Safety of In-vitro Diagnostics for Coagulation Testing – Results of Market surveillance by the BfArM

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The 30th World Congress of Biomedical Laboratory Science
Berlin 18.-22. August 2012

Gesetz zur Änderung des Medizinproduktegesetzes
(Medizinproduktegesetz - MPG)

4rd Amendment on the German Law on Medical Devices

Medizinprodukte-Sicherheitsplanverordnung - MPSV

Ordinance on the Medical Devices Vigilance System

Competent Autority responsible in charge according to MPSV

Medical devices

Federal Institute for Drugs and Medical Devices (BfArM)[#]

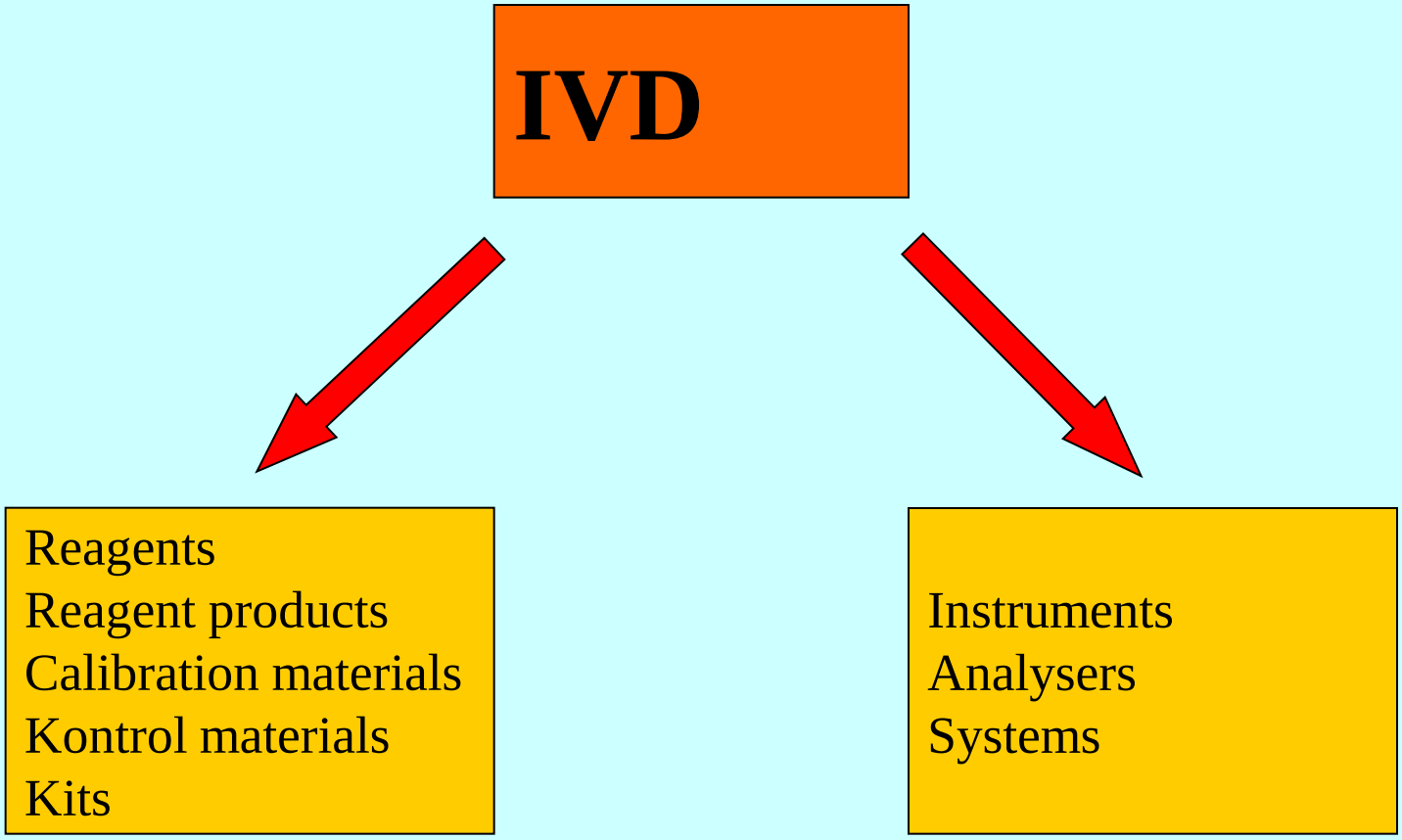
In-vitro diagnostics

Paul Ehrlich Institute (PEI)

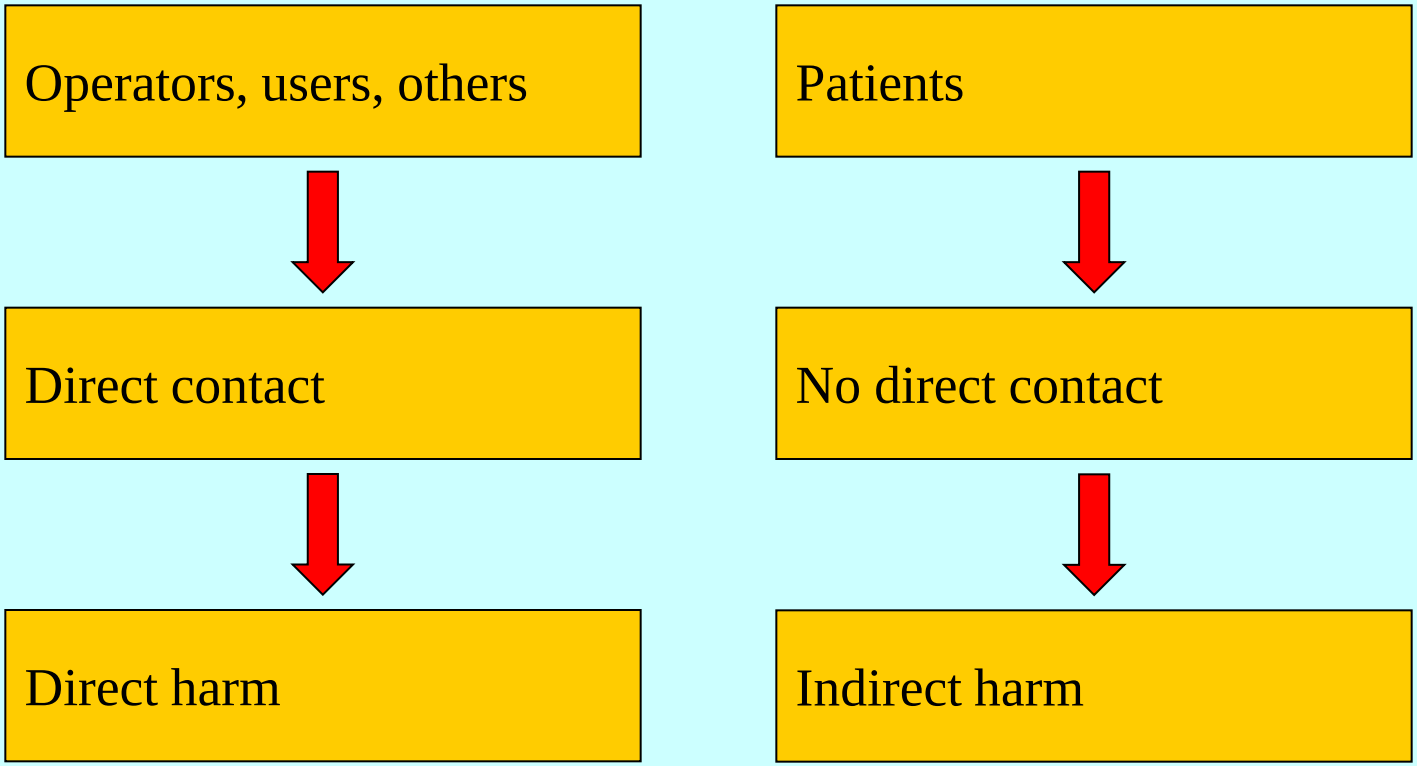
[#]) Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

Definition and classification

according § 3 No. 4 MPG



Risks caused by IVD - I



Risks caused by IVD - II

Examples of direct harm

Risks caused by harmful biological substances (e. g. infection) or chemical compounds (e. g. chemical burns) in cases of practice, storage and disposal

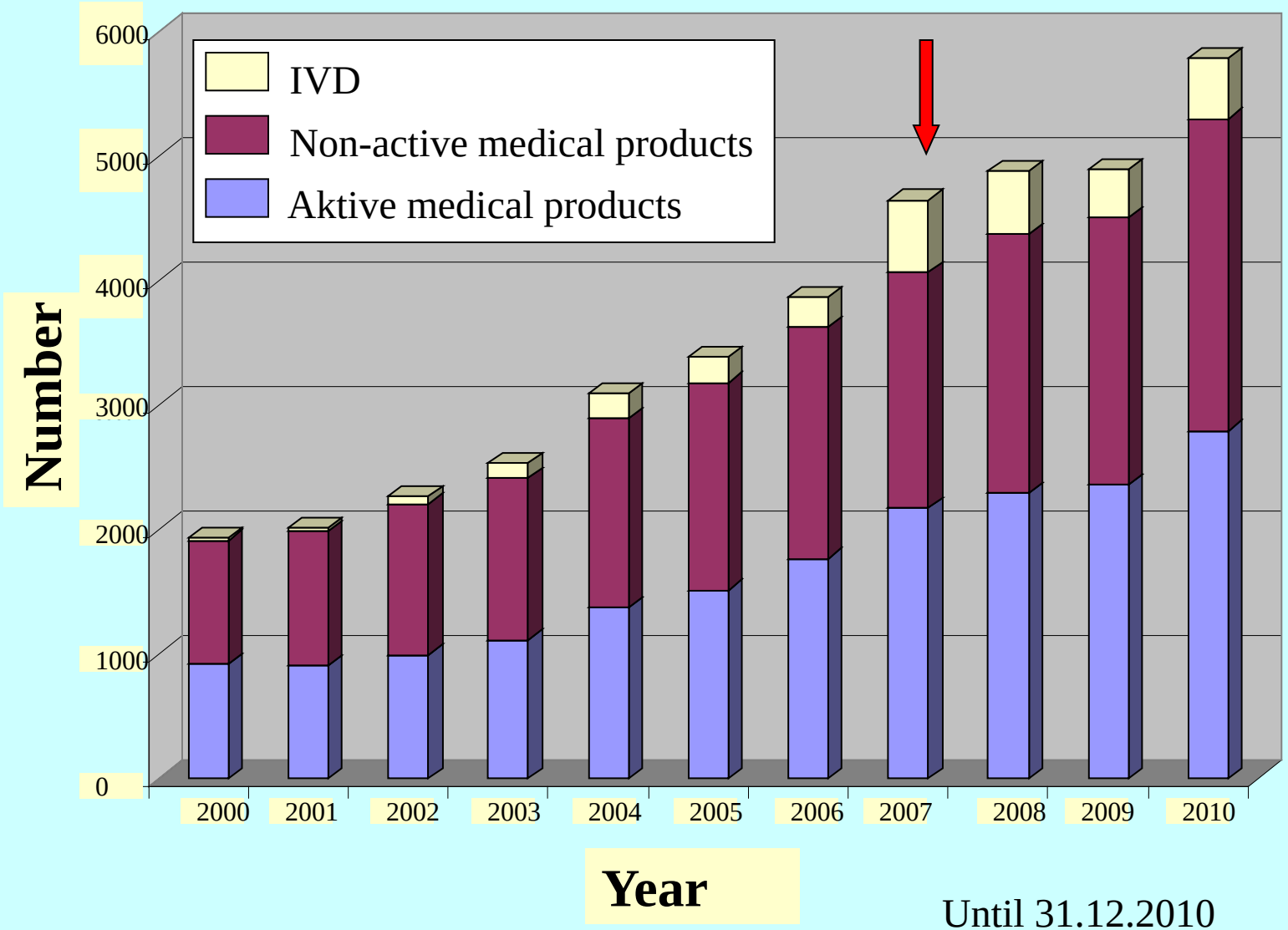
Risks caused by mechanical injury (e. g. needles) or electricity

Examples of indirect harm

Erroneous results followed by medical consequences

- Incorrect medical diagnoses (e. g. falsely-negative result of a serological test)
- Incorrect therapeutic decisions (e. g. erroneous result of a susceptibility test)
- Additional or false diagnostic or therapeutic measures
- Insufficient or inappropriate product design:
  - Non-fulfillment of product performance, e. g. sensitivity, specificity, linearity (limits for dilution), interferences (metabolites, pharmaceuticals)

Number of notifications to the BfArM



Until 31.12.2010

Problems

Even though the regulations on in-vitro-diagnostic medical devices (IVD) are implemented since 1998 in Europe and 2002 in Germany data regarding the market surveillance of these products are sparse

IVD differ strongly in respect to their type (products for professional use vs. products for lay use), clinical use (e. g. haematology, clinical chemistry, endocrinology, bacteriology, virology), type of product (analyser vs. test, reagent, calibrator or control material) and the underlying analytical principle (e. g. photometry, culture technique, immunology, molecular biology)

Because of these differences the data of variant products cannot be compared

Examples of IVD

Publications focussing on market surveillance of IVD in Germany

High-risk products listed in Annex II parts A and B of Directive 98/79/EC (PEI; blood groups, infective diseases)

Patient self tests (BfArM; systems for measurement of blood glucose, systems for measurement of coagulation, pregnancy tests)

IVD for diagnostics of infective diseases (BfArM; tests, reagents, analysers and general consumables)

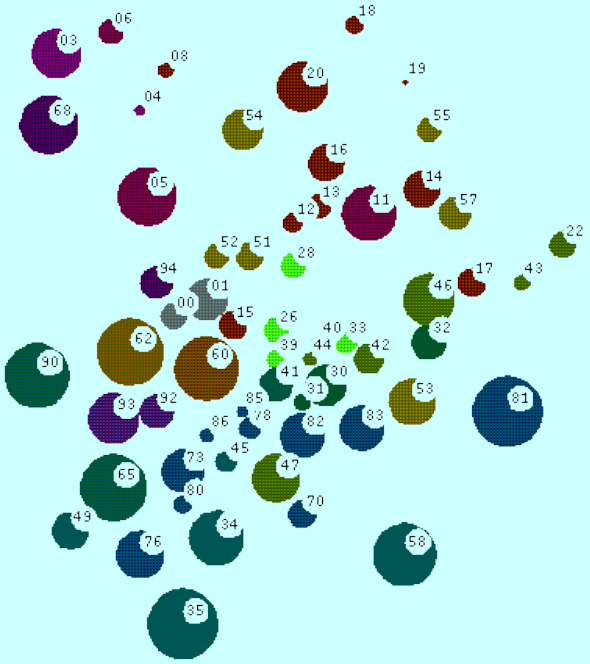
IVD for diagnostics in haematology (BfArM; tests, reagents, analysers and general consumables)

IVD for coagulation diagnostics (BfArM; tests, reagents, analysers and general consumables)

IVD for diagnostics in oncology (BfArM; tests, reagents, analysers and general consumables)

IVD for therapeutic drug monitoring (BfArM; tests, reagents, analysers and general consumables)

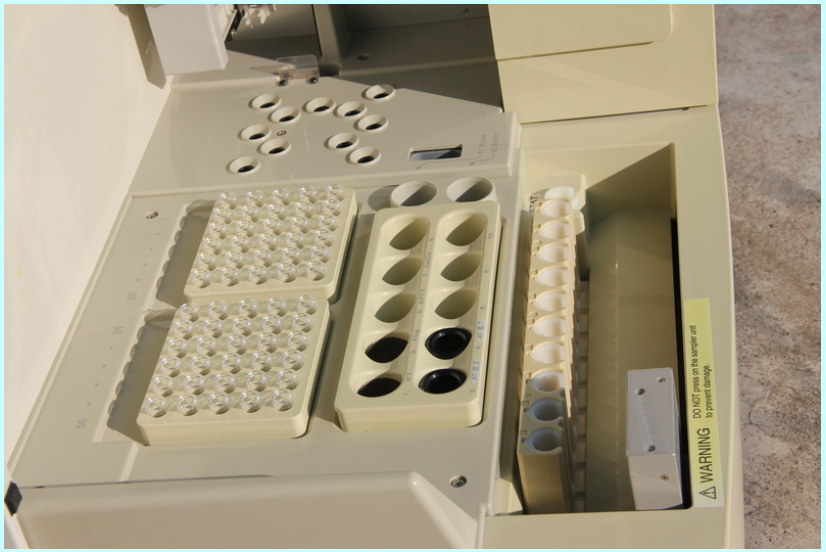
Aim of the study



Analysis of cases related to IVD for coagulation testing (professional use tests, reagents, calibrators, control materials and analysers, systems for lay use testing) in respect to

- the source of notification
- the type of product
- the underlying product failure
- the performed corrective action

IVD for coagulation testing



Materials and methods

Inclusion of all reports received by the BfArM between January 1999 and December 2010

Analysis was made regarding

Product groups:
- Professional use analysers, general consumables
- Professional use tests, reagents, calibrators, controls
- Professional use laboratory tests and test strips for measurement of D-dimers
- Lay use systems for self testing of coagulation in orally anticoagulated patients

Source of notification

Root cause of the product failure

Corrective measure performed by the manufacturer

Products included in this study

2851 Reports 1999 - 2010

- Reports on lay use products for other purposes than coagulation testing (e. g. glucose, pregnancy)
- Reports on professional use products for other purposes than coagulation testing

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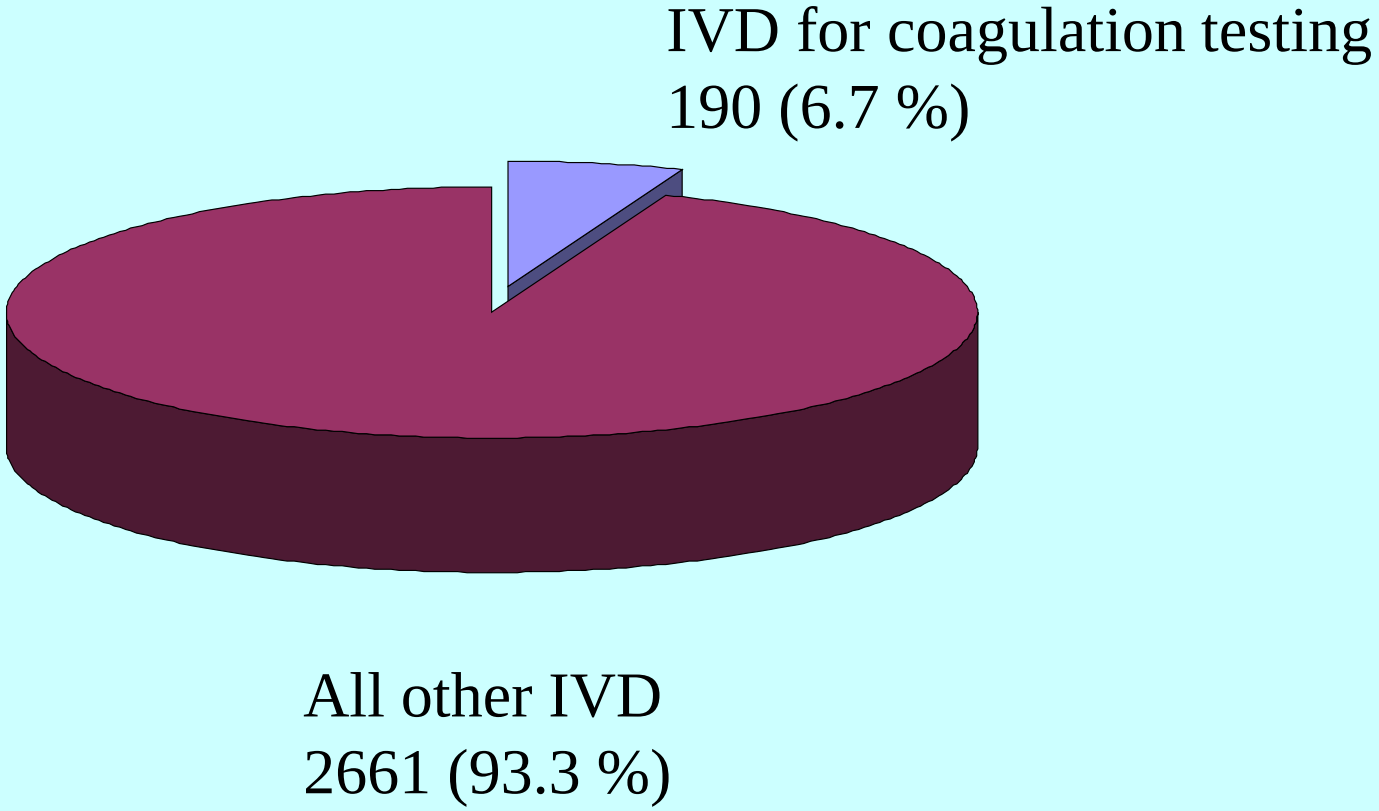
190 Reports on products for coagulation testing:

- 99 Reports on professional use tests, reagents, calibrators and control materials
- 26 Reports on professional use analysers and their general consumables
- 65 Reports on lay use products (tests, analysers)

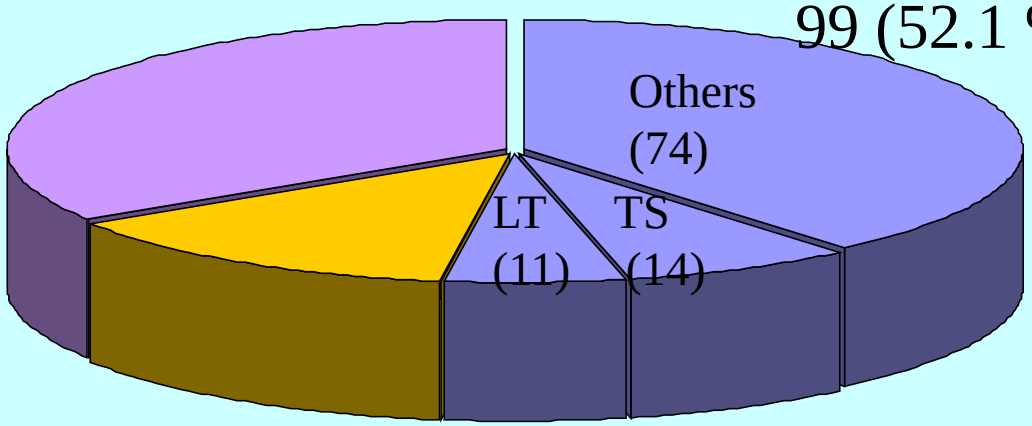
Proportion of IVD for coagulation testing related to all IVD 1999-2000



Types of IVD for coagulation testing related to all IVD for coagulation testing

Lay use systems
(tests and analysers)
65 (34.2 %)

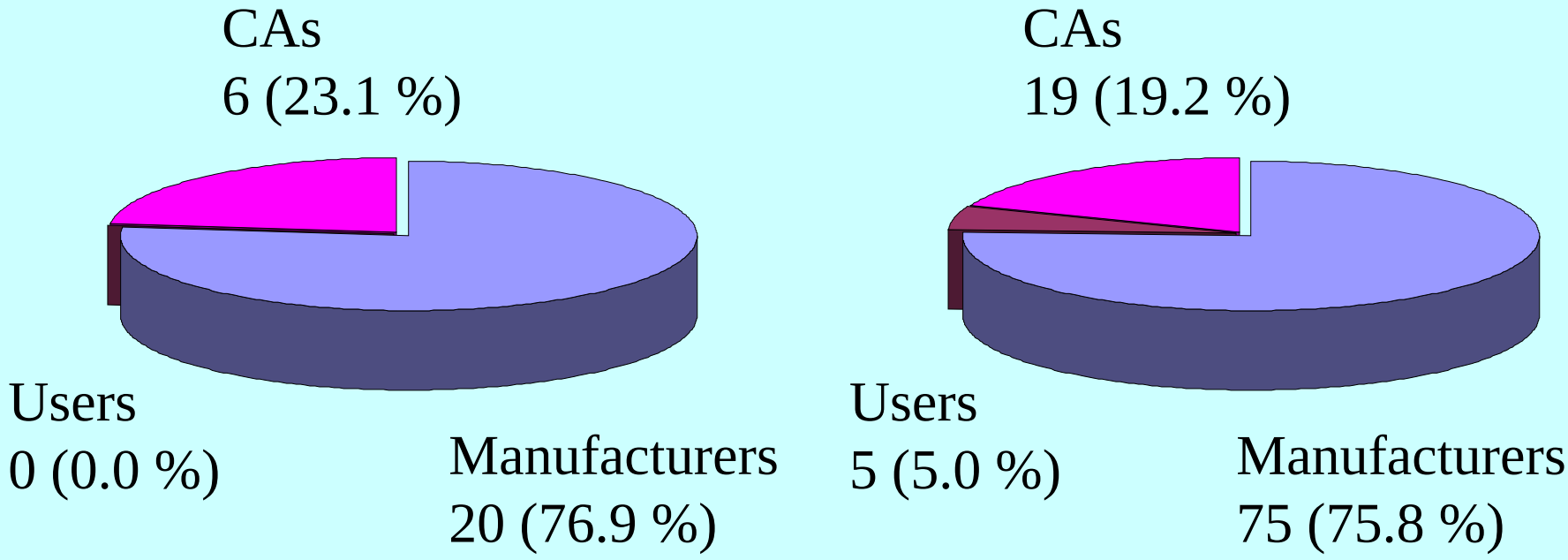
Professional use tests,
kits and reagents
99 (52.1 %)



Professional use analysers
and general consumables
26 (13.7 %)

TS: Test strips for measurement of D-dimers
LT: Laboratory tests for measurement of D-dimers

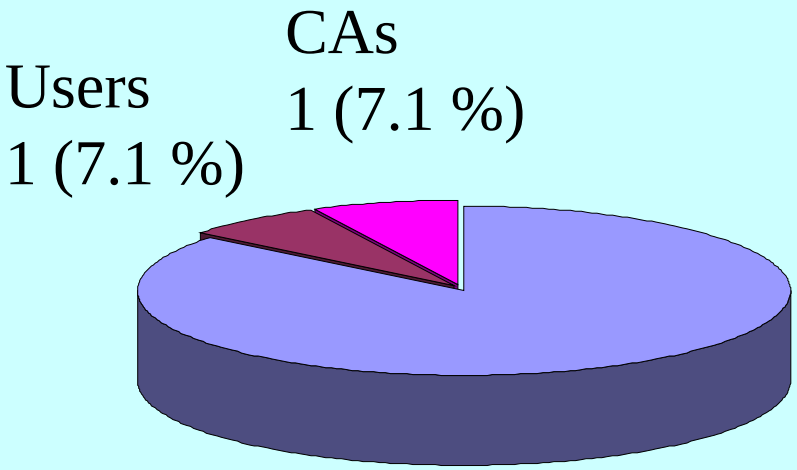
Sources of notification in professional use analysers and tests for coagulation measurement



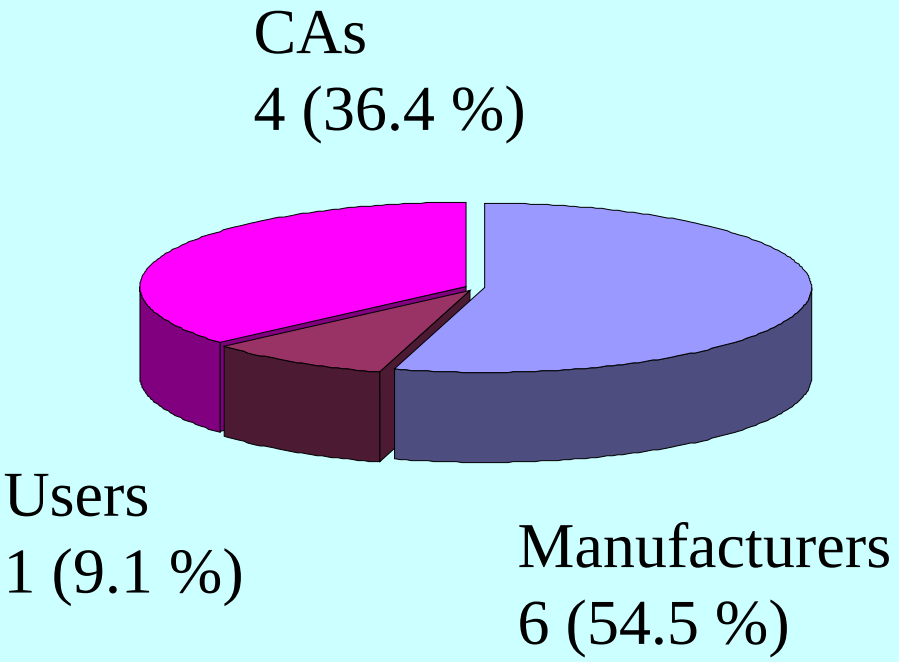
Analysers **Tests/reagents**

Tests: 99 (100.0 %)
Analysers: 26 (100.0 %)

Sources of notification in professional use tests for measurement of D-dimers



Test strips



Laboratory tests

Laboratory tests: 11 (100.0 %)
Test trips: 14 (100.0 %)

Product failures in professional use analysers and tests for coagulation measurement

	Tests/reagents		Analysers		All	
	n	([%])	n	([%])	n	([%])
Number of cases	99	(100.0)	26	(100.0)	125	(100.0)
No product failure	8	(8.1)	1	(3.8)	9	(7.2)
User error	2	(2.0)	0	(0.0)	2	(1.6)
Root cause not identified	25	(25.3)	2	(7.7)	27	(21.6)
Product failure identified	64	(64.6)	23	(88.5)	87	(69.6)
Material defect	17		3		20	
Software error	1		11		12	
Calibration error	4		0		4	
Electrical error	0		0		0	
Mechanical error	0		1		1	
Miss of specification	0		0		0	
Production error	15		3		18	
Incorrect instructions for use	5		1		6	
Non-microbial contamination	0		1		1	
Packaging error	0		0		0	
Microbial contamination	2		0		2	
Interference by other substances	5		0		5	
Constructional fault	4		2		6	
Labelling error	11		1		12	

Product failures in professional use

tests for measurement of D-dimers

	Test strips		Laboratory tests		All	
	n	([%])	n	([%])	n	([%])
Number of cases	14	(100.0)	11	(100.0)	25	(100.0)
No product failure	3	(21.4)	1	(9.1)	4	(16.0)
User error	2	(14.3)	0	(0.0)	2	(8.0)
Root cause not identified	8	(57.2)	0	(0.0)	8	(32.0)
Product failure identified	1	(7.1)	10	(90.9)	11	(44.0)
Material defect	1		0		1	
Software error	0		0		0	
Calibration error	0		1		1	
Electrical error	0		0		0	
Mechanical error	0		0		0	
Miss of specification	0		0		0	
Production error	0		6		6	
Incorrect instructions for use	0		0		0	
Non-microbial contamination	0		0		0	
Packaging error	0		0		0	
Microbial contamination	0		0		0	
Interference by other substances	0		0		0	
Constructional fault	0		1		1	
Labelling error	0		2		2	

Corrective actions in professional use analysers and tests for coagulation measurement

	Tests/reagents		Analysers		All	
	[n]	([%])	[n]	([%])	[n]	([%])
Number of cases	99	(100.0)	26	(100.0)	125	(100.0)
No corrective actions	39	(39.4)	7	(26.9)	46	(36.8)
Corrective actions	60	(60.6)	19	(73.1)	79	(63.2)
Product-/batch recall[#)]	41		15		56	
Cessation of marketing	2		0		2	
Change of design	8		1		9	
Change in production/quality control	40		6		46	
Customer information	58		19		77	
Modification of instruction for use	9		3		12	
Software update	4		9		13	
Modification of labelling	4		1		5	
Modification of raw material	13		2		15	
Customer education[##)]	0		0		0	

[#)] Customer information is mandatory; [##)] Education of all customers only

Corrective actions in professional use tests for measurement of D-dimers

	Test strips		Laboratory tests		All	
	[n]	([%])	[n]	([%])	[n]	([%])
Number of cases	14	(100.0)	11	(100.0)	25	(100.0)
No corrective actions	13	(92.9)	6	(54.5)	19	(76.0)
Corrective actions	1	(7.1)	5	(45.5)	6	(24.0)
Product-/batch recall[#)]	1		4		5	
Cessation of marketing	0		0		0	
Change of design	0		1		1	
Change in production/quality control	1		5		6	
Customer information	1		5		6	
Modification of instruction for use	0		0		0	
Software update	0		0		0	
Modification of labelling	0		1		1	
Modification of raw material	1		0		1	
Customer education[##)]	0		0		0	

[#)] Customer information is mandatory; [##)] Education of all customers only

Conclusions on professional use IVD for coagulation testing - I

Notifications for professional use IVD for coagulation testing are a major subgroup within the group of notifications related to IVD for coagulation testing (125 out of 190 cases)

Within this subgroup notifications for tests are more frequent than for analysers (99 vs. 26 cases)

Most notifications in this subgroup were received from manufacturers (some from their distributors) whereas other sources (CAs, users) were less frequent

Tests and analysers show only little differences in their sources of notification

However, even within the group of tests differences may occur dependent on the type of test (e. g. laboratory tests and test strips for measurement of D-dimers)

Conclusions on professional use IVD for coagulation testing - II

The difference between test strips and laboratory tests for measurement of D-dimers might be caused by different user groups (e. g. general practicioners in cases regarding test strips and laboratories in cases regarding laboratory tests)

The number of notifications with assumed patient harm is remote in the subgroup of professional use IVD for coagulation testing (7 out of 125 cases, all in the group of tests and reagents)

Typically, there was an indirect harm (6 cases) and only 1 case of direct harm to a user

However, in cases with assumed harm product problems were observed in 3 cases only

Conclusions on professional use IVD for coagulation testing - III

Manufacturer investigations confirmed product failures in most cases (69.6 %) and the proportion of confirmed product failures was higher in analysers (88.5 %) than in tests (64.6 %)

Considering a number of cases not effecting the German market in which detailed information of root cases were not available would have resulted in a higher proportion of identified root causes especially in the group of tests

A number of cases with unidentified root causes of product failure was also due to the inclusion of test strips for measurement of D-dimers because in a number of cases neither test strips nor patient samples of the users were available for further testing and investigation of retained test strips only (e. g. with control solutions) provided limited information

Conclusions on professional use IVD for coagulation testing - IV

The number of corrective actions is correlated to the number of confirmed product failures and higher in the group of analysers than in the group of tests (73.1 % vs. 60.6 %)

Consideration of corrective actions outside the German market only (in cases where the product is not distributed in Germany) would have resulted in a further increase of corrective actions

However, there were differences within the group of tests, e. g. test strips vs. laboratory tests for measurement of D-dimers

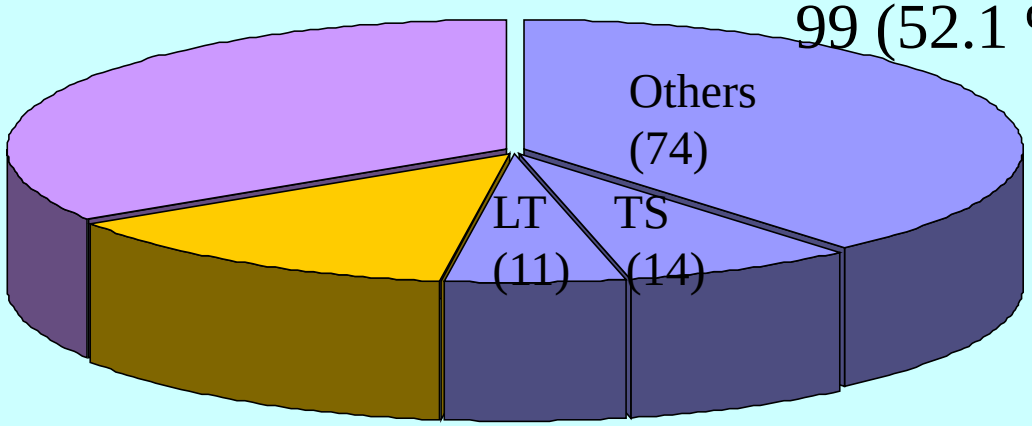
Most frequent corrective actions for products already in the market were customer information and recall

Preventive corrective actions were based on the underlying root cause of product failure and were most frequently changes in production and/or quality control and changes of raw materials in tests and software updates in analysers

Types of IVD for coagulation testing related to all IVD for coagulation testing

Lay use systems
(tests and analysers)
65 (34.2 %)

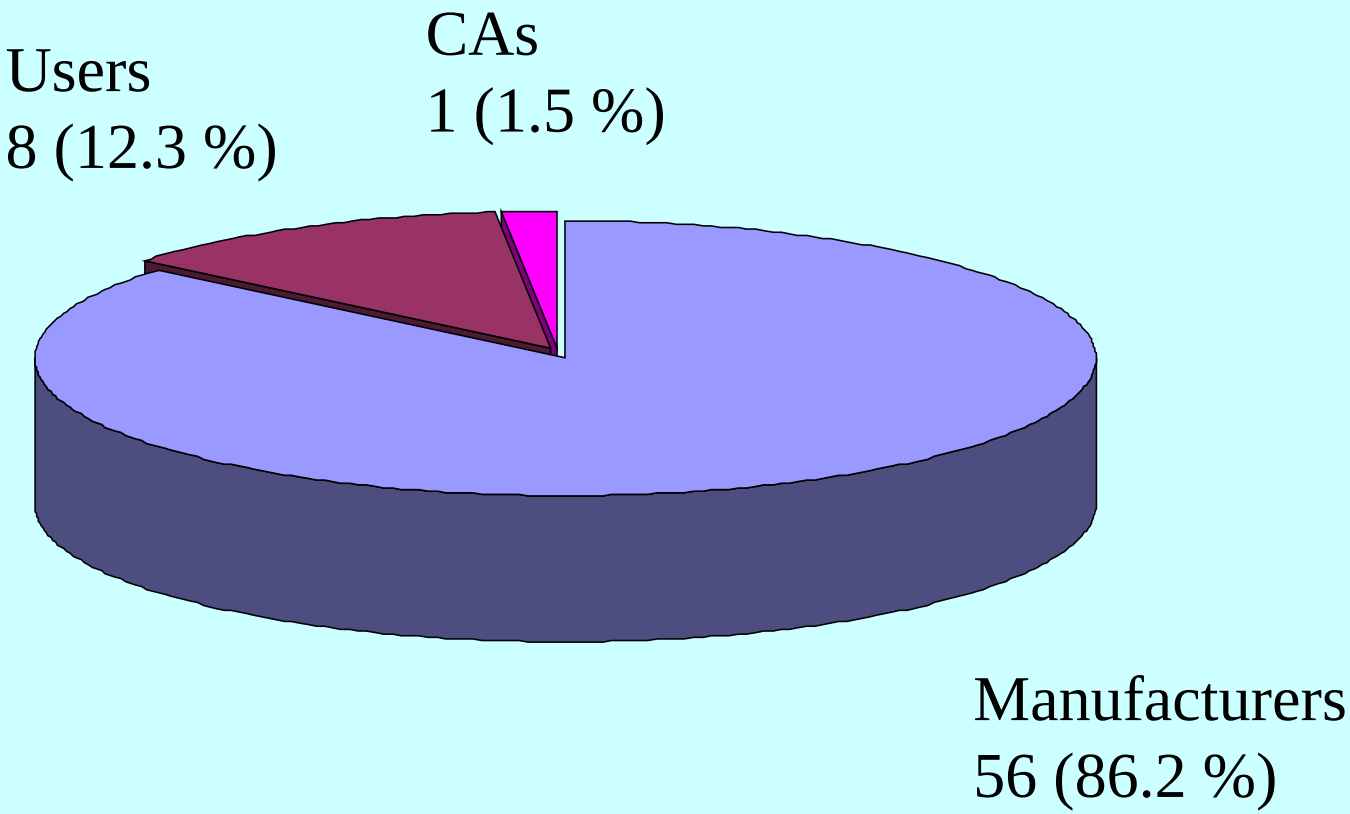
Professional use tests,
kits and reagents
99 (52.1 %)



Professional use analysers
and general consumables
26 (13.7 %)

TS: Test strips for measurement of D-dimers
LT: Laboratory tests for measurement of D-dimers

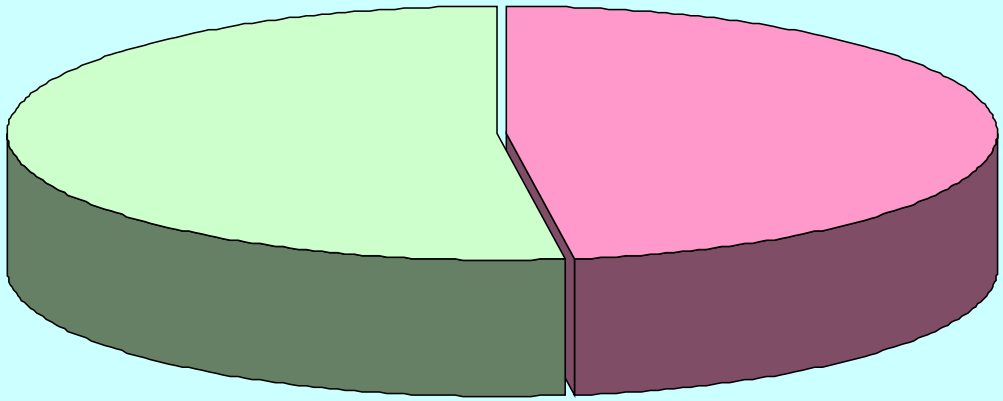
Sources of notification in lay use tests for coagulation measurement



Reported harm
in lay use tests for coagulation measurement

No harm
34 (52.3 %)

Harm
31 (47.7 %)



Reported types of harm: Death, bleeding, infarction, stroke, embolism, change of therapy, delay or stop of surgery

Product failures in self tests for coagulation measurement with and without harm for patients

	Without harm		With harm		All	
	n	([%])	n	([%])	n	([%])
Number of cases	34	(100.0)	31	(100.0)	65	(100.0)
No product failure	7	(20.6)	24	(77.4)	31	(47.7)
User error	2	(5.9)	0	(0.0)	2	(3.1)
Root cause not identified	9	(26.5)	7	(22.6)	16	(24.6)
Product failure identified	16	(47.0)	0	(0.0)	16	(24.6)
Material defect	2		0		2	
Software error	2		0		2	
Calibration error	0		0		0	
Electrical error	1		0		1	
Mechanical error	1		0		1	
Miss of specification	2		0		2	
Production error	3		0		3	
Incorrect instructions for use	2		0		2	
Non-microbial contamination	0		0		0	
Packaging error	1		0		1	
Microbial contamination	0		0		0	
Interference by other substances	1		0		1	
Constructional fault	0		0		0	
Labelling error	1		0		1	

Corrective actions in self tests for coagulation measurement with and without harm for patients

	Without harm		With harm		All	
	[n]	([%])	[n]	([%])	[n]	([%])
Number of cases	34	(100.0)	31	(100.0)	65	(100.0)
No corrective actions	19	(55.9)	30	(96.8)	49	(75.4)
Corrective actions	15	(44.1)	1	(3.2)	16	(24.6)
Product-/batch recall[#)]	11		0		11	
Cessation of marketing	0		0		0	
Change of design	2		0		2	
Change in production/quality control	6		0		6	
Customer information	14		1		15	
Modification of instruction for use	3		0		3	
Software update	3		0		3	
Modification of labelling	0		1		1	
Modification of raw material	0		0		0	
Customer education[##)]	0		0		0	

[#)] Customer information is mandatory; [##)] Education of all customers only

Conclusions on self tests for coagulation testing - I

Notifications for self tests for coagulation testing are a relevant subgroup within the group of notifications related to IVD for coagulation testing (65 out of 190 cases)

Most notifications in this subgroup were received from manufacturers; however, notifications from users trended to be higher than in professional use IVD for coagulation testing

Notifications with assumed patient harm are very frequent in the subgroup of self tests for coagulation testing (31 out of 65 cases) and much more frequent than in professional use IVD for coagulation testing

This might be biased by a relative „overreporting“ from manufacturers because the strict time schedule for reporting in cases of assumed patient harm often requires notification prior to the results of the manufacturer investigation

Conclusions on self tests for coagulation testing - II

Manufacturer investigations excluded product failures in most cases of patient harm (24 out of 31 cases); in the remaining cases often parts of the user products (mostly test strips) were no more available and investigation of retained products showed no product failure

In cases of no patient harm frequency of confirmed product failure was higher because notifications often came from manufacturers after confirmation of product failure

Root causes of product failures in cases of no patient harm were very different depending on the type of product (e. g. production error and miss of specification in test strips and software error and electrical error in analysers)

Conclusions on self tests for coagulation testing - III

In consequence to the low number of confirmed product failure in cases of patient harm there was a very remote number of corrective actions in this group (1 out of 31 cases)

The number of corrective actions in cases of no patient harm was higher than in cases of patient harm (15 out of 34) due to the higher number of confirmed product failures but lower than in professional use IVD for coagulation testing

Most frequent corrective actions for products already in the market were customer information and recall

Preventive corrective actions were based on the underlying root cause of product failure and were most frequently changes in production and/or quality control, modification of the instructions for use and software update

Thank you for your attention