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Safety of Laboratory Analyzers for Infection Testing – Results of the Market Surveillance by the BfArM until End 2007

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Abstract
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 infectiological 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 laboratory analyzers for infection testing and their consumables, but not reagents, kits and general culture media, reported to the BfArM between begin 1999 and end of 2007 were analyzed in respect to the sources of report, the underlying product failure and the performed corrective actions. Within the observation period a total of 1471 reports for IVD were received of which 73 related to the IVD for infection testing were included in our study. Reports were predominantly received from manufacturers (56) and competent authorities (15). Affected products were most frequently those for immunological analysis (42) whereas those based on culturing techniques (17) and molecular biological techniques (14) played only minor roles. In all these groups, laboratory analyzers (55) were more frequently affected than their consumables (18). Investigations of the manufacturers were able to identify the underlying root causes of product failures in 62 cases (84.9%). In 2 cases (2.7%) the root cause remained unclear and in 9 cases (12.3%) a product failure was excluded or a user error was the underlying cause. Product failures in laboratory analyzers were most frequently caused by software errors (31) and constructional faults (8) whereas the predominant cause of product failure in consumables were errors in production and quality control (8). Manufacturers issued corrective measures in 66 cases (90.4%) from which 49 and 17 were related to laboratory analyzers and their consumables, respectively. Based on the underlying root causes of product failures these were predominantly customer information (48), recalls (40), software-updates (30) and design changes (9) in the product group of laboratory analyzers as well as customer information (16), recalls (12) and modifications of production and quality management (11) in the group of consumables. The results and experiences 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 enhanced.

Key words: post market surveillance, infective disease, infection diagnostics, laboratory analyzer

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, Medizinproduktesicherheitsplanverordnung) 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, 4, 5, 6]. The same obligation applies to pharmacies and other retail traders if incidents related to over the counter-products (OTC-products) 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 (see Table 1). In consequence, both CAs work closely together in cases regarding products for immune hematological testing and infection testing to ensure product safety of IVD and blood products.

Table 1. Responsibilities of BfArM and PEI regarding IVD listed in Annex II of Directive 98/79/EC [1, 2, 3, 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] and HTLV-II[1, 2]	IIa	PEI
Hepatitis B, C and D1, 2	IIa	PEI
Congenital infection with rubella[1, 2]	IIb	PEI
Congenital infection with toxoplasma[1, 2]	IIb	PEI
CMV[1, 2, 6]	IIb	PEI
Chlamydia[1, 2]	IIb	PEI
Other products:		
Tumor marker PSA[1, 7]	IIb	BfArM
Hereditary diseases phenylketonuria and Down syndrome (trisomy 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]human T-cell leukemia virus; [6]cytomegalovirus; [7]prostate specific antigen.

In evaluating the reports and other relevant information regarding risks the task of the CA is to characterise 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 decides whether these are adequate. Any necessary field corrective action performed by the manufacturers must be communicated to the customers and users. In Germany this is typically done by field safety corrective action (FSCA); the letter must also be sent to the BfArM for information and publication on the homepage of the BfArM.

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.

Up to now only few data regarding the experience on the market surveillance system have been published [7, 8, 9, 10, 11, 12, 13]. 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 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 frequencies of notifications to the BfArM, the sources of notification, the frequencies and types of product failures as well as the frequencies and types of corrective measures settled by the manufacturers of the affected products. In this study all issues regarding laboratory analyzers for infection testing and their consumables (including their general consumables like buffers and common culture media, but not reagents, kits and common culture media not to be used in analyzers) reported to the BfArM between begin 1999 and end of 2007 were analyzed.

Methods

All notifications on IVD received by the BfArM between begin of 1999 and end of 2007 were included. Detailed analysis was made for analyzers and their general consumables (e.g., buffers and general culture media). Tests and reagents (including special culture media (e.g., for susceptibility testing), calibrators and

controls) which also serve for infection diagnostics were excluded. However, there were some more definitions for in- and exclusion of the corresponding IVD. Products for culture diagnostics require no further definition because those products exclusively serve for diagnostics of infectious diseases. However, IVD based on immunological means often include multifunctional analyzers used in clinical chemistry which serve for routine diagnostics including some parameters for infection testing (e.g., serology of HIV-1, hepatitis B and C). In these cases we included analyzers and consumables if there was a risk for users (e.g., when handling the analyzer) or there was a risk for patients due to erroneous results of tests for infection diagnostics whereas product related problems affecting other laboratory parameters which serve not for diagnostics of infective diseases were excluded. The same procedure for in- and exclusion of cases was made for the minor group of analyzers and consumables based on molecular biological methods. Analyses of the included cases were made in specific subgroups of the products regarding the types of the product (analyzers vs. consumables) and the underlying analytical principles (products based on cultural, 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 (see Table 2). At the end of the observation period BfArM had received a total number of 1471 reports concerning IVD. From these cases 643 (43.7%) were related to OTC-products specified for lay use whereas the majority of reports was related to IVD for professional use (828, 56.3%). From the latter 73 (5.0% of all reports) were analyzers and their consumables for infection diagnostics which were subject of this study.

Table 2. Number of notifications regarding IVD reported to the BfArM in total and analyzers and consumables for diagnostics of infective diseases since begin 1999 until end of 2007.

Year	Total number of notifications regarding IVD n	Notifications regarding analyzers and consumables for diagnostics of infections[1] n (%)
1999	13	1 (7.7)
2000	21	1 (4.8)
2001	33	1 (3.0)
2002	58	4 (6.9)
2003	121	8 (6.6)
2004	200	12 (6.0)
2005	207	16 (7.7)
2006	235	12 (5.1)
2007	583	18 (3.1)
Sum	1471	73 (5.0)

[1]including general consumables (buffers and culture media) for laboratory analyzers but without specific culture media, reagents, calibrators and control materials.

Sources of Reports

From all notifications on products analyzed in this study 56 (76.7%) came from manufacturers and their distributors (only few cases from distributors) and from authorities (15 (20.5%); e.g., national CAs and European CAs). Notifications from other sources (e.g., users, press, scientific organisations and industrial competitors as well as cases initiated on BfArM´s own initiative) played only minor roles (see Table 3). In detail, one notification was received directly from a professional user (hospital laboratory) and another one from a hospital laboratory via the Drug Commission of the German Pharmaceutical Association. Analysis regarding the sources of notification to the BfArM revealed no relevant differences in the proportions of the sources of notification between the different product groups.

Product Groups

From the total of 73 notifications 55 (75.3%) affected laboratory analyzers and 18 (24.7%) their general consumables (e.g., buffers, pipettes, general reagents but not test kits). Within the group of analyzers most reports were related to analyzers based on immunological methods (e.g., immunological typing of strains, serology, enzyme-linked immunosorbent assay (ELISA), Western blot; 36) whereas minor numbers of notifications regarded to analyzers for detection, differentiation or susceptibility testing of bacteria by cultural methods (9) and analyzers based on molecular biological methods (e.g., polymerase chain reaction (PCR), hybridisation assay; 10) (see Table 4). In contrast, only minor differences were observed in the group of consumables (6, 8 and 4, respectively) (see Table 4).

Table 3. Sources of notification regarding analyzers and consumables for diagnostics of infective diseases since begin 1999 until end of 2007.

Source of reports n (%)	Number of reports
Manufacturers and distributors	56 (76.7)
Users[1]	2 (2.7)
Competent Authorities[2]	15 (20.5)
Others[3]	0 (0.0)
Sum	73 (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).

Table 4. Notification regarding analyzers and consumables for diagnostics of infective diseases based on different analytical principles since begin 1999 until end of 2007.

Affected product	Product based on cultural or biochemical methods[1]	Product based on immunological methods[2]	Product based on molecular biological methods[3]	Total Number of products
	n	n	n	n
Analyzers	9	36	10	55
Consumables	8	6	4	18
Total number of products	17	42	14	73

[1]e.g., culture, strain differentiation, susceptibility testing; [2]e.g., immunological typing of strains, serology, ELISA, Western blot; [3]e.g., PCR, hybridisation assay

Frequency and Type of Product Failure

From the notifications regarding analyzers and consumables based on immunological principles (immunological typing of strains, serology, ELISA, Western blots) 36 were related to analyzers and 6 to corresponding consumables (see Table 4). Based on the definition criteria of our study the group of analyzers included a number of products which serve also for diagnostics of other parameters in clinical chemistry (e.g., hormones, protein diagnostics and therapeutic drug monitoring). In 29 cases (80.6%) the cause of analyzer failure was identified. The most frequent causes of analyzer failure were software errors (19 cases; calibration error, sample misidentification or sample mix-up as well as misclassification of samples near the individual cut-off value of the test, increased number of error flags and erroneous results due to analyzer malfunction not identified and flagged by the software (e.g., non-detection of foam in the sample followed by pipetting of false volumes, non-detection of used reaction cartridges remaining in the analyzer, non-detection of impaired motion of the reaction carousel)) and constructional faults (6 cases, short-circuit due to breakage of a sewer plastic flange, calibration error and erroneous results caused by an inappropriate transfer station, aspiration of air instead of washing buffer because of an inappropriate form of the buffer container, analyzer shut down caused by an electromagnetic interference of the novel type of a temperature controller board, risk of electric shock due to insufficient grounding of the analyzer chassis, variability of results depending on changes of the environmental temperature affecting the assay calibration), whereas mechanical errors (2 cases, incorrect pipetting due to a defect in the pump head, fall down of the analyzer cover because of perished gas springs), miss of specification (1 case, falsely-positive results due to a reagent carry over and an improper washing step if two specific tests were performed directly subsequent) and production errors (1 case, incorrect cabling of the fluid sensor of the analyzer) played only minor roles. In the remaining 7 cases (19.4%) a product failure was definitively excluded by the investigations of the manufacturer (1 case, non-validated mixed operation with another analyzer was followed by a result which was not reproducible), user errors were the underlying cause (4 cases, insufficient analyzer maintenance, ignorance of the instruction for use, needle stick injury due to the use of an adapter not recommended by the manufacturer, insufficient maintenance of the analyzer´s optical unit in combination with a delayed exchange of a common reagent solution) or the detailed results of the investigation were not reported to the BfArM (2 cases, erroneous results due to incorrect pipetting, emission of smoke by the analyzer). Corresponding consumables (6) were predominantly affected by production errors (5 cases, splashing and incorrect pipetting of samples by defective pipettes and assay tips, analytical error if sample cups from the manufacturer which were not validated before were used, erroneous cut-off level of a calibrator, low signal due to a production related contamination of the signal reagent) whereas other causes of product failure (1 case of a software failure; evaluation software for ELISA, hemagglutination and blood group typing does not exclude the neglect of erroneous results of control samples by the user) played only a minor role (see Table 6). The reported cases were followed by the receipt of falsely-positive or falsely-negative results sometimes followed by the necessity of sample retesting and potential hazard of the user performing the analysis or the analyzer maintenance.

In the group of analyzers and consumables based on cultural methods (culture, strain differentiation, susceptibility testing) 9 reports were related to analyzers and 8 were related to consumables (see Table 4). Analyzers were most frequently affected by software errors (8 cases, erroneous results if generic barcodes or polycarbonate flasks were used, reset of results from positive to negative after removal of positive sample tubes from the analyzer, delayed data transfer from the analyzer to the laboratory software, incorrect interpretation of results of susceptibility testing after reediting of stored data, erroneous results of susceptibility testing where different bacterial strains were identified to be falsely-sensitive). One more case was caused by a user error (destruction of an incorrectly positioned glass culture flask by closure of the analyzer drawer) (see Table 5). Corresponding consumables were affected by production errors (2 cases, fly in the bottle without impaired sterility, low inoculums of bacteria in a calibrator), labelling error (2 cases, insufficient labelling for filling of culture flasks, doubling of the barcode on the culture flask), microbial contamination (1 case, contamination of culture flasks with Bacillus ssp.) and a software error (1 case, false-negative results in case of generic barcodes on polycarbon-

Table 5. Product failures of analyzers for diagnostics of infective diseases since begin 1999 until end of 2007.

Product failure	Product based on cultural or biochemical methods[1]	Product based on immunological methods[2]	Product based on molecular biological methods[3]	Total number of products
	n (%)	n (%)	n (%)	n (%)
Number of cases	9 (100.0)	36 (100.0)	10 (100.0)	55 (100.0)
No product failure	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.8)
User error	1 (11.1)	4 (11.1)	1 (10.0)	6 (10.9)
Root cause not identified	0 (0.0)	2 (5.6)	0 (0.0)	2 (3.6)
Product failure identified	8 (88.9)	29 (80.6)	9 (90.0)	46 (83.6)
Material defect	0	0	0	0
Software error	8	19	4	31
Calibration error	0	0	0	0
Electrical error	0	0	0	0
Mechanical error	0	2	0	2
Miss of specification	0	1	0	1
Production error	0	1	1	2
Incorrect instructions for use	0	0	1	1
Non-microbial contamination	0	0	0	0
Packaging error	0	0	0	0
Microbial contamination	0	0	0	0
Interference by other substances	0	0	0	0
Constructional fault	0	6	2	8
Labeling error	0	0	1	1

[1]e.g., culture, strain differentiation, susceptibility testing; [2]e.g., immunological typing of strains, serology, ELISA, Western blot; [3]e.g., PCR, hybridisation assay.

ate flasks which are identified as glass flasks by the analyzers algorithm). Additionally, two more cases were caused by user errors (splashing of contaminated medium from culture flasks when aliquots are sampled due to incorrect handling or overfilling) (see Table 6). All reported cases in this group bore an indirect and a direct risk for patients (falsely-positive or falsely-negative results of microbial detection and/or susceptibility testing) and users (infection due to the release of contaminated material from the culture flasks), respectively.

Causes of product failure in the group of analyzers (10) and consumables (4) based on molecular biological diagnostics of infectious diseases were very heterogeneous even though a slight trend towards software errors was observed in the analyzer group (see Tables 4, 5 und 6). In detail, 9 out of 10 failures of molecular biological analyzers were caused by software errors (4 cases, sample misidentification, incorrect sample transfer by the sample processor, erroneous reading of additional barcode types, erroneous result due to algorithm affected by a spike of the optical signal within the reaction), constructional faults (2 cases, appearance of light scatter with risk of falsely-positive results and sample mismatch due an incorrectly adjusted fiber optic cable in combination with a constructional fault, sharp protruding corners of spring clips bearing a risk for personal injury), production errors (1 case, incorrectly installed fiber optic cable resulting in a sample mismatch), errors in the instruction for use (1 case, erroneous pipetting volumes of the reagents in the German translation of the instruction for use only) and labelling errors (1 case, incorrect labelling at the thermal cycler unit with risk for erroneous results which are not flagged by the analyzer). One more case was caused by a user error (insufficient cleanliness and maintenance of the analyzer) (see Table 5). Product failures in the group of corresponding consumables were caused by material defects (1 case, inhibition of the subsequent amplification reaction by the buffer solution used in the kit used for nucleic acid extraction), production errors (1 case, leakage of the lock of a sample tube which was part of a kit), miss of specification (1 case, under determination of viral replicative units by means of the kit for sample pretreatment) and packaging errors (1 case, delivery of reaction cells after end of their shelf-life by the manufacturer) (see Table 6). Product failures of analyzers and consumables based on molecular biological means bore the risk for falsely-positive and falsely-negative results and in some cases the manufacturers recommended retesting of samples analyzed with the affected products.

Corrective Actions

Corrective actions are typically 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 were not distinguished in our analysis. Corrective actions are typically performed in cases of proven product failures. However, in a minority of cases manufacturers may also perform a preventive corrective action in cases where a product failure was excluded, but investigations revealed a potential risk for future failures as well as issues in which user errors are the underlying causes. Additionally, corrective measures can also be performed in cases where the root cause remained unclear but the investigations of 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 is 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 an education of all customers was considered as corrective action, because this fulfils the criteria of a field corrective action. From the total of 73 cases analyzed in our study corrective measures were performed in 66 cases (90.4%). Considering the large differences of underlying product failures in the groups of analyzers and consumables the corrective actions were analyzed separately in these two groups. However, because of the small differences in respect to the underlying analytical principle in these groups, analysis was not made separately for the subgroups of products based on cultural, immunological and molecular biological methods. In the group of analyzers corrective actions were performed in 49 (89.1%) of the reported cases (see Table 7). Corrective actions were predominantly (multiple entries permitted) customer information (48; mandatory in cases of a recall), recall (40) and software-update (30). Other frequent corrective actions were modifications in production or quality management (9) and design changes (9), whereas modifications of the instructions for use (6), modification of labelling (4), modification of raw material (3) and customer education (1) were less frequent. In 6 more cases there were no corrective actions because there was no analyzer failure (1), the root cause re-

Table 6. Product failures of consumables for analyzers for diagnostics of infective diseases since begin 1999 until end of 2007.

Product failure	Product based on cultural or biochemical methods[1]	Product based on immunological methods[2]	Product based on molecular biological methods[3]	Total number of products
	n (%)	n (%)	n (%)	n (%)
Number of cases	8 (100.0)	6 (100.0)	4 (100.0)	18 (100.0)
No product failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
User error	2 (25.0)	0 (0.0)	0 (0.0)	2 (11.1)
Root cause not identified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Product failure identified	6 (75.0)	6 (100.0)	4 (100.0)	16 (88.9)
Material defect	0	0	1	1
Software error	1	1	0	2
Calibration error	0	0	0	0
Electrical error	0	0	0	0
Mechanical error	0	0	0	0
Miss of specification	0	0	1	1
Production error	2	5	1	8
Incorrect instructions for use	0	0	0	0
Non-microbial contamination	0	0	0	0
Packaging error	0	0	1	1
Microbial contamination	1	0	0	1
Interference by other substances	0	0	0	0
Constructional fault	0	0	0	0
Labeling error	2	0	0	2

[1]e.g., culture, strain differentiation, susceptibility testing; [2]e.g., immunological typing of strains, serology, ELISA, Western blot; [3]e.g., PCR, hybridisation assay

Table 7. Corrective actions for analyzers for diagnostics of infective diseases since begin 1999 until end of 2007 (multiple entries).

Type of corrective action	Product based on cultural or bio-chemical methods[1]	Product based on immunological methods[2]	Product based on molecular biological methods[3]	Total number of products
	n (%)	n (%)	n (%)	n (%)
Number of cases	9 (100.0)	36 (100.0)	10 (100.0)	55 (100.0)
No corrective actions	0 (0.0)	6 (16.7)	0 (0.0)	6 (10.9)
Corrective actions[4]	9 (100.0)	30 (83.3)	10 (100.0)	49 (89.1)
Product recall / batch recall	7	25	8	40
Cessation of marketing	0	0	0	0
Change of design	0	7	2	9
Modification of production and/or quality management	0	7	2	9
Customer information[5]	9	29	10	48
Modification of the instruction for use	1	4	1	6
Software-update	8	18	4	30
Modification of labeling	0	2	2	4
Modification of raw material	1	2	0	3
Customer education[6]	0	0	1	1

[1]e.g., culture, strain differentiation, susceptibility testing; [2]e.g., immunological typing of strains, serology, ELISA, Western blot; [3]e.g., PCR, hybridisation assay; [4]multiple entries for the different subgroups of corrective actions were allowed; [5]alone or in combination with a recall (in case of a recall customer information is mandatory); [6]education of a single customer e.g., after a user error was not defined to be a customer education.

mained unclear (1), a user error was the underlying cause (3) or the product affected by a product failure was not marketed in Germany (1) (see Table 7). A different pattern of corrective actions was observed in the group of consumables (see Table 8). In the latter corrective actions were performed in 17 (94.4%) of the reported cases. In detail, these were most frequently (multiple entries permitted) customer information (16), recall (12) and modifications in production or quality management (11). Less frequently, manufacturers performed modifications of the instruction for use (4), modifications of raw materials (2), cessation of marketing (1), software-update (1), modification of labelling (1) and customer education (1). In one more case there was no corrective action because the affected product was not marketed in Germany (see Table 8).

Corrective measures were typically performed in cases of proven product failure (60 out of 62 cases (96.8%), i.e., 82.2% of all cases included in this study; in the remaining two cases the affected product was not marketed in Germany). In one more case in which a product failure has been excluded by the investigations of the manufacturer no corrective action was performed. However, it should be noted that even cases without proven product failure can be followed by corrective measures, e.g., when manufacturer´s investigations reveal a potential risk of product failure which has to be minimised by a preventive action. In our study we further received notifications in which the underlying causes were user error (8; 11.0% of all cases included in this study) or in which the underlying root cause was not identified or not reported (2; 2.7% of all cases). However, even these cases were often followed by preventive corrective actions (5 out of 8 cases (62.5%) and one out of two cases (50.0%)) in order to minimise product related risk in the future.

Discussion

Until end of 2007 a total number of 1471 cases related to IVD were reported to the BfArM. 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 showed that only 5.0% of notifications were related to laboratory analyzers and their general consumables for testing of infectious diseases. However, this low proportion is caused by the extremely high number of notifications regarding OTC-products for self testing (643 until end of 2007). After exclusion of these products which are predominantly systems (analyzers, test strips and few control materials) for monitoring of blood glucose [7] there is

Table 8. Corrective actions for consumables of analyzers for diagnostics of infective diseases since begin 1999 until end of 2007 (multiple entries).

Type of corrective action	Product based on cultural or bio-chemical methods[1]	Product based on immunological methods[2]	Product based on molecular biological methods[3]	Total number of products
	n (%)	n (%)	n (%)	n (%)
Number of cases	8 (100.0)	6 (100.0)	4 (100.0)	18 (100.0)
No corrective actions	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.6)
Corrective actions[4]	8 (100.0)	5 (83.3)	4 (100.0)	17 (94.4)
Product recall / batch recall	5	3	4	12
Cessation of marketing	0	0	1	1
Change of design	0	0	0	0
Modification of production and/or quality management	4	5	2	11
Customer information[5]	7	5	4	16
Modification of the instruction for use	2	1	1	4
Software-update	1	0	0	1
Modification of labeling	1	0	0	1
Modification of raw material	0	1	1	2
Customer education[6]	1	0	0	1

[1]e.g., culture, strain differentiation, susceptibility testing; [2]e.g., immunological typing of strains, serology, ELISA, Western blot; [3]e.g., PCR, hybridisation assay; [4]multiple entries for the different subgroups of corrective actions were allowed; [5]alone or in combination with a recall (in case of a recall customer information is mandatory); [6]education of a single customer e.g., after a user error was not defined to be a customer education.

a remaining number of 828 products for professional use and the 73 cases included in our study are 8.8% of all notifications regarding professional use IVD. In a prior publication [12] we analyzed the notifications regarding tests, reagents, control materials, calibrators and culture media for diagnostics of infectious diseases until end of 2006. In the cited study 90 cases were analyzed which were 14% of all notifications regarding professional use products (642 cases from a total number of 888 cases including OTC-products) in prior observation period [12]. Data of both studies demonstrate that professional use IVD for diagnostics of infectious diseases play a relevant role in medical diagnostics.

In our recent study we focussed on laboratory analyzers and consumables for diagnostics of infectious diseases which are completely in the responsibility of the BfArM and excluded tests, reagents, calibrators, control materials and culture media analyzed before [12]. If required, analysis was made separately for analyzers and consumables as well as the underlying analytical principles (culture, immunology and molecular biology) because of the strong heterogeneity of these products. The largest number of notifications was received for laboratory analyzers based on immunological methods. However, the number of cases included in this group is strongly influenced by the inclusion criteria of our study because this type of analyzers is very frequently used in clinical routine (clinical chemistry analytics including hormones and therapeutic drug monitoring) and we included all cases (potentially) affecting the results of tests in infectiology or the health of users. To a much lower extent this plays also a role for molecular biological analyzers and their consumables but not for products based on culture techniques.

Products for infection diagnostics have some differences when compared to most other IVD. First, the analyzers included in this study are for professional use only and not for use by lay users (i.e., patients). Second, 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. Third, there is a risk for direct hazard caused by these products, e.g., by 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 (56, 76.7%; only few reports from distributors) and CAs (15, 20.5%) 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, 8, 9, 10, 12]. 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 reevaluate the questioned results prior to reporting, e.g., by means of other analytical methods, whereas lay users immediately report them to the BfArM (directly, via their pharmacies or via the Drug Commission of the German Pharmaceutical Association) [7, 10]. However, another possible explanation is an underreporting of issues by professional users which cannot be estimated in its extent.

In principle, the different user groups also affect the quality of the reports, the proportion of product failures related to the number of total reports and the relative number of corrective actions settled by the manufacturers. Data of our prior investigations suggest that reports of professional users often provide better and more detailed information regarding the reported product failure. In consequence, 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, 12].

In the vast majority of cases included in our recent 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 of a more stringent evaluation by the BfArM. Irrespective of the underlying analytical method analyzers are typically affected by software errors. This stands in strong contrast to the observation obtained in tests, reagents, calibrators, control materials and culture media for diagnostics of infectious diseases [12] as well as consumables of analyzers used in infection diagnostics which are both mostly subject of material defects and errors in production or quality management. The differences in the underlying root causes also affect the type of corrective actions performed by the manufacturers to ensure product safety. In detail, like in other product groups analyzed before typical corrective actions in cases of underlying software errors are software-updates whereas the most frequent corrective actions in general consumables as well as in tests, reagents, calibrators, control materials and culture media are modifications of the raw materials used as well as modifications in production and/or quality management [7, 10, 12].

Based on the experience since 1999 some specific problems were identified which affect the outcomes of the investigations performed by the 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 as well as the lack of the affected materials (reagents and samples). In detail, source data regarding the measurement process are often automatically stored on 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. Sometimes it is not evident at the time of the issue if it is caused by an analyzer failure or a test failure. Therefore, in cases where a test failure cannot be excluded, reagents and patient samples should be preserved by the user under appropriate conditions 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.

A specific problem, not only in the field of infection diagnostics, is the mixed use of analyzers from different manufacturers. If this type of use has not been sufficiently validated by the manufacturers and is therefore not recommended by the manufacturers it lies in the only responsibility of the user to validate functionality and safety of the used analyzer combination. The same takes place for the combination of analyzers and tests, reagents, calibrators and controls. However, the analysis of all cases regarding professional use products (i.e., not only IVD for diagnostics of infectious diseases) up to now revealed only few cases of problems caused by mixed use of analyzers and no notifications caused by a mixed use of analyzer and reagent from different manufacturers. Likely, this reflects the requirements in medical laboratories where users are familiar with adaptation and validation of tests on analyzers. However, combination of analyzers from different manufacturers is less frequent and due to the underlying software often more complex to validate making it more difficult to ensure the safety of mixed use.

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 even may be affected by the reported product failure. This group of corrective actions includes recalls, customer information and distribution stop of the affected product. Another type of a 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 software-updates, changes of the affected raw materials, modifications of the product design as well as modifications of the manufacturing 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 the large majority of the cases reported to the BfArM corrective actions were performed by the manufacturers, mostly when the underlying root causes of product failure had been identified. Based on the underlying root causes of product failure we were able to distinguish between analyzers and consumables. How-

ever, within these groups there were no relevant differences between the subgroups based on various analytical principles. In detail, corrective actions were performed in all except two cases (products not in the German market) of proven product failure, in no case where a product failure has been excluded by the investigations of the manufacturers, in one of the two cases where the root cause remained unclear and in 5 of 8 cases where a user error was the underlying problem and therefore confirms the observation of a prior study [10]. The high rate of corrective actions after user errors demonstrates that even in these cases an improvement of product safety can be achieved by thorough investigations performed by the manufacturers. The most frequent corrective action in analyzers and consumables was customer information because in Germany customer information is required for every action in the field and mandatory in every case of a product recall. Recalls (including the replacement of the affected software) were also frequent because this type of a corrective action is the most rapid one to minimise product-related risks. Other types of corrective actions are based on the underlying root causes and were typically software-updates in the analyzer group and changes of raw materials used and modifications in production and/or quality management in the group of consumables. Comparison to data published before for tests, reagents, calibrators, control materials and culture media for infection diagnostics demonstrate that corrective actions for these are very similar to those for general consumables [12]. The latter demonstrates that requirements for ensuring product safety in test materials and consumables are very similar and largely different from those in analyzers.

An important aspect of the market surveillance in Germany is the split responsibility between BfArM and PEI. As mentioned before the BfArM is responsible for registration and evaluation regarding issues of all IVD except those listed in Annex II parts A and B of the Directive 98/79/EC used for immune hematological diagnostics, tissue typing and testing for infectious diseases. Registration and evaluation of issues related to these products lie in the responsibility of the PEI (see Table 1; [1, 3]). However, the analyzers used for running these tests are in the responsibility of the BfArM. In addition, the direct surveillance of the manufacturers (e.g., compliance with the requirements of product conformity, adherence of standards in cases of field corrective actions) is subject of more than 80 local German authorities. In consequence, this causes a close cooperation between the different national authorities. For example, in case of products for infection diagnostics there is a close cooperation between BfArM and PEI if products are affected which play or might play a role for safety of blood products in transfusion services (e.g., donor testing for infectious diseases) because the PEI in Germany is also responsible for the hemovigilance ensuring the safety of blood products, e.g., for transfusion. In detail, BfArM informs PEI in all cases regarding tests, reagents and control materials for immune hematological analysis and tissue typing (only few cases as the most relevant IVD are in the responsibility of the PEI) and all cases regarding laboratory analyzers if IVD falling in the responsibility of the PEI are or might be affected. According to the currently effective regulations [3, 4, 5], manufacturers have to inform the responsible CA within a strict time schedule on issues with their products. However, sometimes it is not clear at the beginning of the notification process if the issue is caused by a failure of the test falling into the responsibility of the PEI or an analyzer failure which lies in the responsibility of the BfArM. In the few cases of this type manufacturers usually inform both German CAs. At a later time based on the results of the investigation the manufacturers provide further details on the issue (test or analyzer failure) to both CAs from which the one which is not the responsible CA then is closing the file. In all cases which are subject of the described cooperation between BfArM and PEI, BfArM further reports the final results of the investigations regarding the root cause of the product failure and the performed corrective measures including preventive measures to the PEI in order to support this CA in their duty to ensure safety of blood products. This system of two responsible CAs (BfArM and PEI) for registration and evaluation of IVD product failures is well functioning even though it is sometimes confusing especially for foreign manufacturers. However, some further feed back regarding the results of market surveillance obtained by the large number of local authorities should be aspired.

In summary, our data once more 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 minimised. 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. Finally, there should be further optimisation 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 as well as information of the public on field corrective actions and risks related to IVD and other medical products, e.g., on homepages of the responsible CAs.

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