Beratung für
Medizinprodukte-Hersteller, -Handel
und Gesundheitseinrichtungen

de|la|roza Consulting

MPG-Update 2010:

Changes by the 4. MPG Amendment
with special consideration of Clinical Trials

Welcome !!!

Rafael J. de la Roza

Abbreviations

BfArM	Bundesinstitut für Arzneimittel- und Medizinprodukte *Federal Institute for Drugs and Medical Devices*
BfS	Bundesamt für Strahlenschutz / *Federal agency for Radiation Protection*
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
EK / EC	Ethikkommission / *Ethics Commission*
EK-Med	Erfahrungsaustauschkreis Medizinprodukte *Experiences Exchange Circle of the German NBs for Medical Devices*
EEA	European Economic Area
GMDN	Global Medical Device Nomenclature
MEDDEV	MEDICAL DEVICES Guidance Document
MPG	Medizinproduktegesetz / German Act on Medical Devices
MPKPV	Verordnung über klinische Prüfungen von Medizinprodukten *German Ordinance on Clinical Investigations of Medical Devices*
MPG	Medizinproduktegesetz / *German Act on Medical Devices*
MPSV	Medizinproduktesicherheitsplan-Verordnung *German Ordinance for a Medical Device Safety Plan*
MPV	Medizinprodukteverordnung / *German Ordinance on Medical Devices*
NBOG-BPG	Notified Body Operations Group – Best Practise Guideline
RöV	Röntgenverordnung / *Ordinance on X-ray Application*
StrlSchV	Strahlenschutzverordnung / *German Ordinance on the Protection against ionisation radiations*
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten / *Central Authority of the German "Bundesländer" for Health Protection with regard to Medicinal Products and Medical Devices*

Agenda

- **Overview on the New Legal Foundations**
  - The Amending Directive 2007/47/EC
  - Amendments to the German Law: The "4. MPG-Novelle"
  - Important Interpretative and Guidance Documents
- **The Innovations in Detail**
  - EU-stipulated Amendments
  - Specific Amendments in the German MD Legislation ("beyond EU")
- **"Clinicals"**
- **SAE Reporting**
- **Guidance Documents and Forms**
- **Questions and Discussion**

Agenda

- Overview on the New Legal Foundations

- *Which EC Directives have been changed?*
- *What has been changed in the German legislation?*
- *Where to find guidance for the interpretation of the new requirements?*

Overview on the New Legal Foundations

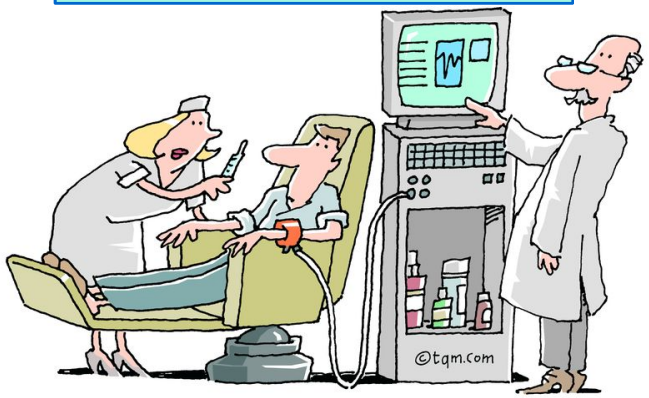
Amended Directives

Amending Directive 2007/47/EC

Active Implantable Med. Devices (AIMD) 90/385/EEC

Medical Devices (MDD) 93/42/EEC

In-vitro-Diagnostic Devices (IVD) 98/79/EC



Overview on the New Legal Foundations

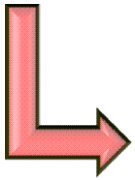
Amendments to the German Law

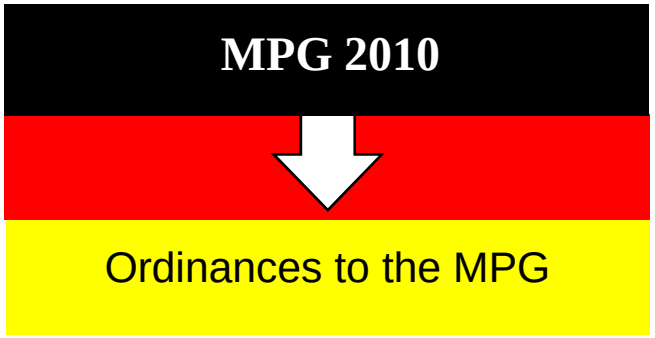
EC Directives
(harmonised)

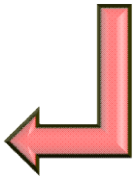
National Regulations

- **Requirements for placing in the market** ***("Essential Requirements" for safety and performance)***
- **further requirements e. g. for application and operation, competent authorities, submissions w. r. t. clinical investigations, etc.**

EU Amendments







PLUS additional national amendments

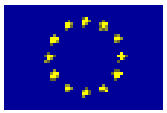
Overview on the New Legal Foundations

Amendments to the German Law

- Medizinprodukteverordnung (MPV)
  Changes in force since 21.03.2010:
  Conformity Assessment Procedures
- Medizinprodukte-Sicherheitsplanverordnung (MPSV) geändert
  Changes in force since 21.03.2010:
  Detection, evaluation, and Control of risks of MD which have been already placed in the market
- Medizinprodukte-Betreiberverordnung (MPBetreibV – *Medical Device Operator Ordinance*)
  Changes in force since 21.03.2010 (partly earlier):
  Installation Operaton, Application, and Maintenance of MD
- DIMDI-Verordnung (DIMDIV – Ordinance on DIMDI
  Changes in force since 21.03.2010:
  Ordinance on the Information System Data Bases on MD
- Medizinprodukte-Gebührenverordnung (BKostV-MPG – MD Fees Regulation)
  Changes in force since 21.03.2010:
  Fees for official acts of the Higher Federal Authorities
- Verordnung über klinische Prüfungen mit Medizinprodukten (MPKP)
  In force since *13.05.2010*

Overview on the New Legal Foundations

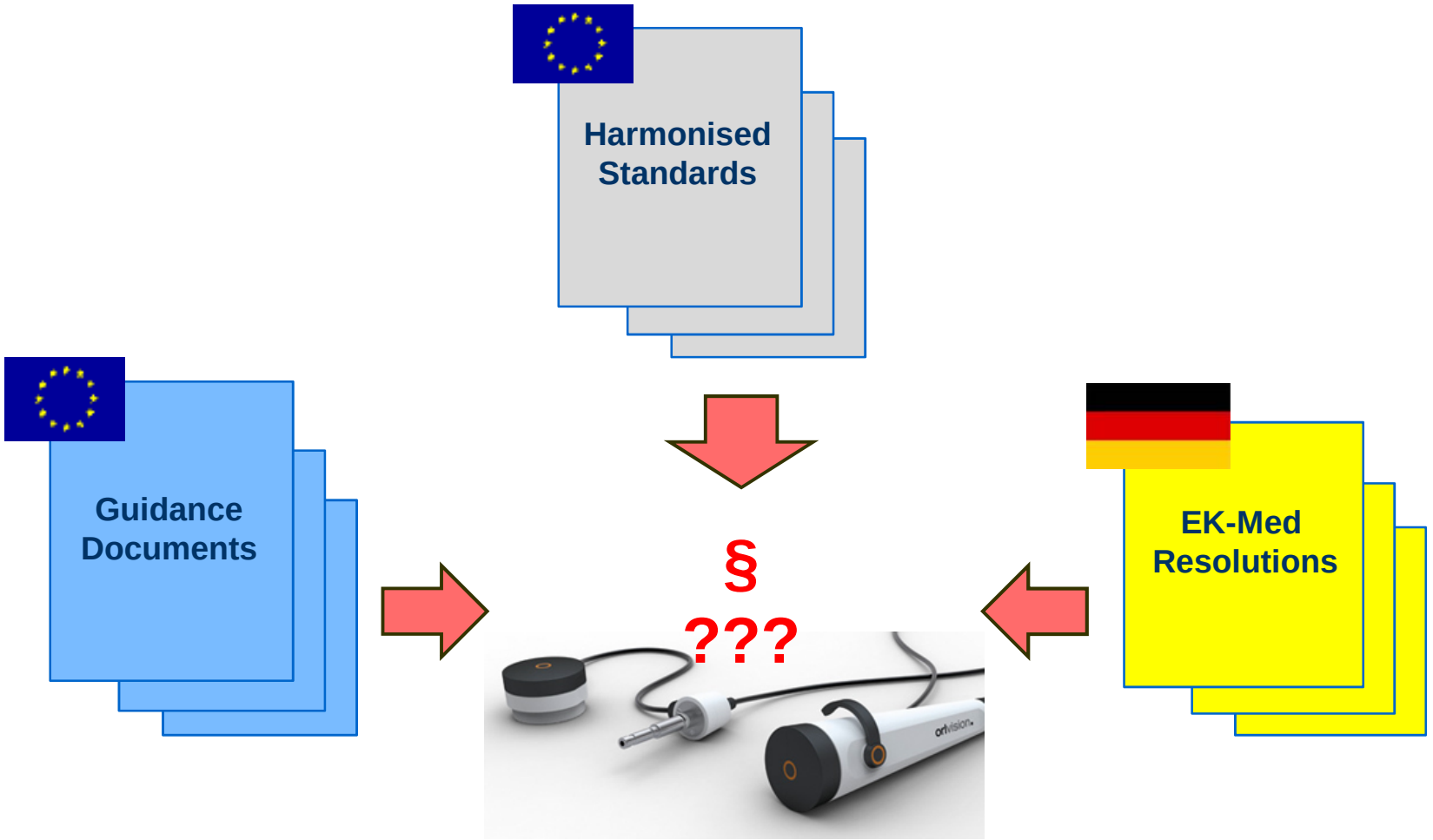
Amendments to the German Law



EC Amendments	Medical Devices	MPG Amendments
YES	MD (93/42/EEC)	**YES**
YES	AIMD (90/385/EEC)	**YES**
NO	IVD (98/79/EC)	**YES**

Overview on the New Legal Foundations

Interpretation and Guidance Documents



Overview on the New Legal Foundations

Interpretation and Guidance Documents

- **Harmonised Standards:**
  - communicated by the EU as a possible way of fulfilling the requirements for MD
  - application not mandatory
  - cause presumption of conformity
  - "Vertical standards" for specific products
    Example:
    EN ISO 5840:2009: Cardiovascular implants
  - "Horizontal standards" – not product-specific
    Examples:
    EN ISO 14155:2009: Clinical investigation of medical devices

Overview on the New Legal Foundations

Interpretation and Guidance Documents

- **Guidance Documents:**
  - e. g. MEDDEV Guidelines, Interpretative Documents, Consensus Statements, NBOG-BPG
  - "quasi-official" guidelines for the application of the MD Directives
  - prepared by joint committees of representatives from the industry, competent authorities, Notified Bodies (NBs), standardisation organisations etc.
  - Advantage:
    Views and suggested solutions are regularly shared by the European authorities and NBs
  - Examples:
    MEDDEV 2.7/1 rev.3: Clinical evaluation – Guide for Manufacturers and NBs
    Consensus Statement MDEG 12-2009: Guidance Notes for Manufacturers of Class I MDs

Overview on the New Legal Foundations

Interpretation and Guidance Documents

- **EK-Med-Beschlüsse ("Resolutions"):**
  - the specific points of views of the German NBs for the application of the MD Directives
  - "quasi-official" German documents, sometimes to "handle with care"
  - prepared by EKMed (work group of the German NBs and ZLG)
  - Advantage:
    Views and suggested solutions are regularly shared by the German authorities and NBs
  - Examples:
    3.12 E12: Klinische Bewertung – Vergleichbarkeit von Medizinprodukten)

    Sometimes 1:1 adoption of European documents, e. g.

    3.9.1 B21: Guidance on Design-Dossier Examination and Report Content (NBOG BPG 2009-1)

Agenda

- The Innovations in Detail

Here you learn which specific changes the new legal situation has caused, e. g. with regard to

- *the Essential Reqirements*
- *the classification of MD, or*
- *the the technical documentations, and*
- *the adoption of the new EU requirements into the German legislation*

The Innovations in Detail: EU-stipulated

Subject		Reference 93/42/EEC	Transposition in German Law
Scope	Software	Art. 1 No. 2	§ 3 Nr. 1 MPG
"Medical Device" means any instrument, apparatus, appliance, *software*, material or other article, whether used alone or in combination, including the software *intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and* necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap …			
Scope	Personal Protective Equipment (PPE)	Art. 1 No. 6	§ 2, 4a MPG
Where a device is intended to be used in accordance with both the provisions on PPE Directive 89/686/EEC and this Directive, the relevant basic health and safety requirements of Directive 89/686/EEC shall also be fulfilled. è *Interpretation of the relation between the revised Directive 93/42/EEC concerning medical devices and Directive 89/686/EEC on personal protective equipment*			
European Databank		Art. 14 a	§ 33 MPG
Regulatory data shall be stored in a European database (EUDAMED) accessible to the competent authorities to enable them to carry out their tasks relating to this Directive on a well-informed basis. Content: • registration data (manufacturers, authorised representatives, devices) • data on certificates issued, modified, supplemented, suspended and refused • data on clinical investigations			

The Innovations in Detail: EU-stipulated

Subject	Reference 93/42/EEC	Transposition in German Law
Machinery	Art. 3	§ 7,1 MPG
Where a relevant hazard exists, devices which are also machinery within the meaning of Directive 2006/42/EC shall also meet the essential health and safety requirements set out in Annex I to that Directive to the extent to which those essential requirements are more specific than the essential requirements set out in Annex I to this Directive. è *Interpretation of the relation between the revised Directives 90/385/EEC and 93/42/EEC concerning (active implantable) medical devices and Directive 2006/42/EC on machinery*		
Ergonomics	Ann. I No. I, 1	§ 7,1 MPG
The risk analysis and safety provisions shall include: • reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which it is intended to be used • consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users) è *EN 60601-1-6:2010: Medical electrical equipment - Collateral standard: Usability* è *EN 62366:2008: Medical devices - Application of usability engineering to medical devices*		
Clinical Data	Ann. I No. I, 6a	§ 19, 1 MPG
Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.		

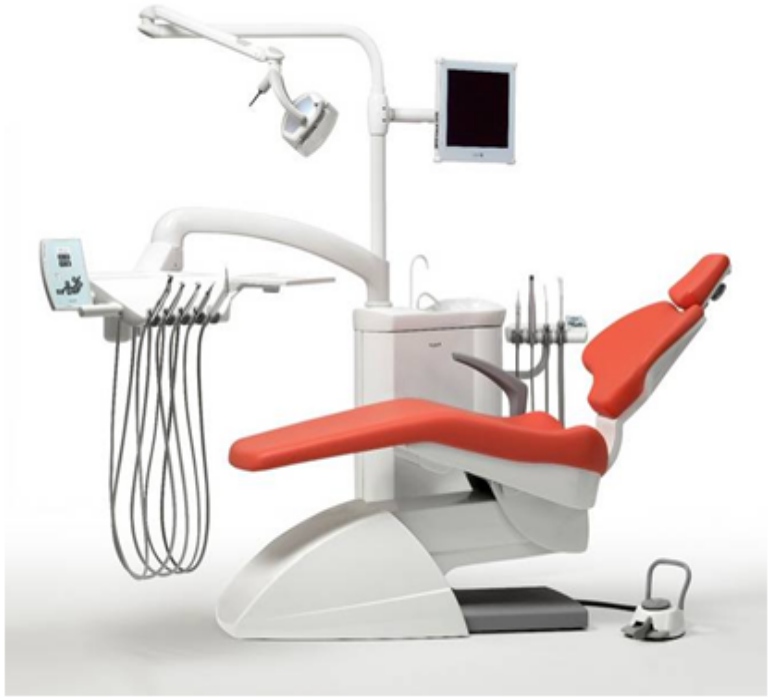
Sicherheit und Leistung

"Machinery": Definition

(a) 'machinery' means:

— an assembly, fitted with or intended to be fitted with a drive system other than directly applied human or animal effort, consisting of linked parts or components, at least one of which moves, and which are joined together for a specific application,

Machinery Directive 2006/42/EG, Art. 2a)



The Innovations in Detail: EU-stipulated

Subject	Reference 93/42/EEC	Transposition in German Law
Hazardous Substances	Ann. I No. 7.5	§ 7, 1 MPG
• The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction (CMR). • If the device or parts of it are intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as "CMR", these devices must be labelled accordingy. è *EUCOMED : Labelling of medical devices containing phthalates* • MD intended use of such devices includes treatment of children or treatment of pregnant or nursing women: specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures.		
Software	Ann. I No. 12.1a	§ 7, 1 MPG
For devices which incorporate software or which are medical software in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification. è *EN 60601-1-4:1996: Medical electrical equipment -- Part 1-4: General requirements for safety - Collateral standard: Programmable electrical medical systems* è *EN 62304:2006: Medical device software - Software life-cycle processes*		

Sicherheit und Leistung

The Innovations in Detail: EU-stipulated

Subject	Reference 93/42/EEC	Transposition in German Law
MD for single-use	Ann. I No. 13	§ 7, 1 MPG
Information to be supplied by the manufacturer: • Labelling (13.3. f): an indication that the device is for single use; the indication of single use must be consistent across the EU • Instructions (13. 6 h): information on known risks if the device were re-used. If in accordance with section 3.1 no instructions for use are needed, the information must be made available to the user upon request.		

Essential requirements

The Innovations in Detail: EU-stipulated

Subject		Reference 93/42/EEC	Transposition in German Law
not a definition	Definitions	Ann. IX, I.1	MPV
	• Stand-alone (medical) software is an actice MD. • The central circulatory system includes the following vessels: arteriae pulmonales, aorta ascendens, *arcus aorta, aorta descendens to the bifurcatio aortae*, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachiocephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior.		
	Application Rules	Ann. IX, II.2.6	MPV
	• The duration of application: Continuous use means 'an uninterrupted actual use of the device for the intended purpose'. • However where usage of a device is discontinued in order for the device to be replaced immediately by the same or an identical device this shall be considered an extension of the continuous use of the device.		

The Innovations in Detail: EU-stipulated

Subject		Reference 93/42/EEC	Transposition in German Law
not adfi ssd C	Rule 5	Ann. IX, III.2.1	MPV
	All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device *or which are intended for connection to an active medical device in Class I* are in Class …		
	Rule 6	Ann. IX, III.2.2	MPV
	All surgically invasive devices intended for transient use are in Class IIa unless they are: • intended specifically to *control*, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III • *intended specifically for use in direct contact with the central nervous system, in which case they are in Class III* ***Example:*** *Epidural and spinal cannula Class IIa è Class III*		
	Rule 7	Ann. IX, III.2.3	MPV
	All surgically invasive devices intended for short-term use are in Class IIa unless they are intended • … specifically to *control*, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III		

The Innovations in Detail: EU-stipulated

Subject		Reference 93/42/EEC	Transposition in German Law
not adfi ssd C	Rule 13	Ann. IX, III.4.1	MPV
	All devices incorporating*, as an integral part,* a human blood derivative are in Class III. ***Note:*** *"Integral part" means that the device and the medicinal substance are physically or chemically combined at the time of administration (i.e. use, implantation,application etc) to the patient.* ***Example:*** *Surgical sealants containing human serum albumin*		
	Rule 15	Ann. IX, III.4.3	MPV
	All devices intended specifically to be used for disinfecting medical devices are in Class IIa. *Unless they are specifically to be used for disinfecting invasive devices in which case they are in Class IIb.*		
	Rule 16	Ann. IX, III.2.3	MPV
	~~Non-active~~ *Devices* specifically intended for recording of X-ray diagnostic images are in Class IIa.		

The Innovations in Detail: EU-stipulated

	Subject	Reference 93/42/EEC	Transposition in German Law
S MQ	PMS	Ann. II, IV, V, VI	MPV
	The manufacturer must maintain a systematic procedure to review experience gained from devices in the post-production phase, *including the provisions referred to in Annex X,* and to implement appropriate means to apply any necessary corrective action. *(similar in Annex VII)* *è MEDDEV 2.12/1 rev.6: Medical devices vigilance system*		
	Subsuppliers	Ann. II, V, VI	MPV
	… where the design, manufacture and/or final inspection and testing of the products, or elements thereof, is carried out by a third party, [the manufacturer must describe] the methods of monitoring the efficient operation of the quality system and in particular the type and extent of control applied to the third party.		

The Innovations in Detail: EU-stipulated

Subject		Reference 93/42/EEC	Transposition in German Law
Design Changes	Clinical Evaluation	Ann. II, 3.2. c)	MPV
	[The QMS] shall include in particular the corresponding documentation, data and records arising from the procedures referred to in point (c). c) • … • *the pre-clinical evaluation,* • ~~the clinical data~~ *the clinical evaluation* referred to in Annex X *(similar in Annex III, V, VI, VII)*		
	Retainment Period of the TD	Ann. II, III, V, VI, VII	MPV
	For implantable MD: *15 yrs.*		
	Sterile Products		MPV
	The technical documentation must include in particular: • *in the case of products placed on the market in a sterile condition, description of the methods used and the validation report* *(similar in Annex IV, V, VI)*		

The Innovations in Detail: EU-stipulated

Subject	Reference 93/42/EEC	Transposition in German Law
MD in Class II a	Ann. II, 7.3	MPV
NB shall assess the technical documentation for at least one representative sample for each device subcategory for compliance with the provisions of this Directive. *(similar in Annex III, V, VI, VII)*		
MD in Class IIb	Ann. II, 7.4	MPV
NB shall assess the technical documentation for at least one representative sample for each generic device group for compliance with the provisions of this Directive. *(similar in Annex IV, V, VI)* *è EK-Med Beschluss 3.9 B 24: Konformitätsbewertung (includes "sampling key")*		

BNyb ecnalli evr uS

The Innovations in Detail: EU-stipulated

Subject	Reference 93/42/EEC	Transposition in German Law
Clinical Trials	Art. 15 Annex X	§ 19 MPG, MPKPV
See the following section of this presentation		

The Innovations in Detail: German Legislation "beyond EU"

Subject	Reference
Reporting Obligations of "Incidents" and SAEs	MPSV
• Extended definition of "Rückruf" (Field Safety Corrective Action – FSCA): *"When advice is given to operators, users or patients for the further safe application or operation for a MD is given"* *NOTE: Each "Rückruf" is subject to mandatory reporting to BfArM!*	§ 2 Nr. 3
• Authorities (addressees) to be informed on FSCA in Germany, which are caused by incidents occurred outside the EEA: *BfArM (previously:* ~~Competent authority of the state of the NB~~*)*	§ 3, 1
• *Serious Adverse Events (SAE) = "schwerwiegende unerwünschte Ereignisse" in the course of clinical trails are subject to mandatory reporting to BfArM*	§ 3, 5

The Innovations in Detail: German Legislation "beyond EU"

Subject	Reference
Classification, Demarcation to other Products	§ 13 MPG
• *In case of a dispute arises between the manufacturer and the NB on the classification of a MD, the NB shall submit the issue to BfArM for a binding decision* (previously: the competent authorities of the 16 Bundesländer). • *BfArM decides moreover on the classification of a MD or of the demarcation of a MD to other products at the request of the manufacturer or of the competent authority* (previously: the competent authorities of the 16 Bundesländer).	§ 13, 2 § 13, 3
Clinical Trials	MPG §§ 19 – 24 MPKPV
• *Additional approval by BfArM / PEI mandatory* (previously: only positive statement by EC required) • *Exceptions possible*	§ 20, 1

Agenda

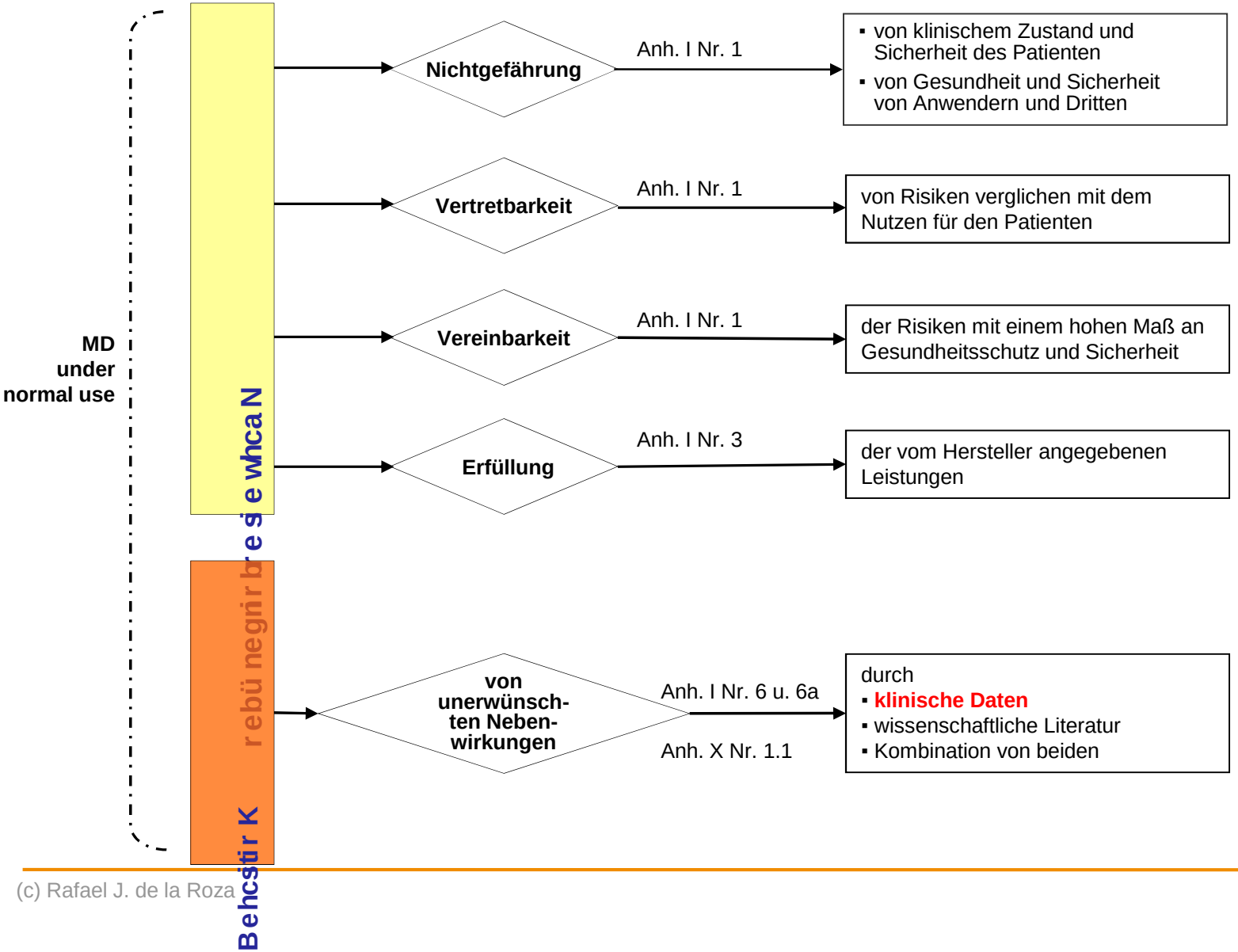
- "Clinicals"

This section includes the German requirements which have to be fulfilled bevor starting clinical trials, in particular with regard to

- *the submission procedures*
- *the documents needed and*
- *the approval procedures.*

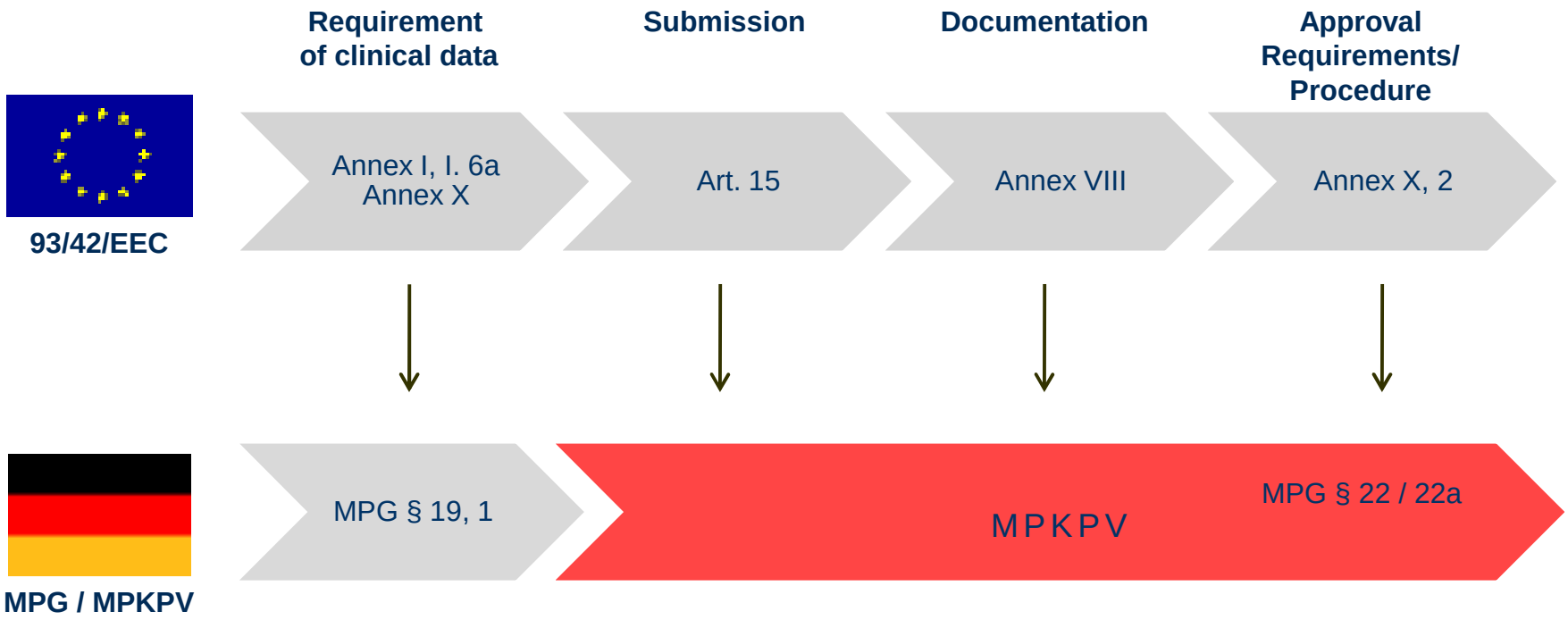
Clinicals

Clinical Evaluation and Clinical Data



Clinicals

General Requirements



Clinicals

General Requirements: Clinical Data

- *As a general rule*, confirmation of conformity with the requirements concerning the characteristics and performances (…) of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio *must be based on clinical data*.
- The evaluation of this data ('clinical evaluation'), where appropriate taking account of any relevant harmonised standards, must follow a defined and methodologically sound procedure.
- Implantable devices and devices in Class III: clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.
- The clinical evaluation and its outcome shall be documented (*part of TF or reference in it*).
- The clinical evaluation and its documentation must be actively *updated* with data obtained from the PMS. Where PMCF is not deemed necessary, this must be duly justified and documented.
- Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, *adequate justification* for any such exclusion has to be given …

  (Annex X No. 1 MDD)

Clinicals

General Requirements: Clinical Data

‘Clinical data’ means (Art. 1 No. 2 k) MDD; § 3 No. 25 MPG)**:**

- the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:
  - clinical investigation(s) of the device concerned; or
  - clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
  - published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated

Clinicals

General Requirements: MPKPV

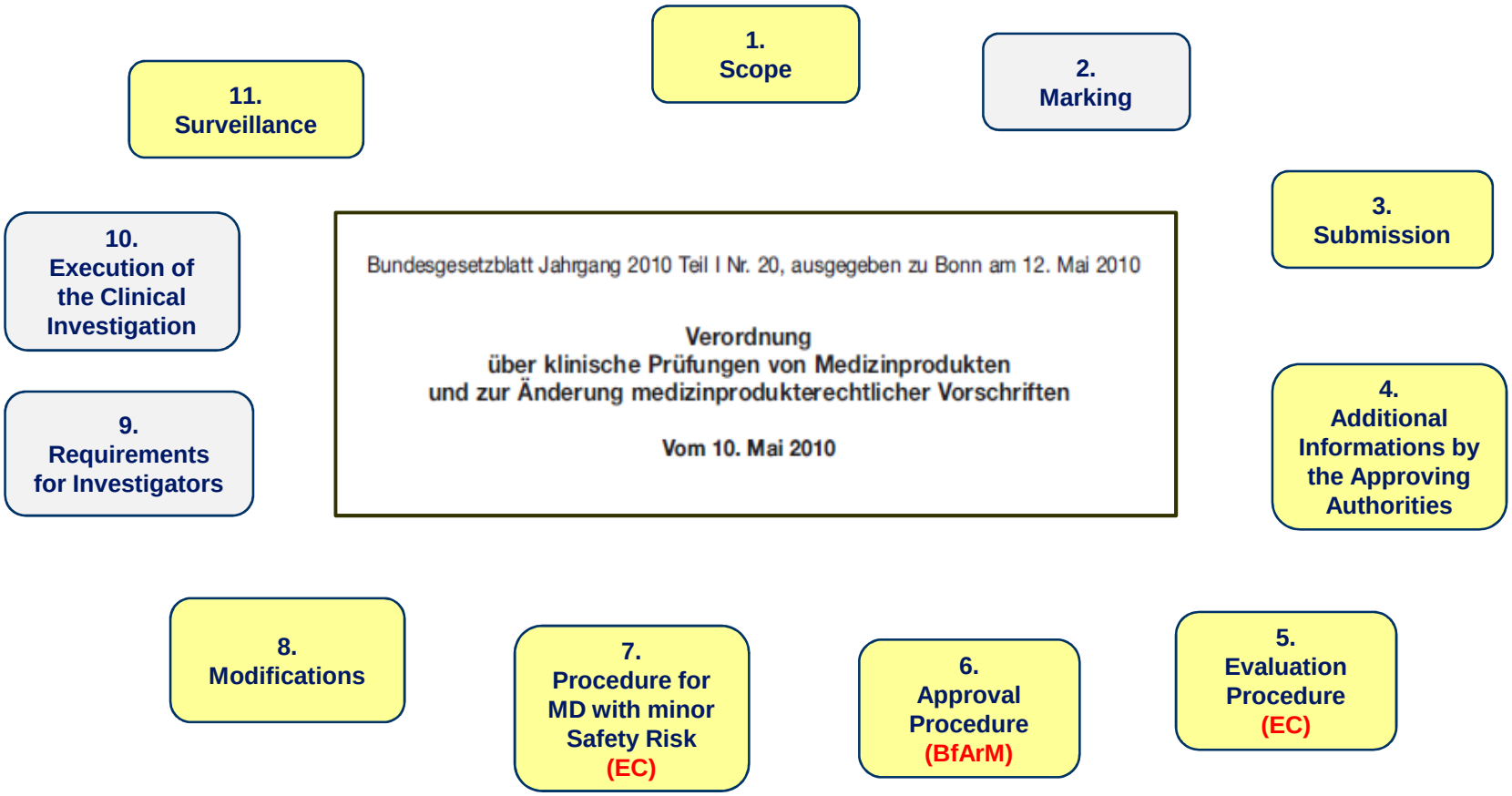
Before starting (§ 20, 1 MPG)**:**

- positive evaluation of the planned clinical trial by the competent EC; focus on ethical and legal aspects (§ 5, 4 MPKPV)
- *approval by BfArM (performance evaluation for some IVD acc. to Annex II IVDD: Paul-Ehrlich-Institut – PEI);* focus on safety / scientific methodology (§ 6, 4 MPKPV)
- *a sponsor (or his representative) must be based in one of the EEA states* (not in Switzerland or Turkey)
- the investigation must be performed *in suitabale facilities*

Clinicals

General Requirements: MPKPV

Structure of MPKPV (in force since 2010.05.13)



Clinicals

General Requirements: MPKPV

§ 1: Scope

- Clinical investigation / performance evaluations with the purpose of
  - conformity assessment of MD / IVD acc. to MPV
  - conformity assessment aiming at a new intended purpose
  - the evaluation of an MD with CE marking with respect to its clinical safety and performance, if additional invasive or other physically straining investigations are conducted for this purpose

NOTE: The provisions apply also on international multi-centre studies, of which only parts are performed in Germany.

Clinicals

General Requirements: MPKPV

§ 1: Exclusions from the Application Scope

The approval and further stipulations for clinical trials do not apply, if the MD bears already the CE marking, except

- that the subject of the investigation is a new intended purpose of the MD, or
- additional invasive or other physically straining investigations are conducted
- performance evaluations of IVD, for which a non-surgical invasive sampling of specimens from the oral cavity is performed

Clinicals

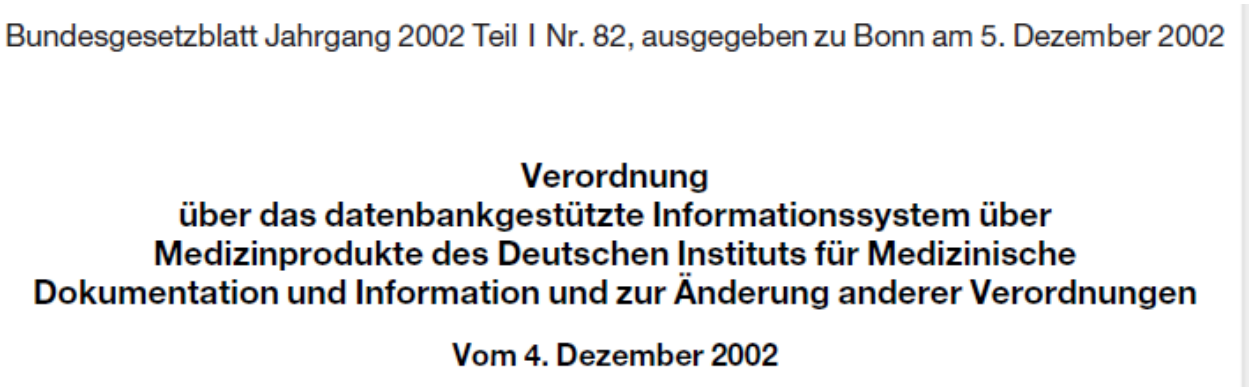
General Requirements: MPKPV

§ 3: Submission

- Applicant: the sponsor (§§ 22,1 and 22a, 1 MPG)
- EC to be adressed if more than one investigator is involved: the EC which is competent for the chief investigator ("Hauptprüfer" – more than one investigators in the same facility) oder principal investigator ("Leiter" – multi-centre investigations)
- via DIMDI website, i. e. in electronic form (mandatory hand-signed documents to such as the trial protocol must be sent additionally by "paper mail")
- DIMDI notifies the reception of the submission to the sponsor, to BfArM (PEI) and to the EC
- in case of multi-centre studies: DIMDI informs each competent EC (for each facility where the study is performed)
- Documents to be attached: see BfArM Information, similar Checkliste Antrag KP)
- the statement of the EC has to be supplemented

Clinicals

DIMDI



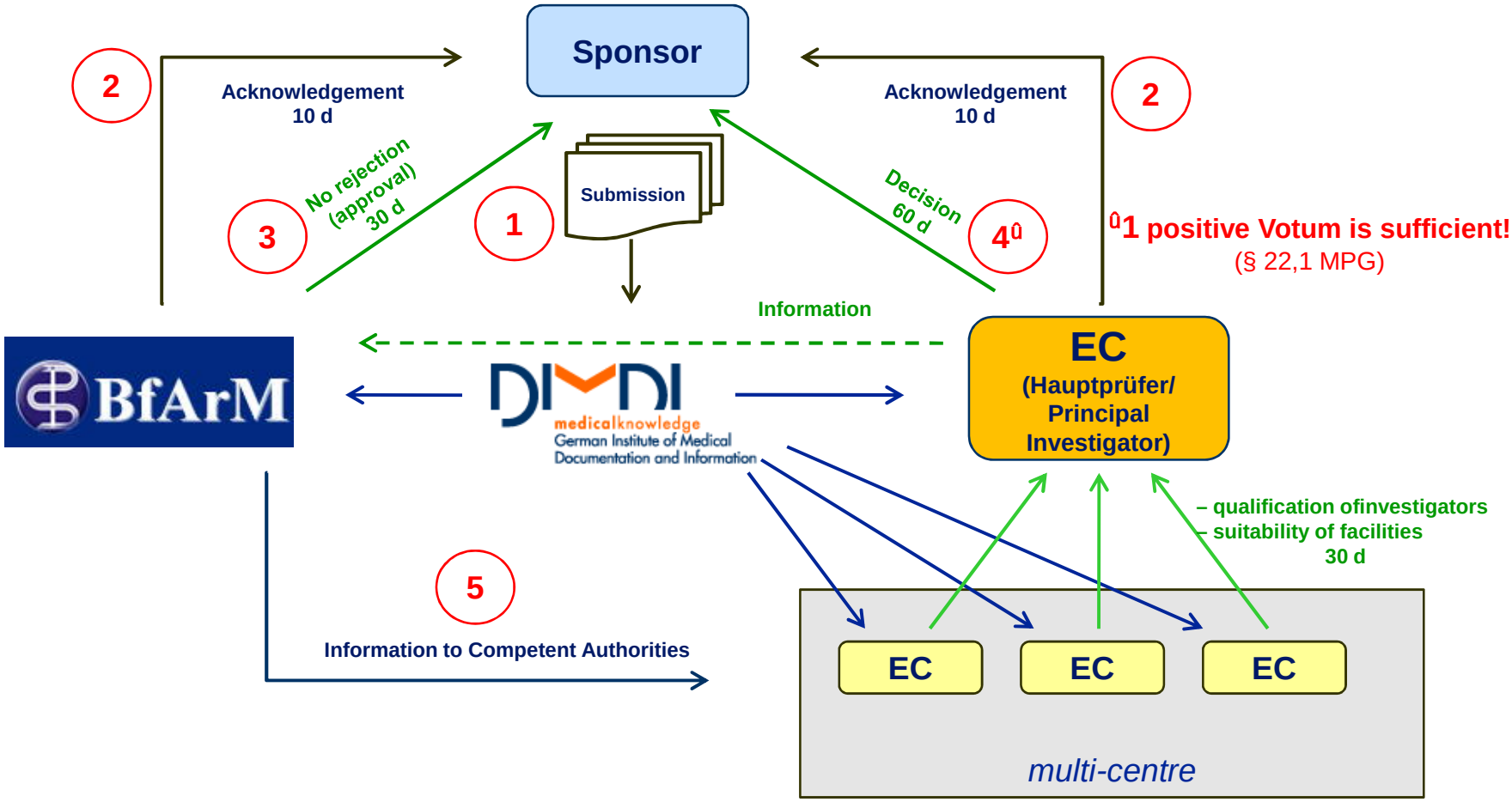
Bundesgesetzblatt Jahrgang 2002 Teil I Nr. 82, ausgegeben zu Bonn am 5. Dezember 2002

Verordnung
über das datenbankgestützte Informationssystem über Medizinprodukte des Deutschen Instituts für Medizinische Dokumentation und Information und zur Änderung anderer Verordnungen

Vom 4. Dezember 2002

- **DIMDI** receives notifications
  - on MD certficates issued, suspended or withdrawn by NBs
  - manufacturers and European Representatives
  - decisions of competent authorities on "MD issues" (demarcation, classification)
  - MD risk assessments
  - clinical trials
- DIMDI submits notifications to competent authorities / ECs etc.
- DIMDI maintains databases for the above purposes
- DIMDI is no competent (approving/rejecting) authority

Clinicals*: Decision Routes



*) NOTE: For devices using uses radioactive substances or X-rays additional appovement by Bundesamt für Strahlenschutz (BfS) required

Clinicals

General Requirements: BfS Submissions

Submission

- Anyone who uses radioactive substances or ionisation radiation for the purpose of medical research, requires permission (§ 23 StrlSchV)
- Requirements for the approval: § 24 StrlSchV

- Anyone who applies X-ray radiation for the purpose of medical research on human beeings, requires permission (§ 28a RöV)
- Requirements for the approval: § 28b RöV

- Approving authority for both is Bundesamt für Strahlenschutz (BfS)

Clinicals

General Requirements: BfS Submissions

Requirements for BfS-Approval: Ionisation Radiation (§ 24 StrlSchV)

- Trial Protocol which demonstrates (among others) the urgent necessity for the study project and the necessary health protection measures
- Description of protection measures
- "Strahlenschutzverantwortlicher" (owner of the operation permission) und "Strahlenschutzbeauftragter" (designated person for the organisation and execution of legally required protection measures)
  (§ 31 StrlSchV)
- Statement of a registered EC (§ 92 StrlSchV);1 votum is sufficiant
- Submission in paper form (1 copy)
- Minimum processing time: 4 months

- Detailled advice on the application and required forms on the BfS website
- Requirements for submission of applications for clinicals trials with **X-ray devices** are similar

Clinicals

General Requirements: MPKPV

§ 4: Additional Information by Authorities

- The competent authorities shall distribute further informations in particular w. r. to "clinical submissions" via their websites

  è BfArM website

  è PEI website

Clinicals

General Requirements: MPKPV

§ 5: Evaluation Procedure (EC)

- acknowledgement by EC to sponsor within 10 days
- in case of missing documents or other deficiencies: notification to the sponsor
- time period of 60 days for final evaluation starts only after full completion of the submission documents
- EC may request one time additonal informations from the sponsor (interrupts above time-period until their submission)
- EC shall submit their decision to the sponsor within 60 days
- … with a copy to BfArM / PEI

NOTE: Each EC may ask the sponsor / the sponsor / the investigators directly for missing documents.

Clinicals

General Requirements: MPKPV

§ 6: Approval Procedure (BfArM / PEI)

- acknowledgement by BfArM to sponsor within 10 days
- in case of missing documents or other failures: notification to the sponsor
- sponsor is allowed to start the clinical trial, unless he has he has not received a contradictory decision by BfArM within 30 days
- BfArM may request one time additional informations from the sponsor (interrupts above time-period until their submission)
- in case of subjections by BfArM the sponsor shall be informed and may correct the application within 90 days
- BfArM decides on the corrections within 15 days

Clinicals

General Requirements: MPKPV

§ 7: Exceptions for MD with Minor Risks (only BfaRM / PEI Approval)

The sponsor may apply to BfArM / PEI an exception of the approval for the following MD categories:

- for MD
  - of Class I
  - for non-invasive MD of Class IIa
  - for MD bearing the CE marking and the clinical trial of which would entail additional invasive or otherwise stressful examinations, unless this trial concerns a different intended purpose of the medical device
- for IVD
  - for which an invensive specimen sampling is performed only or in a significantly additional quantity for the purpose of performance evaluation
  - for which in the course of the performance evaluation additional invasive or otherwise stressful examinations are executed

Clinicals

General Requirements: MPKPV

§ 7: Exceptions for MD with Minor Risks

- Application Requirements:
  - a comprehensive risk assessment
  - as proof that a MD or an IVD as mentioned
  - for MD that are to be used in sterile condition:
    proof of validation of the manufacturer's sterilisation procedures or statements regarding the reprocessing or sterilisation procedures to be performed by the trial site
  - the application has to be submitted electronically via the DIMDI website
- Immediate ("unverzüglich") acknowledgement by BfArM / PEI to sponsor within 10 days
- The approval shall be deemed to be given if BfArM / PEI do not submit a contradictory response within 10 days

Clinicals

General Requirements: MPKPV

§ 8: Modifications

- Sponsor notifies to BfArM / PEI each modification in the documentation via DIMDI website
- Major changes have to be applied to:
  - BfArM / PEI (request for expertise ["Begutachtung"])
  - EC (request for evaluation ["Bewertung"])

Definition: Major changes are such changes which

- § may have an effect on the safety of patients
- § include modification to the documents on which the trials are based
- § influnce the requirements which have been assessed by the EC

Clinicals

General Requirements: MPKPV

§ 8: Modifications

(see also § 22c MPG)

- If BfArM / PEI establish that a notified "modification" results in a major change, they inform the sponsor accfordingly.
- EC and BfArM / PEI evaluate the sponsor on the acceptance of the changes
- Time frame: 30 days

Clinicals

General Requirements: MPKPV

§ 11: Surveillance

- The competent authority ("Bundesländer"!) shall monitor the compliance of the performed clinical trials with the trial plan and further legal provisions
- In case of deficiencies they take the appropriate measures for the safety of probands, users and other involved persons

Clinicals

General Requirements

Completion or Breakoff (§ 23a MPG)

- The sponsor notifies the completion or breakoff with 90 days to BfArM / PEI
- In case of breakoff: within 15 days, indicating the reasons therefore
- Final report to BfArM / PEI within 12 months afer completion / breakoff

Agenda

- SAE Reporting

Here are the new German provisions for reporting of Serious Adverse Events (SAE) described:

- *What has to be reported?*
- *To which authorities?*
- *Who is responsible?*

SAE Reporting

MPSV

Definition (§ 1 No. 7)**:**

"Severe adverse event" is any undesirable event occurred in the course a of a clinical trial or performance evaluation that is subject to approval which, directly or indirectly, has led, might lead to or might have led to the death of a proband, or user or of other persons or to a serious deterioration in their state of health
without considering that this event was caused by the MD / IVD.

è applies also to SAEs which have occurred in a trial that has been exempted from the approval obligation (acc. to § 7 MPKPV)

SAE Reporting

MPSV

- **Resonsibility** (§ 3, No. 5):
  - the sponsor and
  - the investigator or main investigator
  - addressee: BfArM / PEI
- International multi-centre studies, if parts of them are performed in Germany:
  - SAEs occurred in other EEA states must be notified to the competent authorities of theses states (sponsor)
  - SAEs occurred abraod (not only EA states) must also be notified to the German authorities (sponsor)
- **Time-frame:** without delay (§ 5)
- **Mantatory form** to be used (§ 7) è electronic submission

SAE Reporting
MPSV

Follow-up Action: BfArM / PEI

- acknowledge receipt to the reporting persons (§ 3, No. 6) and
- perform risk evaluation of the SAE and the corrective actions by the sponsor
- involve the sponsor and if deemed necessary other responsible bodies and authorities including EC (§§ 8 - 10)
- informs the reporting person(s) about the conclusions of the assessment (§ 13)

SAE Reporting

MPSV

Follow-up Action: Sponsor and Investigators

- have to take immediate actions if circumstances occur which might affect the safety (not only SAEs!) of probands, users or third persons (§ 14a)
- Risk analysis and assessment are to be updated regularly in the course of the clinical trial (BfArM)
- especially important when evaluating SAE and the implementation of corrective measures

Agenda

- Guidance Documents and Forms

In this section you find

- *references to documents which give further advice for the submission of clinical trials application*
- *forms and templates for the necessary documents to avoid delay in the processing of the application by the authorities*

NOTE: All the sedocuments can be downloaded in the internet or are attached to this presentation as separate files.

Guidance Documents and Forms

Legal foundations	
German legislation in fulltext	Juris Website
Standards	
EN 14155	Klinische Prüfung von Medizinprodukten an Menschen Teil 1: Allgemeine Anforderungen (2009-11) Teil 2: Klinische Prüfpläne (2009-11)
EN 14971	Medizinprodukte - Anwendung des Risikomanagements auf Medizinprodukte (2009-10)
EU Guidance Documents (Overview)	
MEDDEV Guidelines	
MEDDEV 2.7/1 rev.3 (2009-12)	Clinical evaluation: Guide for Manufacturers and Notified Bodies *Includes crieria when the evaluation must be based on a clinical investigation*
Appendix 1: (2008-12)	Clinical evaluation on coronary stents
MEDDEV 2.7/2 (2008-12)	Guide for Competent Authorities in making an Assessment of Clinical Investigation Notification *Includes a checklist of items that must be covered by the submission documents – interestuing to see the "other side´s view!"*
MEDDEV 2.12/2 (2004-05)	Clinical Evaluation - Post Market Clinical Follow-up (PMCF)

Guidance Documents and Forms

EK-Med Resolutions	
3.9 A 7 (2006-04)	Wirksamkeitsnachweis von fraglichen Medizinprodukten *Includes a large checklist which the German competent authorities and NBs use when they inspect clinical evaluations / clinical data*
3.12 E12 (2004-10)	Klinische Bewertung – Vergleichbarkeit von Medizinprodukten
Forms and Templates	
Landesamt für Gesundheit und Soziales Berlin	Checkliste Antrag KP
	Arbeitshilfe Teilnehmerinformation
	Arbeitshilfe Einwilligungserklärung
	Arbeitshilfe Angaben zur Eignung der/des Prüferin/s und der Prüfeinrichtung
de la Roza	Checkliste Grundlegende Anforderungen
	Formblatt Risikoanalyse (Auszug)

Your questions, please…

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… also later to:

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