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SAFETY OF REAGENTS FOR INFECTION TESTING: RESULTS OF THE MARKET SURVEILLANCE BY THE FEDERAL INSTITUTE FOR DRUGS AND MEDICINAL DEVICES UNTIL END 2006

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The European Directive 98/79/EC on *in vitro* diagnostic medical devices (IVD) stipulates the marketing and post market surveillance of IVD in the European Economic Area. In cases of issues and field corrective actions, the manufacturers have to inform the responsible Competent Authorities (CA). In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) is the responsible CA for most IVD, with a small subset of IVD for immune hematological and infection testing as well as tissue typing as specified in Annex II of the Directive, being within the responsibility of the Paul-Ehrlich-Institute (PEI). In this study, all issues regarding reagents for infection testing, but not laboratory analyzers, reported to the BfArM between begin 1999 and end of 2006 were analyzed in respect to the source of report, the underlying product defects, and the performed corrective actions. Within the observation period a total of 888 reports on IVD were received of which 90 related to the IVD for infection testing included in our study. Reports were predominantly received from manufacturers (55) and Competent Authorities (29). Affected products were most frequently those for serological analysis (42) and culturing techniques (36), whereas molecular biological tests played only a minor role (12). Investigations of the manufacturers were able to identify the underlying root causes of product failures in 68 cases (75.6 %). In 16 cases (17.8 %) the root cause remained unclear and in 6 cases (6.6 %) a product failure was excluded or a user error was the underlying cause. Most frequently product failures were caused by material defects (25), production errors (11), microbial contamination (6), and labelling errors (5). Manufacturers issued corrective measures in 73 cases (81.1 %). Based on the underlying root causes of product failures, these were predominantly (multiple entries) customer information (71), recall (58), modifications in production or quality management (50), modifications of the raw materials (17), and modifications of the instructions for use (12). The results and experience obtained since 1999 suggest that the system for post marketing surveillance of IVD is an established tool to ensure product safety even though the current system can be further optimised.

Key words: *infection diagnostics, infective disease, in-vitro diagnostics, post market surveillance*

INTRODUCTION

The Directive 98/79/EC regulates the conformity assessment, marketing and the post marketing surveillance of in-vitro diagnostic medical devices (IVD) in Europe (1). The regulations of the European Directive have been implemented in Germany by means of the 2nd Amendment on the German Law on Medical Devices (MPG, Medizinproduktegesetz) on January 1st 2002 (2). The latter has been supplemented by the Ordinance on the Medical Devices Vigilance System (MPSV, Medizinprodukte-Sicherheitsplanverordnung) from June 24th 2002 (3). In brief, the manufacturers are obliged to systematically review the experience gained from devices on the market, to implement corrective actions and to report incidents and recalls to the responsible Competent Authority (CA). According to the MPSV, also professional operators and users have to report incidents to the CA that they observe when using the products (3-6). The same obligation applies to pharmacies and other retail traders if incidents related to over-the-counter-products (OTC) sold by them to lay people come to their knowledge. In Germany the Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte) and the Paul-Ehrlich-Institute (PEI) are responsible for registration and evaluation of issues related to IVD. The latter is responsible for only few IVD for infection testing and immune hematological diagnostics as well as tissue typing as specified in Annex II of Directive 98/79/EC (1, 3). However, even in cases of reagents and tests in the responsibility of the PEI the laboratory analyzers on which these tests are performed lie within the responsibility of the BfArM (*Table 1*). In consequence, both CAs work closely together in cases regarding products for immune hematological and infection testing to ensure product safety of IVD and blood products.

In evaluating the reports or other relevant information regarding risks, the task of the CA is to characterize the risk (in terms of probability of occurrence of harm and severity of the harm) and to assess it for acceptability. In case of unacceptable risks, the necessary corrective action can be determined. If manufacturers have already taken measures under their own responsibility, the CA can decide whether or not these are adequate. Any necessary field corrective action performed by the manufacturers must be properly communicated to the customers and users. In Germany, this is typically done by a field safety corrective action; the letter must also be sent to the BfArM for information and publication *via* the internet.

As CE-marked devices in principle are subject of free movement in the entire European Economic Area (EEA), there is a need for information to be exchanged between CAs, in particular when a field corrective action is initiated. The Directive requires that the European CAs inform each other and the European Commission of issues that led to corrective actions. Having been informed through a vigilance report, all CAs can then monitor the corrective action in their area of responsibility and evaluate whether similar products of other manufacturers are also affected by the observed problem.

Table 1. Responsibilities of BfArM and PEI regarding IVD (1-4).

	Annex of Directive 98/79/EC	Responsibility
Products for immune hematological testing and tissue typing:		
Blood groups of the AB0 system[1, 2]	IIa	PEI
Blood groups of the Rhesus system (C, c, D, E, e)[1, 2]	IIa	PEI
Blood groups of the Kell system [1, 2]	IIa	PEI
Blood groups of the Duffy and the Kidd system [1, 2]	IIb	PEI
Irregular anti-erythrocyte antibodies[1, 2]	IIb	PEI
Markers for HLA[3)] typing, markers DR, A and B[1, 2]	IIb	PEI
Products for infection testing:		
Markers of HIV[4)] infection (HIV-1 and HIV-2)[1, 2]	IIa	PEI
HTLV-I[5)] und HTLV-II[1, 2]	IIa	PEI
Hepatitis B, C und D[1, 2]	IIa	PEI
Congentital infection with rubella[1, 2]	IIb	PEI
Congenital infection with toxoplasma[1, 2]	IIb	PEI
Cytomegalovirus (CMV)[1, 2]	IIb	PEI
Chlamydia[1, 2]	IIb	PEI
Other products:		
Tumor marker PSA[1, 6]	IIb	BfArM
Hereditary diseases phenylketonuria and Down syndrome (trisomia 21, including software)[1]	IIb	BfArM
Products for self testing:		
Systems for measurement of blood glucose[1]	IIb	BfArM

[1]Reagents and reagent products for detection, confirmation and quantification;
[2]Analyzers on which these tests are performed are in the responsibility of the BfArM;
[3]HLA: Human leukocyte antigen;
[4]HIV: Human immune deficiency virus;
[5]HTLV: Human T-cell leukemia virus;
[6]PSA: Prostate specific antigen.

Up to now, only few data regarding the experience on the market surveillance system have been published (7-11). Additionally, the group of IVD is very heterogeneous regarding the users of the products (professional users *vs.* lay users), the type of the products (e.g., tests, calibrators, control materials, culture media, and laboratory analyzers), the underlying analytical methods (e.g., culture, biochemistry and molecular biology) as well as the clinical field, where the products are used (e.g., clinical chemistry, hematology, coagulation, microbiology, and therapeutic drug monitoring). There are also large differences in the frequency of notifications to the BfArM, the source of notification, the frequency and type of product failures, and the frequency and type of corrective measures settled by the manufacturers of the affected products. In this study issues reported to the BfArM until end of 2006 and related to IVD specified for

infection diagnostics were analyzed. This included culture media as well as tests and reagents, but not laboratory analyzers and their consumables.

METHODS

The study was approved by a local Ethics Committee. All notifications on IVD received by the BfArM between begin of 1999 and end of 2006 were included. Detailed analysis was made for tests and reagents (including culture media, calibrators and controls) which serve for infection diagnostics. Analyzers and their consumables (e.g., buffers and common culture media but not tests) were excluded. IVD for infection testing listed in Annex II parts A and B of Directive 98/79/EC were also not considered. Analyzes were made in specific subgroups of the products regarding the type of the product (e.g., culture media, products based on culture, immunological, and molecular biological methods) in order to provide more detailed data regarding the product failures and the corresponding corrective measures.

RESULTS

Number of reports

Within the observation period, BfArM received an annually increasing number of issues regarding IVD. The number showed a strong increase after implementation of MPG and MPSV in 2002 (*Table 2*). At the end of the observation period, BfArM had received a total number of 888 reports concerning IVD. From these cases 246 (27.7%) were related to OTC products specified for lay use whereas the majority of reports was related to IVD for professional use (642; 72.3%). From the latter, 90 (10.1% of all reports) were tests for infection diagnostics which were subject of this study.

Sources of reports

From all notifications on products analyzed in this study 55 (61.1%) came from manufacturers and their distributors (only few cases from distributors) and from authorities (29; 32.2%; e.g., national CAs and European CAs). Notifications from other sources (e.g., users, press, scientific organisations, industrial competitors, and cases initiated on BfArM's own initiative) played only minor roles (*Table 3*). Notifications from users were received directly from professional users (hospital and resident laboratories) or *via* the Drug Commission of the German Pharmaceutical Association. One case was initiated by the BfArM, as the corrective measure issued by the manufacturer of the affected product had not been reported to the BfArM. There were no relevant differences in the proportions of the sources of notification between the different product groups.

Product groups

From the total of 90 notifications, 54 (60.0%) affected IVD for detection, differentiation, or susceptibility testing of bacteria (*Table 4*). The remaining

Table 2. Number of notifications regarding IVD reported to the BfArM in total and for tests, reagents, and culture media for diagnostics of infective diseases since begin 1999 until end of 2006.

Year	Total number of notifications regarding IVD n	Notifications regarding tests, reagents, control materials, and culture media for diagnostics of infections[1] n (%
1999	13	1 (7.7)
2000	21	5 (23.8)
2001	33	3 (9.1)
2002	58	5 (8.6)
2003	121	8 (6.6)
2004	200	30 (15.0)
2005	207	20 (9.7)
2006	235	18 (7.7)
Sum	888	90 (10.1)

[1]Without general consumables (buffers and culture media) for laboratory analyzers

Table 3. Sources of notification regarding tests, reagents, controls, calibrators, and culture media for diagnostics of infections.

	Number of reports n (%)
Manufacturers and distributors	55 (61.1)
Users	5 (5.6)
Competent Authorities[2]	29 (32.2)
Others[3]	1(1.1)
Sum	90 (100.0)

[1]Professional users (hospitals and resident laboratories) and drug commissions;
[2]National und international authorities (authorities of German countries and international CAs);
[3]On BfArM´s own initiative and notifications from other sources (e.g., medical associations and competitors)

product groups were IVD for virological diagnostics (18; 20.0%), culture media (culture plates and liquid media; 13; 14.4%), and for diagnostics of moulds and parasites (3; 3.3% and 2; 2.2%, respectively).

The received reports were also classified according to the underlying analytical principles. Products for culture diagnostics (including detection by means of biochemical selective media, differentiation media, and inhibition by means of antibiotics or antimycotics) served predominantly for the detection or identification of bacteria (22; 24.4%) or were culture media for general purpose (13; 14.4%). The underlying methods of these products were based on visual examination (especially in cases regarding culture plates) or automated laboratory analyzers. Only 1 report on a product for culture diagnostics pertained to a Gram

Table 4. Product groups of IVD for diagnostics of infective diseases (90).

	Product based on culture, biochemical methods, or staining[1] n (%)	Product based on immunological methods[2] n (%)	Product based on molecular, biological methods[3] n (%)	Total number of products n (%)
Products for use in bacteriology[4]	22 (24.4)	23 (25.6)	9 (10.0)	54 (60.0)
Products for use in virology	0 (0.0)	15 (16.7)	3 (3.3)	18 (20.0)
Products for use in mycology[4]	1 (1.1)	2 (2.2)	0 (0.0)	3 (3.3)
Products for use in parasitology	0 (0.0)	2 (2.2)	0 (0.0)	2 (2.2)
Culture media[5]	13 (14.4)	Not applicable	Not applicable	13 (14.4)
Total number of products	36 (40.0)	42 (46.7)	12 (13.3)	90 (100.0)

[1]E.g., culture, strain differentiation, susceptibility testing, staining;
[2]E.g., immunological typing of strains, serology, ELISA, Western blots;
[3]E.g., polymerase chain reaction (PCR), hybridisation assays;
[4]Without solid or liquid culture media for common use or for laboratory analyzers and without materials for operation of incubators;
[5]Solid or liquid culture media for common use but not for analyzers and materials for operation of incubators (except laboratory analyzers).

staining solution for differentiation of bacteria (*Table 4*). Products based on immunological means (42; 46.7%; e.g., enzyme linked immunoabsorbant assays (ELISA) and Western blots) served in 23 cases for the detection of bacteria and in 15 cases for the detection of viruses, whereas products for the detection of parasites and moulds were less frequently affected (2 and 2, respectively) (*Table 4*). Products based on molecular biological means were subject of 12 reports (13.3%) from which 9 were related to diagnostics of bacteria and 3 to diagnostics of viruses (*Table 4*).

Frequency and type of product failure

Analysis of the product failures demonstrated strong differences in the number and type between the various product groups which, therefore, were subject to subgroup analyses (*Table 5*). In products based on culture methods (23, except culture media), the underlying root causes of product failures were predominantly errors in production or quality management (6; degradation of the substrate caused by humidity within the production process or damage of the package followed by penetration of humidity, use of an erroneous substrate, contamination of the antibiotic disc for susceptibility testing with another antibiotic, too low concentration of the antibiotic used for susceptibility testing because of its poor solubility, and evaluation of product performance by means of an inappropriate bacterial strain), material defects (4; quality defect of the used antibiotic,

inaccurate composition of the used culture bouillon, and quality defect of the used dye), miss of the specification (4; non-detection of some strains of *Pseudomonas aeruginosa* in sputum of patients with cystic fibrosis, non-detection or erroneous identification of rare strains of *Gonococci* or *Salmonella ssp*. as well as vancomycin resistant strains of *Staphylococcus aureus*, because of their atypical biochemical reactions), and labeling errors (3; erroneous labeling of flasks with antibiotics, erroneous printing of card codes or identification strips), whereas software errors (2; isolated erroneous determination of the minimum inhibitory concentrations (MIC) for antibiotics in susceptibility testing), and constructional faults (2; continued use of a solvent which was no more appropriate after modification of the product design, increased degradation of the antibiotic after exposition to humidity due to a modification of the product formulation) were less frequent. In the remaining cases, there was no product failure (1; the manufacturer proactively communicated a software update which was necessary after a modification of the product design in order to prevent the risk for erroneous results due to a further use of the old software version), or the underlying root cause was not identified (1; diminished growth of *Campylobacter jejuni* due to unknown causes). Even though the underlying product failures were very different in this group, their possible consequences on clinical diagnostics and patient treatment were very uniform. In detail, these were erroneous identification of bacteria strains and incorrect results of antibiotic susceptibility testing (*Table 5*).

Product failures of culture media (13, from which 1 served for the maintenance of a microaerophilic milieu in the incubator) were most frequently affected by an impaired sterility (5; contamination of culture plates or liquid media with bacteria or moulds, microbial contamination of a liquid reagent pack for microaerophilic incubation), whereas material defects (4; hemolysis in agars containing sheep blood) and production errors (2; insufficient stability of the antibiotic in the agar due to the production process, insufficient adjustment of the windings of the tubes and their caps although both were within their tolerance limits resulting in a sample leakage) were less frequent. In the remaining cases, a manufacturer related product failure was excluded (1; fissure in the agar of a tube due to a transport damage), or the underlying cause remained unclear (1; hemolysis of a blood agar, the affected product was not available for further investigation by the manufacturer, retained samples showed no alterations). Typical consequences of product failures in this group were the lack of usability and the risk for falsely positive results regarding the detection of bacteria or moulds. In addition, the leakage of a sample transport medium can be followed by an infection risk of the personnel handling the transport medium at its transport or even in the laboratory (*Table 5*).

In the group of products for immunological testing no differences of product failures were found with respect to the intended use (diagnostics of bacteria, viruses, moulds, or parasites), so that no differential analysis was made. If product

Table 5. Product failures of tests, reagents, controls, calibrators, and culture media for diagnostics of infections (90).

Product failure	Product based on culture or biochemical methods or staining[1]	Product based on immunological methods[2]	Product based on molecular, biological methods[3]	Culture media[4]	Total number of products
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of cases	23 (100.0)	42 (100.0)	12 (100.0)	13 (100.0)	90 (100.0)
No product failure	1 (4.3)	2 (4.8)	0 (0.0)	1 (7.7)	4 (4.4)
User error	0 (0.0)	1 (2.4)	1 (8.3)	0 (0.0)	2 (2.2)
Root cause not identified	1 (4.3)	13 (31.0)	1 (8.3)	1 (7.7)	16 (17.8)
Product failure identified	21 (91.3)	26 (61.9)	10 (83.3)	11 (84.6)	68 (75.6)
Material defect	4	12	5	4	25
Software error	2	0	2	0	4
Calibration error	0	2	0	0	2
Miss of specification	4	0	0	0	4
Production error	6	3	0	2	11
Incorrect instructions for use	0	2	2	0	4
Non-microbial contamination	0	1	0	0	1
Packaging error	0	1	0	0	1
Microbial contamination	0	1	0	5	6
Interference by other substances	0	3	0	0	3
Constructional fault	2	0	0	0	2
Labeling error	3	1	1	0	5

[1]E. g., culture, strain differentiation, susceptibility testing, staining; solid or liquid culture media for common use or for laboratory analyzers as well as materials for operation of incubators are excluded;

[2]E. g., immunological typing of strains, serology, ELISA, Western blots;

[3]E. g., polymerase chain reaction (PCR), hybridisation assays;

[4]Solid or liquid culture media for common use but not for laboratory analyzers and materials for operation of incubators (except laboratory analyzers).

failures were identified, the underlying root causes were most common material defects (12; impaired quality or stability of the conjugate, impaired stability or sensitivity loss of the latex reagent, inappropriate serum or serum with a crossreactivity to other viruses, and variable quality of other raw materials). Other less frequent causes were interferences (3; prozone effect in patient samples with high antibody titres, heterophilic antibodies in the patient sample reacting with the test antibody, interference with a compound contaminating the antibiotic of another manufacturer without clinical consequences for patients treated with this antibiotic), production errors (3; contamination of the product with a substance used in its production which was not completely removed later on, reduced reactivity of the latex reagent due to a production error, too low antibody concentration of the reagent due to insufficient regulations in its production), calibration errors (2; erroneous limits of the standards used in the kits), incorrect instructions for use (2; translation error in the German version of the instruction for use, limitations of the serological test in transitional samples after recent infection not sufficiently

described), non-microbial contamination (1; contamination with compounds released from the glass ware in the production process), microbial contamination (1; contamination of the kit control solution with moulds), packaging error (1; some kits contained an antiserum of another kit serving for the diagnostics of another bacterium), and labelling error (1; kit contained only an English instruction for use although marketed in Germany). In 2 cases, a product failure was definitively excluded (the performance of the test was within its specification provided by the manufacturer in the instructions for use, even though particular antigens of distinct bacterial strains were not detected, the test calibration was within the reference values provided by the Robert-Koch-Institute which was not conform to the users expectations) and in 1 case the issue was caused by a user error (use after the end of the product shelf life). However, in a large number of cases (13), the underlying root cause of the proven product failure was not identified (9), or not reported to the BfArM, because the products were not marketed in Germany (4). The number of cases in which the root cause was not communicated decreased after the BfArM strengthened the requirements for final reports from the manufacturers. Typical consequences of product failures related to immunological products were falsely positive or falsely negative results of quantitative (e.g., measurement of antibody titres) or qualitative (e.g., tests for diagnostics of infection and Western blots) tests, erroneous results of control samples, and the lack of usability or erroneous calibration followed by incorrect results (*Table 5*).

Failure modes of molecular biological products (12) were most frequently caused by material defects (5; interference between albumin and microparticles in the reagent, chemical contamination of a used raw material, insufficient polymerisation of a resin used in the test, use of an incorrect intermediate product, and increased concentration of dye particles in the test conjugate). The other root causes were software errors (2; sample misidentification in case of a combined use together with a liquid handling system of another manufacturer, display of an erroneous result because of an incorrect measurement unit after correct measurement), an incorrect instruction for use (2; erroneous template for evaluation of the results, translation error in the German text version providing incorrect fluid volumes for pipetting), and a labelling error (1; declaration of an incorrect shelf life). In the other issues of this group, the underlying root cause remained unclear (1) or the product failure was caused by a user error (1; a change of sensitivity of a confirmation test performed in one laboratory was not reported to the other laboratory). Typical consequences of the product failures in this group were falsely positive or falsely negative test results and non-usable results because of incorrect values of control materials (*Table 5*).

Corrective actions

Corrective actions were performed for reduction of risks of products which are already on the market (e.g., customer information and recall) or for future products

to enhance their safety (e.g., changes of raw materials and changes in production or quality management). However, both types of corrective actions are closely linked (often termed corrective action and preventive action; CAPA) and, therefore, not distinguished in our analysis. Corrective actions were typically performed in cases of proven product failures. However, in a minority of cases they were also performed for prevention, e.g., in cases where a product failure was excluded, but investigations revealed potential risk for future failures. Corrective measures were also performed in few cases where the root cause remained unclear and the manufacturers identified potential weak points in the product quality.

In our analysis, we defined cases in which corrective actions were performed only in other countries, but not in Germany, (e.g., in cases where the affected product was not marketed in Germany) as cases without corrective actions. Education of a single customer, e.g., after user errors, was also not defined as corrective action, whereas the education of all customers was considered as corrective action, because this fulfils the criteria of a field corrective action.

From a total of 90 cases analyzed in our study, corrective measures were performed in 73 cases (81.1%). From the latter, 2 were preventive actions in cases without product failure and 11 were performed in cases in which the underlying root cause of the product failure remained unclear, or was not communicated to the BfArM. In none of the cases, user errors were followed by corrective measures. In 17 of the reported cases (18.9%) no corrective actions were performed. However, this number included 10 cases in which corrective actions were performed only in other countries, because the affected products were not marketed in Germany (*Table 6*).

Even though there were large differences regarding the type of the analytical principles (product based on culture, immunological, and molecular biological means), or clinical indications (use in bacteriology, virology, mycology, and parasitology) of the products, and in the underlying root causes of the product failures, the consecutive corrective actions were very similar in the different subgroups. Therefore, no differentiation was made between the different product groups. The most frequent corrective measures were (multiple entries permitted) customer information (71; mandatory in cases of a recall) and recall (58; product or batch recall). Other frequent corrective actions were modifications in production or quality management (50), modifications of the used raw materials (17; mostly changes of the batch and not of the type of the material) and modifications of the instruction for use (12) whereas modifications in test design or reagent formulation (7), software updates (4), cessation of marketing (4), and modifications of labelling (1) were less frequent (*Table 6*).

DISCUSSION

Until the end of 2006, a total number of 888 cases related to IVD were reported to the BfArM and the annual number of reports is still increasing.

Table 6. Corrective actions for tests, reagents, controls, calibrators, and culture media for diagnostics of infections (90).

	Product based on culture or biochemical methods or staining[1]	Product based on immunological methods[2]	Product based on molecular biological methods[3]	Culture media[4]	Total number of products
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of cases	23 (100.0)	42 (100.0)	12 (100.0)	13 (100.0)	90 (100.0)
No corrective actions	3 (13.0)	8 (19.0)	3 (25.0)	3 (23.1)	17 (18.9)
Corrective actions[5]	20 (87.0)	34 (81.0)	9 (75.0)	10 (76.9)	73 (81.1)
Product recall/batch recall	17	23	8	10	58
Cessation of marketing	1	2	1	0	4
Change of design	3	2	1	1	7
Modification of production and/or quality management	12	27	5	6	50
Customer information[6]	20	32	9	10	71
Modification of the instruction for use	3	6	2	1	12
Software update	3	0	1	0	4
Modification of labeling	1	0	0	0	1
Modification of raw material	4	8	2	3	17
Customer education[7]	0	0	0	0	0

[1]E. g. culture, strain differentiation, susceptibility testing, staining; solid or liquid culture media for common use or for laboratory analyzers, and materials for operation of incubators are excluded;
[2]E. g. immunological typing of strains, serology, ELISA, Western blots;
[3]E. g. polymerase chain reaction (PCR), hybridisation assays;
[4]Solid or liquid culture media for common use but not for laboratory analyzers and materials for operation of incubators (except analyzers);
[5]Multiple entries for the different subgroups of corrective actions;
[6]Alone or in combination with a recall (in case of a recall customer information is mandatory);
[7]Education of a single customer, e. g. after a user error was not defined to be a customer education.

However, there is an unknown rate of underreporting (from manufacturers and their distributors and especially from users of the affected products), which cannot be estimated. Our analysis shows that 10.1% of notifications were related to IVD for testing of infective diseases. In our study, we excluded a number of reports regarding laboratory analyzers and their consumables and focussed on IVD for testing only. We made this exclusion, because the group of laboratory analyzers is very heterogeneous with respect to the underlying analytical principles, root causes, potential clinical consequences of product failure, and the intended use. The majority of the analyzers are also used for laboratory analyses other than diagnostics for infective diseases.

Products for infection diagnostics have some differences when compared to most other IVD. Firstly, with only few exemptions, which up to now were not subject to reporting to the BfArM, these products are for professional use only and not for use by lay users (i.e., patients). Secondly, IVD for infection

diagnostics are not only a potential cause of harm for the diagnosed patient, but also bear a risk for spread of infective diseases (i.e., public health risk) in case of falsely negative test results. Thirdly, there is a risk for direct hazard caused by these products, e.g., by leakage of tubes for transport of infective material after sampling or splashing of infectious liquids when analyzed. In principle, these higher risks should be considered while evaluating the reported failures of products for infection testing.

In our study on products for infection diagnostics, most reports came from manufacturers and their distributors (55; 61.1%; only few reports from distributors) and CAs (29; 32.2%); whereas other sources of notification, especially users, played only a minor role. This observation confirms the results of our prior publications regarding products for professional use and stands in strong contrast to the results obtained in OTC products for lay use, where user reports (from patients and pharmacies) played an important role (7-10). In principle, this can be explained by another use of complaint handling by professional users compared to lay users. It is likely that professional users re-evaluate the questioned results prior to reporting, e.g., by means of other analytical methods, whereas lay users immediately report them to the BfArM (7, 10). However, another possible explanation is an underreporting of issues by professional users.

The different user groups also affect the quality of the reports, the proportion of product failures related to the number of total reports, and a relative number of corrective actions settled by the manufacturers. In detail, reports of professional users often provide better and more detailed information regarding the reported product failure. The rate of confirmed product failures in case of professional use products is significantly higher than in case of products for lay use, even though in a small subset of cases the product failure cannot be proved by the investigations of the manufacturers, or a user error is the underlying cause (7, 10).

In the vast majority of cases included in our study, a product failure was confirmed by the investigations of the manufacturers and the underlying root causes were identified. However, in some cases root causes were not identified or not reported to the BfArM (in cases of issues and corrective actions not affecting the German market). The number of the latter is low and still decreasing, because these cases are, in the meantime, also subject to a more stringent evaluation by the BfArM. Even though there are product specific differences of the root causes of product failure in culture media, reagents, tests, calibrators, and control materials, they were very similar. In detail, the most frequent root causes were defects of the used raw materials and errors in production and/or quality management.

Based on the experience since 1999, some specific problems were identified which affect the outcome of investigations performed by manufacturers. For example, the identification of the root causes in cases of product failures sometimes is affected by the time delay between the observation of the issue by the user and the notification of the manufacturer and/or the CA and by the lack

of the affected materials (reagents and samples). In detail, source data regarding the measurement process are often automatically stored in the analyzers by electronic means for some time before they are overwritten by more recent data. In case of an issue, a rapid notification would enable the manufacturer to use these valuable data for identification of the underlying root cause. In cases of a test failure, the reagents should be preserved by the user and provided to the manufacturer for further investigation. This would provide better information regarding a test failure than an investigation of retained reagents of the same batch only. Furthermore, in cases of issues in patient samples (e.g., falsely negative or positive results) patient samples also should be preserved, because manufacturers then can investigate sample specific causes of product failure (e.g., in cases of interferences of other analytics, variations of microbial strains affecting the product specifications, and transitional samples of patients after recent infection).

In principle, there are two types of corrective actions. The first one has the goal to reduce the risk of IVD which are already on the market and are, or may be, affected by the reported product failure. This group of corrective actions includes recalls, customer information, and a distribution halt of the affected product. Another type of corrective action is the preventive action by which the manufacturer tries to reduce the risk of products which will be delivered in the market in the future. The latter type of a corrective action includes changes of the affected raw materials, modifications of the product design and of the production process, or the quality management system. However, there is often no discrimination between both types of action, which are often summarised as "corrective action/preventive action" (CAPA). Therefore, we did also not differentiate in our analyses between the two types of measures.

In a large majority of the cases reported to the BfArM, corrective actions were performed by manufacturers, mostly when the underlying root causes of product failure had been identified. Even though the subgroups of IVD analyzed in our study were very diverse, the corrective actions were often similar and were most frequently customer information, recalls, modifications of production and/or quality management, and modifications of raw materials. Interestingly, corrective actions were also performed in few cases, where a product failure was excluded or the underlying root cause remained unclear, as the investigations of the manufacturers showed potential product risks which had to be minimized. User errors were not followed by corrective measures, as education of single customers does not fulfil the criteria of a field corrective action. However, it should be noted that even customer errors can be followed by field corrective actions performed by manufacturers (10).

In summary, our data suggest that the European surveillance system for IVD is functioning. However, the system should be further improved in some points in order to increase product safety. The rate of underreporting of incidents, especially from users should be further reduced, e.g., by consequent

information. Furthermore, the time prior to reporting of incidents to the responsible CA should be minimized. This is of relevance especially in case of IVD for infection testing as failure of these products bears a potential public health risk due to the risk for spread of infective diseases. In order to improve the outcomes of the root cause investigations by the manufacturers, users should be informed to preserve reagents and patient samples under appropriate conditions and provide them to the manufacturer for further investigation in cases of potential product failure. Finally, there should be further optimization of the European market surveillance system itself, regarding the development of a functioning European database for medical products (Eudamed), the establishing of uniform criteria and procedures for information of CAs within the EEA by means of vigilance reports and information to the public on field corrective actions and risks related to IVD and other medical products, e.g., on the homepages of the responsible CAs (11).

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