patients is mostly indirect, it is often impossible to verify without any doubt whether reported near incidents can be regarded as isolated cases or not. Furthermore, it can be difficult to judge near incidents in which no harm was caused, but where harm could result if the incident was to occur again elsewhere. In this context, about 80% of the cases recorded by PEI were assessed to bear a serious or life-threatening risk in case of recurrence (Fig. 5).



**Fig. 5. Risk assessment of the PEI cases 2004.** Hatched columns indicate effects of health/safety impairment related to the cases as reported (unknown = no harm verified), black columns indicate potential effects in case of recurrence.

In 2004, 15 of 52 cases recorded by PEI met the criteria to be communicated as vigilance reports (14, 15). 4 vigilance reports *sent* by PEI were without exception related to List A

devices (2 HIV cases, 1 HCV case, 1 ABO case). Although these cases were assessed as “near incidents”, since no direct harm could be confirmed, Europe-wide product recalls were performed because serious risks in case of recurrence were assessed. Vigilance reports were exclusively *received* from Switzerland and were related to recalls of the product categories of List A (2 cases), List B (6 cases) and “others” (3 cases) (Fig. 6).



**Fig. 6. Information exchange by vigilance reports.** Among the 52 notifications recorded by PEI in 2004, 4 vigilance reports were sent by PEI to the European Commission, the European Member States and the other GHTF Members. 11 vigilance reports were received from Switzerland (Non-EEA).

### 3.2.2 Evaluation of incident causes

Incidents and near incidents may have a variety of causes. Incorrect results obtained with an IVD may arise from a faulty designed or labelled IVD, from unfavourable patient sample characteristics, from user mistakes or from shortcomings in the regulatory framework (deficiencies in laws, CTS, standards).

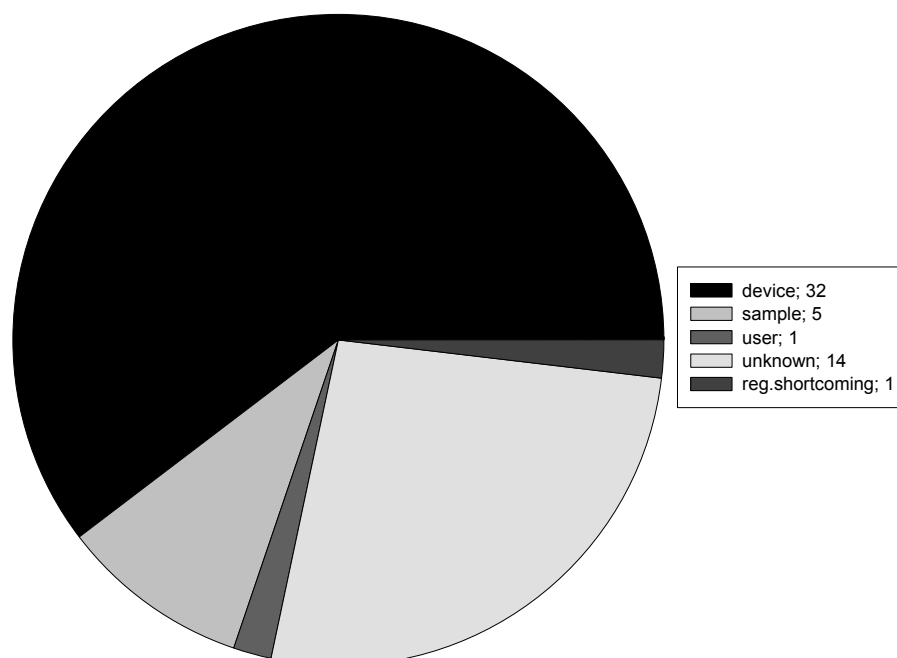
For more than 60% of the cases assessed by PEI in 2004, a product defect could be confirmed (32 of 52) (Fig. 7). For about half of these notifications, deviations were confirmed for device performance parameters like the sensitivity, specificity, precision and reproducibility. Inadequacies in the device robustness, as far as the stability along the shelf life or observed interferences are concerned, were observed in nearly 30% of these cases and then caused performance deficiencies. Packaging errors, labeling and product



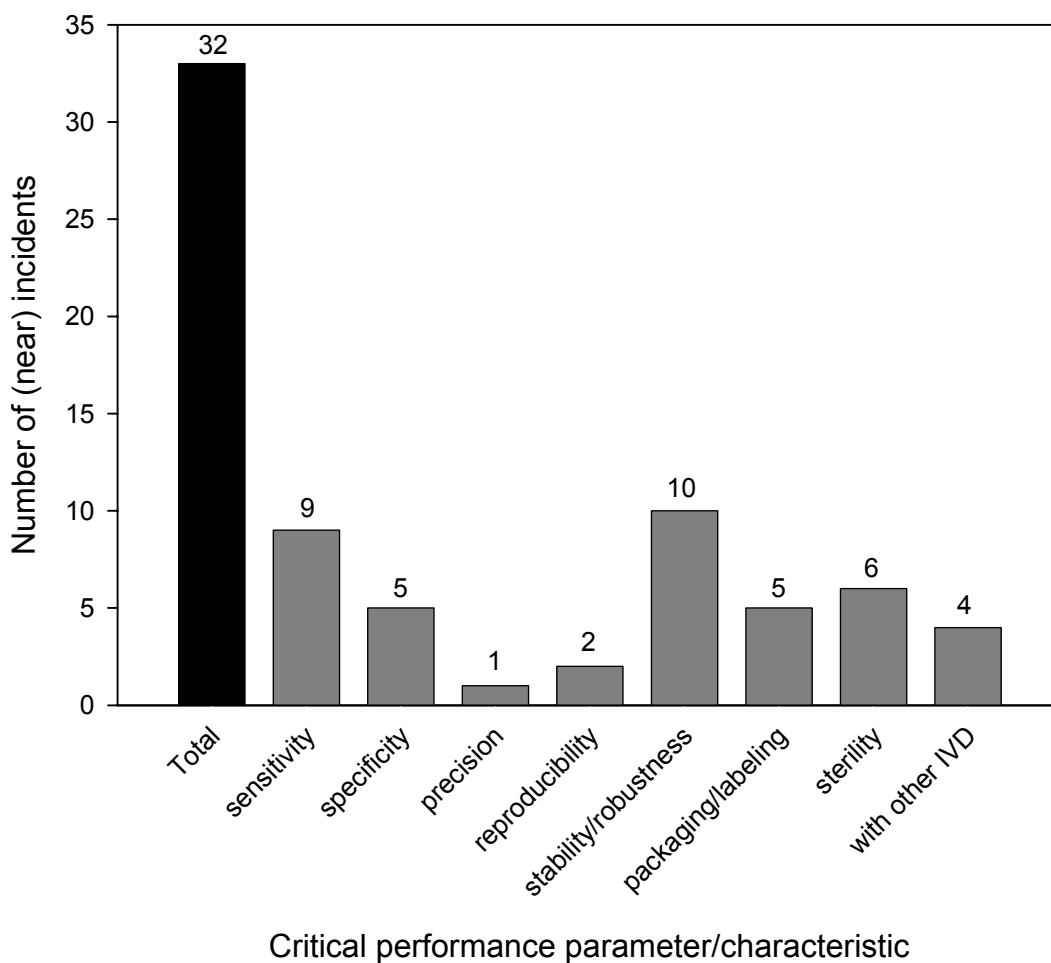
information deficiencies were observed in 5 cases. Lack of sterility caused by mistakes in the manufacturing process were reported for 6 cases (Fig. 8). Notably, device deviations, when initially observed by users and notified to manufacturers or the competent authority, were solely identified by internal quality control procedures of the users. Inadequate results in connection with external quality assessment schemes were not reported.

About 10% of (near) incidents could be related to unfavourable sample characteristics mostly leading to false negative diagnostic results (Fig. 7). These cases mainly refer to samples characterized by pre-seroconversion (HIV, HCV) or very weak blood group characteristics (ABO, irregular anti-erythrocyte antibodies) that produced ambiguous results when analysed by professional users in test comparisons. Considering the skills and experience of professional users, it is not surprising that user mistakes were confirmed in only very few cases (Fig. 7). However, for a large portion of nearly one third of cases, no root causes of the incidents could be verified (Fig. 7). This is due to the fact that remodelling of the cases is often insufficient or impossible because samples in question are not any more available or inadequately documented by the users.

Regulatory shortcoming was found to be in connection with one case where serious insufficiencies in the device design were observed and gave reason for the proposal of a consolidation of the CTS (see 3.3.2).



**Fig. 7. Incident causes as confirmed after case evaluation by PEI for the year 2004.** Notifications resulted from device deviations, sample status or user mistakes. Regulatory shortcoming was related to one case. For a considerable number of cases, no root cause was established (unknown).

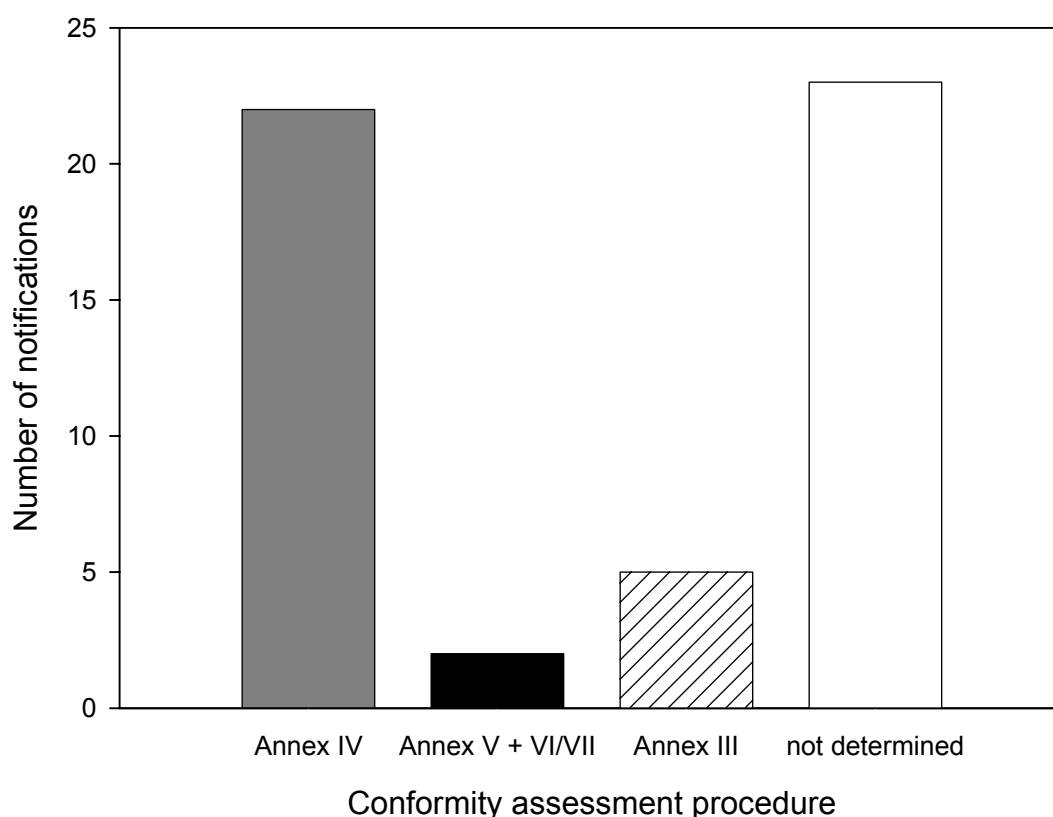


**Fig. 8. Determination of the critical characteristics causing device deviations.** From the total of 32 cases in 2004 related to device deviations, inadequate performance parameters and characteristics were established.

### 3.2.3 Premarket conformity assessment

The postmarket, reactive vigilance system is part of a safety network that shares interfaces with the premarket conformity assessment system. These interfaces include consultations between the manufacturer, the competent authority and the notified body on matters relating to the conformity assessment of a device and possible implications to the incident. Testing laboratories involved in premarket performance evaluation of a device may also be concerned. In order to assess the potential impact of the applied premarket modules on the postmarket vigilance experience, data on the conformity assessment procedures chosen by the manufacturers were evaluated (Fig. 9). Among the 52 notifications recorded during 2004, only 2 were related to devices where a combination of module B (EC type examination) and module D (quality assurance production) was applied in premarket conformity assessment. These cases were not communicated in terms of vigilance reports. A ten-times higher number was confirmed for notifications related to devices where module H (full quality assurance system) was applied. Although a definite conclusion does not seem possible yet

(because of the considerable number of cases where no data were obtained), the results indicate a clear tendency for the full quality assurance system as preferred conformity assessment procedure. However, provided that this tendency can be confirmed, no correlation between the choice of the premarket conformity assessment and the vigilance data seems detectable.



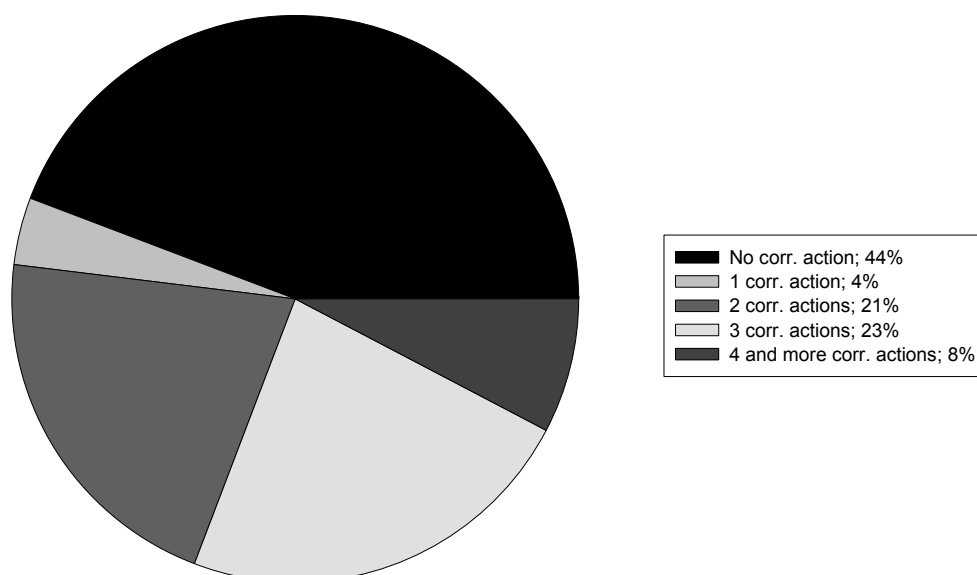
**Fig. 9. Conformity assessment procedures for devices related to (near) incidents in 2004.** Annex IV (dark grey, full quality assurance system), Annex V + VII (black, EC type examination + quality assurance production) and Annex III (hatched, EC declaration of conformity for other devices) were chosen for premarket conformity assessment. For the remaining cases, no data were obtained (white).

Results from performance evaluation studies constitute an essential part of the technical documentation of in vitro diagnostics. Whenever reference to data from the literature is not possible or sufficient to confirm compliance to the essential requirements and the common technical specifications (for List A devices), performance evaluation data resulting from studies at external testing sites need to be provided. Upon request of the competent authority for information on the availability of performance evaluation data, on the number of external studies and the number of testing sites involved in performance evaluation of the devices related to notification reports in the year 2004, only 20% of the manufacturers (12 among 52) clearly indicated the availability of data from performance studies. Among these cases, only 7 reported the performance of external studies that took place at a maximum of 4 testing sites. Mostly, even in connection with serious cases including the communication of vigilance

reports, the manufacturers and authorized representatives had no insight or overview on the performance evaluation data of the devices in question and reported difficulties to make these data available due to the international networks of the companies.

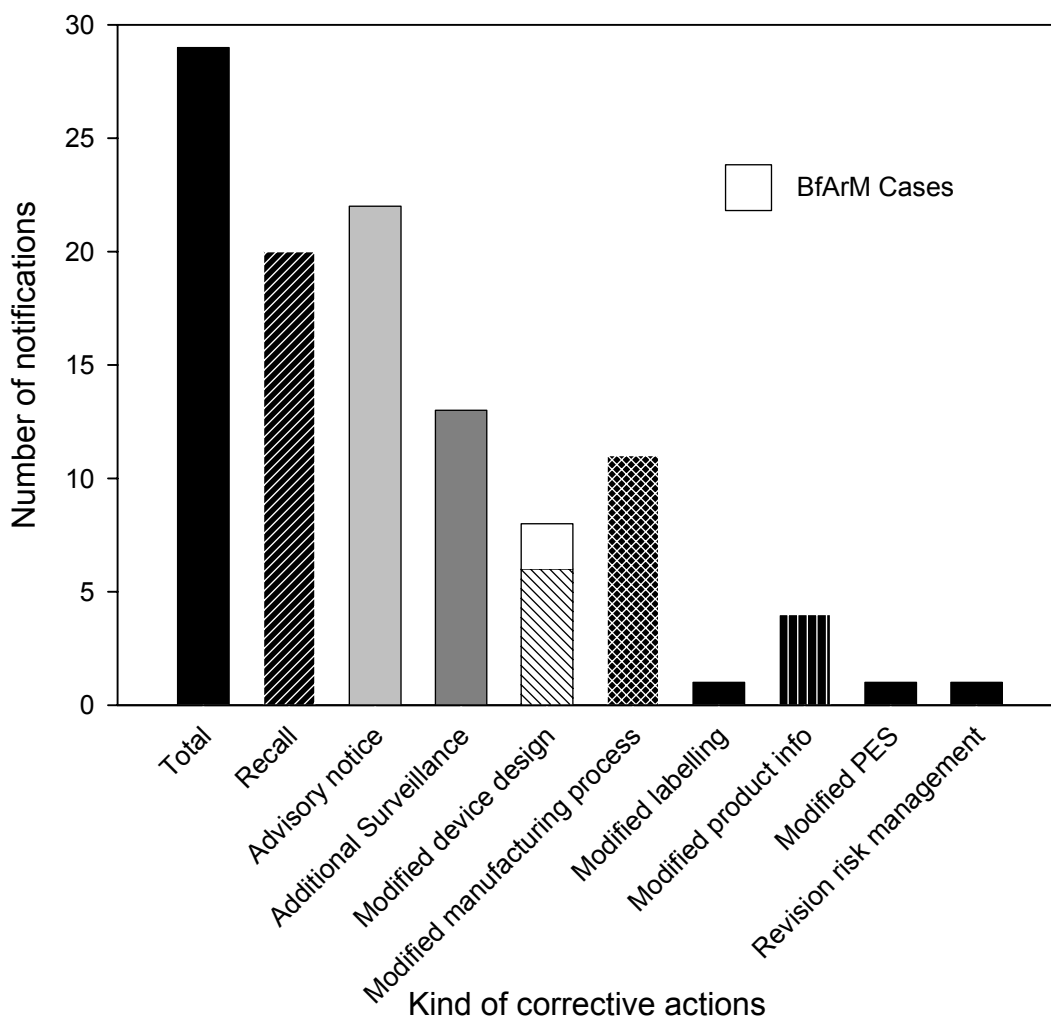
### 3.2.4 Corrective actions

The number of cases where corrective actions were performed (56% of the cases) correlates well with the number of confirmed product defects. Corrective action was performed by the manufacturers. No measures were deemed necessary in 23 of the reported cases (44%), again correlating with the proportion of cases, where no root cause was established, or that were caused by user mistakes or sample characteristics. In general, the total number of corrective measures per case increased with the potential risk related to the case (Fig. 10).



**Fig. 10. Quantification of corrective measures related to PEI cases 2004.** The number of measures taken per case are indicated. Percentage numbers refer to the total number of 52 cases reported (100%).

Corrective measures mainly included recalls, customer advisory notices and modifications in the manufacturing process. Design modifications and modifications of the instructions for use or product labeling were of minor frequency. Although “further surveillance” was announced as part of the measures for about one third of the cases, only very few measures were specifically related to premarket conformity assessment procedures as there are, for example, modified performance evaluation studies or revisions of the risk management system. Notably, the explicit introduction of post market performance evaluation for in vitro diagnostics (as counterpart for post market clinical follow-up of active implantables and medical devices) (18) was never suggested by manufacturers (Fig. 11).



**Fig. 11. Types of corrective actions taken by manufacturers in 2004.** Several corrective measures per case are possible. PES = performance evaluation studies.

### ***3.3 Serious incidents and corresponding vigilance reports***

By the description of three exemplary cases that were recorded by PEI in the years 2004 and 2005, the European vigilance system for high risk in vitro diagnostics and its interfaces with premarket activities of the concerned parties shall be further analysed. Emphasis was laid on a critical evaluation of the performed conformity assessments in the premarket phase, the notification practices, the progress and outcome of the risk assessments and the European information exchange system for relevant data of in vitro diagnostics.

#### **3.3.1 Case report No. 1**

Based on user complaints regarding inadequacies of the performance of a List A in vitro diagnostic medical device, the manufacturer notified an incident with a delay of about 100 hundred days towards the competent authority PEI (14).

As corrective action initiated by the manufacturer, an incomplete product information note was published. As further corrective action, the product labelling was modified to reflect the revised product performance.

After having performed an initial risk assessment of the case, PEI communicated a vigilance report. However, it was difficult for the competent authority to judge the extent of the incident as far as the number of affected Member States was concerned. Here, PEI was almost completely dependent on the information and documentation provided by the manufacturer, which was delayed because of communication difficulties inside the company.

Following the strong authority's requests, the company's complaint management system was modified in order to fit the notification requirements especially regarding the notification time-scale and the cooperation attitude towards the authorities (14).

During further considerations, the comparison with data from the premarket conformity assessment revealed that the device did not fully comply with the CTS by the time of a notified body's on-site assessment of the manufacturer. Further documentation could not prove compliance with the CTS by the time of the placing on the market.

Internal laboratory investigations were performed by the manufacturer to establish the root cause of the device deficiency. Further investigations are in process.

### **3.3.2 Case report No. 2**

During the batch testing ("verification of the manufactured products") of a List A device, a certain batch was not released by the notified body's test lab. The lab observed a dramatic signal reduction when freshly drawn sera ("same day samples") were tested. The dilution of the samples resulted in significantly higher signal ratios. The manufacturer immediately notified this case to PEI and initiated adequate corrective measures. A vigilance report was communicated by PEI. The scientific evaluation and assessment of the incident revealed a serious design deficiency of the device leading to false negative test results when freshly drawn samples or samples characterized by specific coinfections were tested. As further measures the design of the test was modified and the device underwent extensive performance evaluation at external testing sites. This case initiated a discussion on a potential shortcoming of the CTS that so far did not require the specific testing of same day samples. The scientific evaluation concerning a consolidation of the CTS within the European IVD expert group is in process.

### **3.3.3 Case report No. 3**

In connection with the placing on the market of an OEM product (OEM = original equipment manufacturer), PEI was informed that a CE-marked List A infection serology test system showed deficits in the diagnosis of patients in the early seroconversion. Evaluation of the test

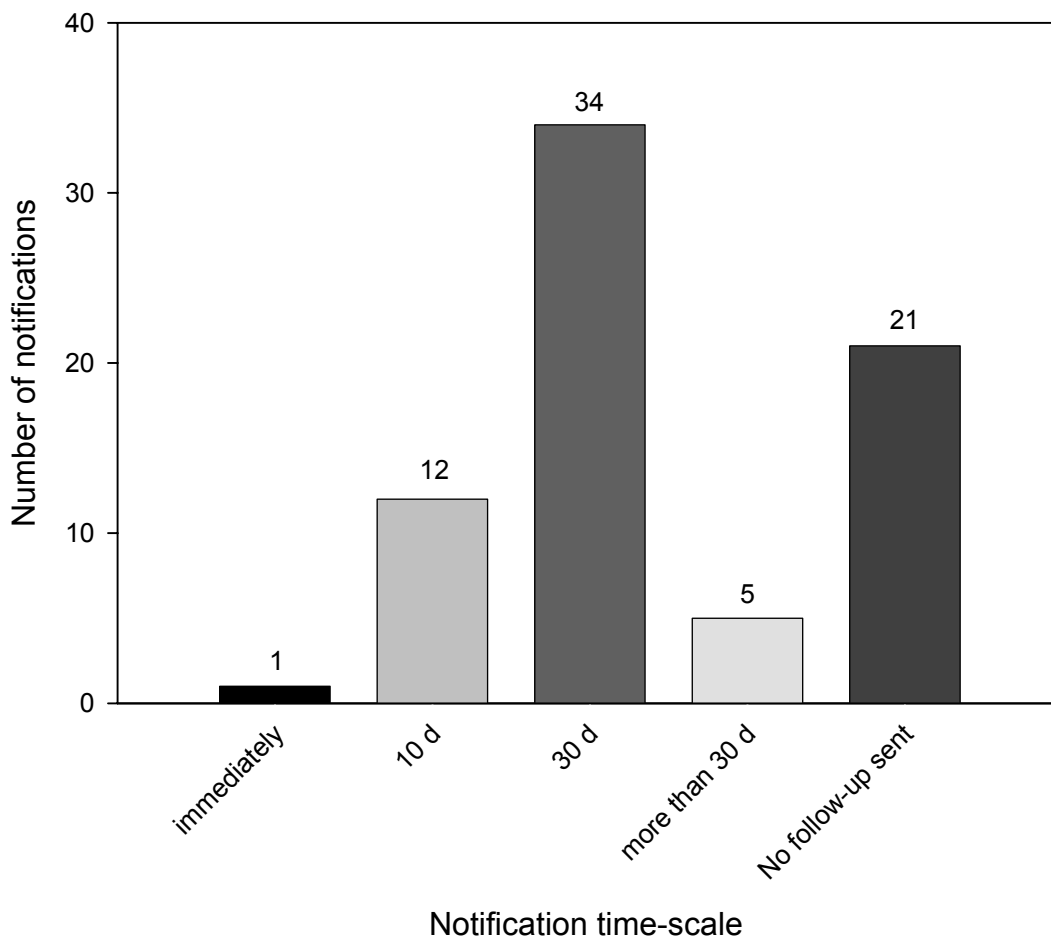
performance by the German testing laboratory PEI-IVD confirmed that the device did not represent a state-of-the-art test system because of its limited sensitivity to detect seroconversion in the early infection phase. Therefore, the device did not comply with the CTS when placed on the European market after performance of the original conformity assessment (compare CTS, General principles 3.1.8). Further evaluations by the competent authority revealed a lack of performance evaluation data for the CE-marked device. What is more, although a test report commissioned by the notified body involved in the original conformity assessment did not recommend the test for CE marking, the certificates for CE-marking were issued.

As corrective measure, the original manufacturer placed the test system from the market. After communication of the vigilance report by PEI, a Member state initiated particular health monitoring measures according to Article 13, IVDD. The procedure is in process.

### ***3.4 Vigilance monitoring by the competent authority PEI***

The medical device vigilance system is based on a cooperative and effective information exchange between the parties involved. Characteristics of this information exchange concern the notification time-scale and the overall conduct of investigation performed to evaluate the reported incidents.

In 2004, more than 60% of the cases were reported within 30 days after the event took place, which correlated with the number of notifications that were confirmed to show no or only small effects related to public health impairment (Fig. 12, compare Fig. 5). The number of notifications received within 10 days or earlier again correlated with the number of cases with critical or life-threatening consequences in case of recurrence (compare Fig. 5). However, a considerable number of notifications (about 10%) were performed against the recommendations in a time-scale later than 30 days after the event (14). Unfortunately, cases with potential serious risk to public health were included here (see case report No. 1). In about 40% of the cases, follow-up or final reports have only been sent to PEI following the direct requests of the competent authority (Fig. 12). In these cases, the recommended information exchange procedure as it is mainly performed between the qualified person for vigilance and the competent authority was not yet followed (14).



**Fig. 12. Notification time-scale and information exchange for (near) incidents reported to PEI in 2004.** Cases were reported within a range of immediate notification and much later than 30 days.

The special situation in Germany concerning the separation of the competences between the two authorities BfArM and PEI challenged the notification procedure in about 10% of the cases. Here, the notification was initially reported to BfArM and then transmitted to PEI.



## 4. Discussion

### ***4.1 Vigilance experience and implications for manufacturers***

Following the German implementation of the vigilance system in 2002, the initial reporting phase was characterized by very few notifications that substantially increased during the last years and seemed to reach a stable average number per year for 2004 and 2005. The manufacturers are mainly responsible for the initiation of the vigilance system and therefore mostly contributed to the number of notifications recorded by PEI. The data suggest that the notification practice is now better established among the European IVD manufacturers than by the time of implementation of the new provisions.

For the majority of cases assessed by PEI in 2004, product defects could be confirmed. Inadequacies concerning the device robustness (stability, interferences, sterility), the performance characteristics and the product information (including packaging and labeling) were most abundant. As corrective measures, manufacturers mostly reacted with advisory notices, recalls and only in one third of the cases with a modification of the manufacturing process.

Although the number of corrective actions increased with the seriousness of the cases, it was obvious that most of the measures constituted corrections mainly reactive in nature. They were often not followed by further or advanced measures referring, for example, to the risk management of the manufacturers or to their concept of performance evaluation studies.

As revealed by this study, enhanced activities should therefore be performed by manufacturers to continually monitor and analyse any post-production information on devices (like notifications and vigilance reports) in order to revise current risk assessments and in order to maintain an effective risk management process (28). For the large portion of cases, where no root causes could be verified, the product monitoring by the manufacturers in the postmarket phase is also essential. Hereby obtained results should be considered as input for the risk management process maintained by the manufacturer (10, 28). In the field of in vitro diagnostics, risk assessment is often challenged by the difficulty to *clearly judge* the (potential) consequences of (near) incidents. This is also reflected by the results of this study, where only about half of the notifications were *confirmed* to show no or only small effects related to public health impairment. In this context, an effective postmarket surveillance system continuously maintained by the manufacturer is of great importance, since it helps to complete product characterization during the life-cycle of a product by detailed product monitoring. Information exchange between the manufacturers and the competent authorities may then improve the tools for risk assessment in case of incidents and near incidents, respectively.

A general lack of availability, insight or even documentation itself of performance evaluation data for the devices in question was observed during this study. For a considerable number of cases, the assessments also revealed that performance evaluation studies obviously have not been performed along the whole shelf-life of the product to ensure the quality and safety of the device. However, product deficiencies were sometimes only seen *outside* the manufacturer's site emphasizing the relevance of independent clinical testing outside the manufacturer's premises in the premarket conformity assessment.

#### ***4.2 Vigilance experience and implications for premarket conformity assessment bodies***

Notified bodies, their subcontractors and (medical) laboratories are premarket conformity assessment bodies. Usually, notified bodies are private organisations that, in case of conformity assessment procedures according to module H, are involved in the conformity assessment of the manufacturer's quality management system and furthermore, - in case of List A devices -, in the design examination and verification of manufactured products. When incidents are communicated as vigilance reports by the competent authority, they are usually automatically communicated to notified bodies by their governmental designating authority.

In total, the data obtained during this study confirmed the suitability of the notified bodies' role as independent third parties for premarket conformity assessment. For example, the "batch testing" of List A devices performed by notified bodies proved to be an efficient method to ensure that safe and state-of-the-art devices are placed on the market. However, single cases demonstrated that noncompliance with the CTS is not always sufficiently realized by the notified bodies. It is therefore essential that notified bodies continuously maintain a high level of competence that must be controlled by the designating authority.

In the context of product monitoring, the data reviewed during this study suggest that notified bodies should focus on aspects that seem to represent main challenges for the manufacturers: The functioning of the risk management system implemented by the manufacturers and the extent of performance evaluation studies. It should be checked whether possible effects of changes in the design- and production phase of a device and the postproduction experiences are adequately taken into consideration by the manufacturers. Since "grandfathering" of devices is not accepted by the CTS, notified bodies must control whether comparisons of the device in question with other CE-marked products on the market are adequately performed. When reports on (potential) device deficits get more frequently, notified bodies should assess more intensively the performance evaluation studies of the manufacturers. Here, it should be analysed whether the study concepts adequately consider the evaluation of all performance parameters along the whole shelf-life of a product, and whether sufficient testing outside the manufacturers site by external testing labs is planned.

In this context, the information exchange of the vigilance system could be improved by unrestricted communication of all notifications to the notified bodies (and not only of those communicated as vigilance reports). This could help to improve the interaction between the proactive components of premarket conformity assessment and the mainly reactive characteristics of the vigilance system.

This study confirms the essential role of testing laboratories as conformity assessment bodies involved in premarket performance evaluation of in vitro diagnostics. The majority of these laboratories are medical laboratories that provide the necessary clinical environment to evaluate the device performance by testing samples in the broad range of biovariability. It should be stressed that performance evaluation studies solely performed inside the manufacturer's premises are not acceptable in the view of European legislation, - a fact which is sometimes not adequately considered (8).

Although medical laboratories in practice are often not directly subcontracted by notified bodies, these bodies significantly rely on laboratory results during their conformity assessments (29). The testing competence of laboratories involved in performance evaluation studies is therefore of decisive importance and should be ensured by the implementation of quality management systems. This may be confirmed by laboratory accreditation. Today, a considerable number of laboratories all over Europe is accredited on the basis of the standards EN ISO/IEC 17025 (30) or EN ISO 15189 (31). These standards include a number of useful requirements for management and technical aspects of laboratory testing. However, these standards can not be regarded as giving rise to the full presumption of conformity in connection with legal requirements set by European directives (32). Therefore, in the context of performance evaluation, laboratory competence may concern more aspects than considered in these standards. Laboratory testing for performance evaluation of in vitro diagnostics also requires the compliance with the criteria set in Annex IX, IVDD, as there are, for example, the impartiality and independence of the laboratory (4, 5, 28, 33). Laboratory competence includes the availability of sufficient scientific staff who possess adequate experience and knowledge necessary to assess the biological and medical functionality and performance of devices. Laboratories solely accredited on the basis of the aforementioned standards often are simply users of in vitro diagnostics but may lack the necessary experience for adequate device performance evaluation. For example, the data reviewed in this study indicate that testing laboratories should be able to evaluate critically the product information in terms of their completeness and appropriateness related to the intended device use. The laboratory should also check whether a study is planned along the whole shelf-life of the product. Testing labs should be able to evaluate any changes in the product components in comparison with products that were tested earlier.

Laboratory accreditation systems established in the Member States should therefore adequately consider these specific requirements for performance evaluation testing. For these reasons, laboratory accreditation in the field of in vitro diagnostics is in Germany performed by the designating authority ZLG. Accreditation rules for laboratories shall here ensure the compliance with legislative and normative requirements that are beyond the basic laboratory standards EN ISO/IEC 17025 or EN ISO 15189 (5, 9, 34).

### ***4.3 Vigilance experience and implications for public authorities***

In principle, the case documentation and risk assessment performed by PEI during the year 2004 confirmed the functioning and efficacy of the relatively new implemented vigilance system related to high risk in vitro diagnostics. Each case was critically assessed and evaluated according to the criteria for information exchange by vigilance reports. Consequently, vigilance reports were communicated in one third of the cases enabling the Member States to take adequate measures to protect the health and safety of patients and IVD users all over Europe. In order to prevent incident repetitions, information exchange at the national level often not only included the manufacturers and PEI, but also the competent authorities of the Länder, the ZLG, the users and the conformity assessment bodies.

Since the cases were related to postmarket routine device use, it was surprising that not even 20% of the notifications were performed by users in the professional field. Increased informing of the professional users on the novel provisions for vigilance reporting by the public authorities therefore seems to be recommended to ensure a complete and responsible notification practice among IVD users. At the national level, transparency in the notification procedure may also be improved by clear information about the institutions BfArM and PEI and their competences in connection with the vigilance system.

The directive 98/79/EC considers the relevance of external quality assessment schemes (EQAS) for the postmarket evaluation of the performance and safety of in vitro diagnostics. The mandated and recently published standard EN ISO 14136 (16) emphasizes the responsibility of proficiency testing organisations to integrate the results obtained by their quality programs into the vigilance system, whenever aspects related to IVD performance are concerned. As the PEI data indicate, the notification practice is not yet well established among the EQAS institutions. Further informing of this part of medical practitioners therefore also seems recommended by public authorities.

On the one hand, risk assessments performed by competent authorities help to discover risks related to deficiencies that might be linked to inadequate design, manufacturing or use of devices. On the other hand, vigilance monitoring serves as effective tool for the continuous re-evaluation of the regulatory framework for in vitro diagnostics that is constituted of legal provisions laid down in the IVDD and of supplementary standards and specifications like the

CTS in the case of List A devices. For example, on the basis of the PEI vigilance experience of the year 2004, a consolidation of the CTS is currently discussed that refers to the testing of same day samples in HIV serology. The slightly increased number of inadequately determined anti-E samples in blood group serology gave also reason for enhanced future monitoring by PEI, since the CTS currently do not explicitly include a range of week RhE samples in the performance evaluation criteria for anti-E reagents. Future assessments will show whether a re-evaluation of the CTS might be necessary in this aspect.

With regard to the key importance of performance evaluation data especially for high risk in vitro diagnostics, further monitoring by public authorities should focus on the availability of complete, clear and adequate data from performance evaluation studies involving a sufficient number of test samples analysed in external laboratories as testing sites. Interestingly, the currently performed review of the legislation for medical devices regulated by Directive 93/42/EEC will include enhanced clinical testing of these products during the premarket conformity assessment phase (35). The future vigilance experience for in vitro diagnostics will show whether the current legislation fits the safety requirements in this context or whether further requirements for performance evaluation testing of IVD are necessary.

Possible improvements of the postmarket information exchange system for high risk in vitro diagnostics mainly refer to the data exchange between the manufacturers and the competent authorities. This study has shown that in a considerable number of cases, central parts of the device documentation, like for example performance evaluation data, were not known or not available for the qualified persons for vigilance. Consequently, risk assessment by the competent authority was hindered or at least limited in certain cases. It should therefore be considered whether, - at least for List A devices -, a facilitated mechanism could be established that provides more data transparency for the competent authorities in cases where serious risks are ahead. This could include the requirement for manufacturers to make permanently available the summaries of certain device performance data, for example.

Finally, risk assessments and the European information exchange system could largely be supported, if functional, complete and Europe-wide databases existed that enabled the competent authorities to rely on objective data for the performance, certification, distribution and vigilance of devices placed on the European market. Today, competent authorities of the Member States mainly use national databases that do not provide the functions planned for the European database. Enhanced activities for the installation of EUDAMED as fully functional European database for medical devices are therefore recommended.

## 5. Conclusions

Among the postmarket information systems in the field of medical devices, the vigilance system for in vitro diagnostics was most recently established and is characterized by a number of peculiarities that are based on the nature of the products and their particular relevance to public health in the field of high risk devices.

Shortcomings leading to incidents with potential risk to public health mainly concern the lack of independent and sufficient diagnostic evaluation of the test systems in the premarket conformity assessment phase. The serious consequences that may occur in case of noncompliance with the CTS are not always taken into consideration by the notified bodies that are standing between responsible and competent conformity assessment and economic interests related to manufacturers as their customers. Strict surveillance of notified bodies by governmental designating authorities is therefore essential.

The relevance of independent batch testing of List A devices was confirmed during this study. However, the mode and frequency of the verification of manufactured List A devices so far is not harmonized on the European level among the notified bodies and therefore remains unclear.

Corrective measures performed by manufacturers were shown to be mainly reactive in nature. To prevent incident repetition, focus should be laid on preventive actions aimed at the improvement of the risk management process and of IVD performance evaluation during premarket conformity assessment.

Risk assessments by the competent authority are currently largely dependent on the data provided by the manufacturers as only source. Inadequate cooperation between the involved parties may then limit appropriate considerations and assessments. When fully functional, the European database for medical devices could essentially improve the information exchange system and therefore provide effective tools for risk prevention in connection with high risk in vitro diagnostics.

Finally, a periodic review of the CTS and related standards on the basis of vigilance data seems appropriate to guarantee that devices of state-of-the-art quality and safety are placed on the European market.

## 6. Summary

Since December 2003, any in vitro diagnostic medical devices are placed on the European market according to the new IVDD requirements. Due to safety reasons, especially high risk in vitro diagnostics covered by Annex II of the Directive are the focus of public and regulatory attention. In order to ensure a high level of public health protection, the installation of a complex postmarket information system is required that constitutes a safety network with interfaces between the parties involved in premarket conformity assessment and in postmarket surveillance activities.

By review of the incident notification data registered by the competent authority PEI during the year 2004, the present study evaluates the European and German vigilance system for high risk in vitro diagnostics and discusses possible implications for the bodies related to the European medical devices system.

The total number of 52 cases was analysed on the basis of criteria used for risk assessment of the incidents and near incidents. Vigilance reports were communicated in one third of the cases enabling the Member States to take adequate measures to protect the health and safety of patients and IVD users all over Europe. In general, the information exchange at the national level was effective and included the relevant parties, as there are manufacturers, PEI, competent market surveillance authorities of the Länder, users, the conformity assessment bodies and the designating authority ZLG.

Whereas the notification practice seemed adequately established among the IVD manufacturers, the low contribution of medical practitioners (IVD users and EQAS organisations) to incident notification suggested the need for increased informing of these professionals about the IVD vigilance system.

For the majority of (near) incident notifications, product defects could be confirmed. Because remodelling of cases was often insufficient or impossible, no root causes could be verified for nearly one third of cases. Unfavourable patient sample characteristics, user mistakes and shortcomings in the regulatory framework were of minor importance for the evaluation of incident causes.

In most cases, the extent of corrective actions initiated by the manufacturers correlated with the seriousness of the incidents demonstrating that risk assessments were usually performed adequately and in close cooperation with the competent authority. However, preventive actions that refer to processes during premarket conformity assessment, especially adequate revisions of the risk management systems and of performance evaluation concepts, constituted major challenges for the manufacturers.

As revealed by this study, enhanced activities should therefore be performed by manufacturers to continually monitor and analyse any post-production information on devices in order to maintain effective risk management systems. Since product shortcomings leading to incidents mainly concerned the lack of independent diagnostic evaluation in the premarket conformity assessment phase, more emphasis should be placed on results from clinical IVD testing that constitute an essential part of the technical documentation.

In this context, this study confirmed the essential role of medical testing laboratories as conformity assessment bodies involved in the premarket performance evaluation of in vitro diagnostics. When the testing competence of these laboratories is confirmed by accreditation, this procedure should adequately consider the specific requirements for performance evaluation testing in order to ensure the compliance with legislative and normative requirements that are beyond the basic laboratory standards used for accreditation of routine diagnosis.

The data obtained during this study support the suitability of the notified bodies' role as independent third parties for premarket conformity assessment. The relevance of their assessment including the verification of the manufactured products for List A devices was confirmed. However, single cases demonstrated that non-compliance with the CTS was not always sufficiently realized by the notified bodies. It is therefore essential that notified bodies continuously maintain a high level of competence that must be controlled by the designating authority.

The present study showed that vigilance monitoring by the competent authority serves as effective tool for the re-evaluation of the regulatory framework for in vitro diagnostics. Based on the PEI vigilance experience of the year 2004, a consolidation of the CTS concerning the testing requirements for the evaluation of effects of potentially interfering substances is in process. Future vigilance data will show whether further re-evaluations concerning the requirements for performance evaluation testing of IVD might be necessary. Although the relevance of independent batch testing of List A devices was confirmed during this study, the mode and frequency of the verification of manufactured List A devices so far are not harmonized on the European level and therefore remain unclear. Clear consideration of this important aspect in the European regulatory framework could contribute to more transparency.

The vigilance system for high risk in vitro diagnostics could largely benefit from enhanced data transparency between manufacturers, notified bodies and competent authorities. Where serious risks are ahead, the effectiveness of risk assessments could be improved, when competent authorities could use facilitated mechanisms for getting access to the manufacturers' data. Less restricted communication of incident notifications to the notified bodies could improve the interaction between the proactive components of premarket



conformity assessment and the mainly reactive characteristics of the vigilance system. When fully functional, EUDAMED could essentially improve the European information exchange system and therefore provide effective tools for risk prevention and health protection in connection with high risk in vitro diagnostics.

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