453

REGULATION OF THE GOVERNMENT

of July 7, 2004

stipulating the technical requirements for in vitro diagnostic medical devices

The Government stipulates, pursuant to Section 22 of Act No. 22/1997 Coll., on the technical requirements for products and amending and supplementing some laws, as amended by Act No. 71/2000 Coll. and Act No. 205/2002 Coll. (hereinafter the "Act"), to implement Sections 11, 12 and 13 of the Act and to implement Act No. 123/2000 Coll., on medical devices and on amendment to some related laws, as amended by Act No. 130/2003 Coll. and Act No. 274/2003 Coll. (hereinafter the "Act on Medical Devices"), as follows:

Section 1

In relation to the directly applicable regulation of the European Communities[1]), this Regulation stipulates

a) the technical requirements for in vitro diagnostic medical devices[2]) (hereinafter "in vitro diagnostic devices"), and

b) common technical specifications for in vitro diagnostic devices.

Section 2

(1) In vitro diagnostic devices constitute specified products pursuant to Section 12 (1) of the Act with respect to which conformity of their properties shall be assessed pursuant to this Regulation.

(2) This Regulation shall also apply to

a) in vitro diagnostic devices produced and intended for use for the purposes of analyses in clinical laboratories, without being subject to commercial transactions;

b) mechanical laboratory equipment especially designed for in vitro diagnostic device examinations;

c) in vitro diagnostic devices manufactured from tissues, cells or substances of human origin;

d) accessories of in vitro diagnostic devices that are treated as separate in vitro diagnostic devices;

e) in vitro diagnostic devices consisting in calibrators and control materials needed by the user to establish or verify performances of devices[3]).

(3) This Regulation does not apply to:

a) instruments, apparatus, appliances, materials or other articles, including software, which are intended to be used for research purposes, without any medical objective;

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[1]) Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.
Commission Decision 2002/364/EC of 7 May 2002 on common technical specifications for in vitro-diagnostic medical devices.

[2]) Section 2 (2) (c) of Act No. 123/2000 Coll., on medical devices and on amendment to some related laws.

[3]) Section 3 (e) of Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll.

b) internationally certified reference materials and materials used for external quality assessment schemes;

c) reagents which are produced within health-institution laboratories for use in that environment and are not subject to commercial transactions;

d) medical devices[4]) for invasive taking of samples from the human body;

e) in vitro diagnostic devices manufactured and used only within the same health institution, without having been transferred to another user;

f) other medical devices manufactured from substances of human origin [except for in vitro diagnostic devices referred to in paragraph 2 (c) above)].

Section 3

Definition of Terms

Furthermore, for the purposes of this Regulation:

a) in vitro diagnostic device for self-testing means an in vitro diagnostic device intended by the manufacturer to be able to be used by lay persons in a home environment;

b) performance means the set of properties of in vitro diagnostic devices specified by the manufacturer for the purpose of use of these in vitro diagnostic devices intended by the manufacturer;

c) in vitro diagnostic device for performance evaluation means an in vitro diagnostic device intended by the manufacturer to be subject to performance evaluation studies in clinical laboratories or in other appropriate environments; these activities are not carried out on premises of the manufacturer;

d) authorized representative means a person established in a Member State of the European Union who is authorized by the manufacturer in writing to act on his behalf with authorities and bodies in the Member States of the European Communities, with regard to the requirements following from the manufacturer from this Regulation;

e) placing on the market means the first making available in return for payment or free of charge of in vitro diagnostic devices other than in vitro diagnostic devices intended for performance evaluation with a view to their distribution as goods intended for sale in the Member States of the European Communities, regardless of whether they are new or fully refurbished;

f) putting into service means the instant when in vitro diagnostic devices are provided to the final user as being ready for the first time for their intended purpose;

g) calibration and control materials means any substance, material or article intended by their manufacturer either to establish measurement relationships or to verify the performance characteristics of in vitro diagnostic devices in conjunction with their intended purpose of use;

h) accessory means an article which, whilst not being an in vitro diagnostic device, is intended specifically by its manufacturer to be used together with an in vitro diagnostic device to enable it to be used in accordance with its intended purpose; medical devices for invasive taking of samples from the human body are not considered to be accessories of in vitro diagnostic devices;

i) new in vitro diagnostic device means an in vitro diagnostic device if

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[4]) Regulation of the Government No. 336/2004 Coll., stipulating technical requirements for medical devices and amending Regulation of the Government No. 251/2003 Coll., amending some Regulations of the Government issued to implement Act No. 22/1997 Coll., on technical requirements for products and amending and supplementing some laws, as amended.

1. there have been no such in vitro diagnostic device continuously available on the Community market during the previous three years for the relevant analyte or other parameter;
2. it uses a procedure involving analytical technology not continuously used in connection with a given analyte or other parameter in the Member States of the European Communities during the previous three years.

Section 4

General Principles

(1) In vitro diagnostic devices must comply with the requirements stipulated in Annex No. 1 to this Regulation that are applicable for them (hereinafter the "essential requirements") with respect to the intended purpose of use. The essential requirements shall also be considered to be complied with if in vitro diagnostic devices correspond to the harmonized standards[5]); the harmonized standards pursuant to this Regulation also include common technical specifications for in vitro diagnostic devices[6]).

(2) When samples are taken from the human body (hereinafter "samples") and when substances derived from the human body are withdrawn and used, the procedure must comply with the international treaty[7]) and ethical principles[8]).

(3) Where in vitro diagnostic devices referred to in Section 5 (1) and (2), when correctly installed, maintained and used for their intended purpose, may compromise the health and/or safety of users or the safety of property, the procedure shall be governed by the Act, Act on Medical Devices and the special regulation[9]). The following shall be considered to be a reason for such a procedure, in particular:

a) non-compliance with the essential requirements referred to in paragraph 1 above;
b) incorrect application of harmonized standards if it is declared that they were used; or
c) shortcomings in the harmonized standards themselves.

(4) Information provided to the user pursuant to paragraph 8 of Part B of Annex No. 1 to this Regulation must be in the Czech language, except for symbols referred to in Annex No. 1 to this Regulation or in the relevant harmonized standard[10]).

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[5]) Section 4a of Act No. 22/1997 Coll., on technical requirements for products and amending and supplementing some laws, as amended by Act No. 71/2000 Coll., Act No. 102/2001 Coll., Act No. 205/2002 Coll. and Act No. 226/2003 Coll.

[6]) Commission Decision 2002/364/EC of 7 May 2002 on common technical specifications for in vitro-diagnostic medical devices.

[7]) Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, promulgated under No. 96/2001 Coll. of Int. Treaties.

[8]) Helsinki Declaration Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly in Tokyo, 1975, 35th World Medical Assembly in Venice, 1983, the 41st World Medical Assembly in Hong Kong, 1989, in Somerset West, South Africa, 1996, and in Edinburgh, 2000.

[9]) Act No. 64/1986 Coll., on the Czech Trade Inspection, as amended by Act No. 240/1992 Coll., Act No. 22/1997 Coll., Act No. 110/1997 Coll., Act No. 189/1999 Coll., Act No. 71/2000 Coll., Act No. 145/2000 Coll., Act No. 102/2001 Coll., Act No. 321/2001 Coll., Act No. 205/2002 Coll., Act No. 309/2002 Coll., Act No. 223/2003 Coll. and Act No. 439/2003 Coll.

[10]) CSN EN 980 "Marks for labeling medical devices".

Section 5

Placement on the Market and Putting into Service of In Vitro Diagnostic Devices

(1) In vitro diagnostic devices may be placed on the market[11]) provided that

a) they have been subject to assessment of conformity in accordance with Section 8;

b) they comply with the essential requirements and other provisions hereof applicable thereto;

c) a certificate of conformity has been issued for them pursuant to this Regulation; and

d) a CE marking[12]) has been affixed to them.

(2) In vitro diagnostic devices may be put into service only if they meet the conditions referred to in paragraph 1 above and if they have been supplied and installed in an appropriate manner in accordance with the intended purpose of use.

(3) After being placed on the market, in vitro diagnostic devices must be monitored as regards their safety and quality in accordance with Section 12.

(4) The provisions of paragraphs 1 to 3 above also apply to in vitro diagnostic devices provided for performance evaluation to laboratories or other persons who comply with the requirements specified in Section 8 (4) and in Annex No. 8 to this Regulation.

Section 6

Exhibition of In Vitro Diagnostic Devices

In vitro diagnostic devices that do not comply with the requirements of this Regulation may be shown at exhibitions, trade fairs and otherwise, provided that a visible sign clearly indicates that such in vitro diagnostic devices cannot be marketed or put into service until they have been made to comply with the requirements of this Regulation; specimens taken from the participants to the presentation may not be used in presentation of in vitro diagnostic devices.

Section 7

Common Technical Specifications

(1) Common technical specifications stipulate

a) the criteria for
   1. performance evaluation and review of in vitro diagnostic devices; and
   2. batch release;

b) reference
   1. methodologies; and
   2. materials;

for in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation and, where necessary, for in vitro diagnostic devices covered by List B in Annex No. 2 to this Regulation.

(2) In duly justified cases, common technical specifications may be replaced in design and manufacture of in vitro diagnostic devices by some other solution that ensures at least the same level of safety and quality of in vitro diagnostic devices.

(3) The common technical specifications are specified in Annex No. 10 to this Regulation.

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[11]) Section 3 (f) of Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll.

[12]) Regulation of the Government No. 291/2000 Coll., stipulating the graphic design of the CE marking.

(4) If compliance with the essential requirements cannot be fully verified according to the common technical specifications, the procedure pursuant to the Act shall apply[13]).

Section 8

Conformity Assessment Procedures

(1) For in vitro diagnostic devices other than those covered by Annex No. 2 to this Regulation and in vitro diagnostic devices intended for performance evaluation, the manufacturer shall, in order to affix the CE marking, follow the procedure referred to Section 9 and pursuant to Annex No. 3 to this Regulation and draw up the written EC declaration of conformity required before placing the in vitro diagnostic devices on the market. For in vitro diagnostic devices for self-testing, the manufacturer shall, prior to the drawing up of the written EC declaration of conformity, fulfill the supplementary requirements set out in paragraph 6 of Annex No. 3 to this Regulation or follow the procedure referred to in paragraphs 2 or 3.

(2) For in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation, except for in vitro diagnostic devices intended for performance evaluation, the manufacturer shall follow, for the purpose of affixing the CE marking in accordance with Section 9, the procedure pursuant to

a) Annex No. 4 to this Regulation; or
b) Annex No. 5 to this Regulation, together with the procedure pursuant to Annex No. 7 to this Regulation.

(3) For in vitro diagnostic devices included in List B of Annex No. 2 to this Regulation, except for in vitro diagnostic devices intended for performance evaluation, the manufacturer shall follow, for the purpose of affixing the CE marking in accordance with Section 9, the procedure pursuant to

a) Annex No. 4 to this Regulation; or
b) Annex No. 5 to this Regulation, together with the procedure pursuant to Annex No. 6 or Annex No. 7 to this Regulation.

(4) In case of in vitro diagnostic devices for performance evaluation, the manufacturer shall follow the procedure pursuant to Annex No. 8 to this Regulation and draw up the statement set out in that Annex before such in vitro diagnostic devices are made available. This provision shall in no way prejudice the regulations relating to the ethical aspects[8]) of carrying out performance evaluation studies using tissues or substances of human origin.

(5) When assessing conformity of in vitro diagnostic devices, the manufacturer or, where appropriate, the notified body[14]) shall take account of the results of evaluation and verification that was, where appropriate, carried out during the manufacturing process in accordance with this Regulation.

(6) The manufacturer must keep the declaration of conformity, the technical documentation referred to in Annexes No. 3 to 8 to this Regulation, and reports, certificates, as well as other decisions issued by the notified bodies, as appropriate, and make them available to the competent state administrative bodies for inspection purposes for a period ending five years after the last in vitro diagnostic device was manufactured.

(7) The manufacturer may instruct his authorized representative to initiate the procedures provided for in Annexes No. 3, 5, 6, and 8 to this Regulation.

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[13]) E.g., Section 4a (1) and (3), the first sentence, of Act No. 22/1997 Coll., as amended by Act No. 205/2002 Coll. and Act No. 277/2003 Coll.

[14]) Section 11 (7) of Act No. 22/1997 Coll., as amended by Act No. 205/2002 Coll.

(8) If the documentation referred to in paragraph 6 above has not been provided by the manufacturer, it shall be provided, at request, by the authorized representative, if appointed by the manufacturer.

(9) If the procedure in assessment of conformity involves the notified body, the manufacturer or, as appropriate, the authorized representative shall request that the notified body participate in assessing conformity based on the corresponding scope of authorization. The notified body may request the essential information or data for approval or adherence to the selected procedure in assessment of conformity.

(10) The certificates of the notified body issued in accordance with Annexes No. 3, 4 and 5 to this Regulation shall be valid for a period not exceeding 5 years; the term of these certificates may be prolonged by another period of 5 years on the basis of an application of the manufacturer.

(11) The records and correspondence relating to the procedures referred to in paragraphs 1 to 4 above must be in the Czech language or, as appropriate, in some other language agreed on between the notified body and the manufacturer or, as applicable, his authorized representative.

(12) The procedure in cases where, by means of derogation, conformity of in vitro diagnostic devices need not be assessed, is stipulated in the Act on Medical Devices[15]).

(13) The provisions of paragraphs 1 to 11 above shall apply *mutatis mutandis* to natural and legal persons who manufacture in vitro diagnostic devices and put them into service in that they use them in their professional activities.

Section 9

Marking of In Vitro Diagnostic Devices

(1) A CE marking must be affixed to in vitro diagnostic devices other than those intended for performance evaluation, which comply with the essential requirements, prior to their placement of on the market.

(2) The marking of in vitro diagnostic devices pursuant to paragraph 1 above must appear in a visible, legible and indelible form on the device, where practicable and appropriate, and on the instructions for use. The CE marking must be accompanied by the identification number of the notified body involved in the procedures referred to in Annexes No. 3, 4, 6 and 7 to this Regulation

(3) Marks and descriptions that could be, by mistake, considered to be marks whose meaning or design is similar to the CE marking, may not be placed on in vitro diagnostic devices. Other marks may be placed on in vitro diagnostic devices, their packaging or instructions enclosed with the in vitro diagnostic devices provided that the visibility and legibility of the CE marking is not impaired thereby.

(4) The individual parts of the CE marking affixed to in vitro diagnostic devices must, as a rule, have the same height which must not be less than 5 mm. This minimum height may be waived for small-scale in vitro diagnostic devices.

(5) If in vitro diagnostic devices are subject to special regulations from other viewpoints and such regulation stipulates the duty to affix a CE marking, in that case, such mark indicates that the in vitro diagnostic devices are also in accordance with the requirements applicable thereto pursuant to those special regulations. However, if one or more regulations permit, for a transitional period, that the manufacturer choose which provisions he will follow, the CE marking indicates conformity only with those regulations or provisions thereof that were employed by the producer. In that case, the documentation, notices or instructions for use required by those regulations and enclosed with

[15]) Section 7 of Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll.

the relevant products must include a list of applied regulations and also of Directives, as published in the Official Journal of the European Communities, whose requirements were transposed by those legal regulations.

Section 10

Wrongly Affixed CE Marking

(1) If it is established that the CE marking has been wrongly affixed to an in vitro diagnostic device, the manufacturer or his authorized representative shall end the infringement according to instructions of the Czech Trade Inspection[16]).

(2) If such infringement has not been ended pursuant to paragraph 1 above, special regulations shall apply[17]).

(3) The provisions of paragraphs 1 and 2 above shall also apply where the CE marking has been affixed in accordance with the procedures in this Regulation, but inappropriately, on products that are not covered by this Regulation.

Section 11

Notification of Bodies and In Vitro Diagnostic Devices

(1) A manufacturer, who has his registered office or place of business in the Czech Republic and places in vitro diagnostic devices on the market under his own name, shall notify the Ministry of Health (hereinafter the "Ministry"), in accordance with the Act on Medical Devices[18]), of data on forms whose specimens are given in Annexes No. 11, 12 and 13 to this Regulation; the manufacturer shall notify in particular:

a) of the address of that place;
b) of information relating to
    1. the reagents, reagent products and calibration and control materials in terms of common technological characteristics; or
    2. analytes and of any significant change thereto including discontinuation of placing on the market;
    3. for other in vitro diagnostic devices, the appropriate indications;
c) in the case of in vitro diagnostic devices covered by Annex No. 2 to this Regulation and of in vitro diagnostic devices for self-testing
    1. of data allowing for their identification;
    2. of the analytical and, where appropriate, diagnostic parameters as referred to paragraph 3 of Part A of Annex No. 1 to this Regulation;
    3. of the outcome of performance evaluation pursuant to Annex No. 8 to this Regulation;
    4. of certificates and any significant changes thereto related to subparagraphs 1 to 4 above, including discontinuation of placing on the market.

(2) New in vitro diagnostic devices to which a CE marking has been affixed shall also be subject to notification pursuant to paragraph 1 above.

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[16]) Section 3 (a) to (c) of Act No. 64/1986 Coll., as amended by Act No. 240/1992 Coll. and Act No. 145/2000 Coll.
[17]) Section 7a of Act No. 64/1986 Coll., as amended by Act No. 205/2002 Coll. and Act No. 226/2003 Coll. Section 19 (1) of Act No. 22/1997 Coll., as amended by Act No. 71/2000 Coll., Act No. 205/2003 Coll. and Act No. 226/2003 Coll.
[18]) Section 31 of Act No. 123/2001 Coll., as amended by Act No. 130/2001 Coll.

(3) For in vitro diagnostic devices referred to in Annex No. 2 to this Regulation and for in vitro diagnostic devices for self-testing, the Ministry shall require, provided that these in vitro diagnostic devices are placed on the market and put into service in the Czech Republic

a) information allowing for their identification;

b) information on their marking (e.g. CE marks, labels, symbols, signs);

c) instructions for use.

(4) Transitionally, pending the establishment of a European databank, if a manufacturer, who places in vitro diagnostic devices on the market under his own name, does not have his registered office or place of business in the Czech Republic, the data referred to in paragraphs 1 to 3 above shall be notified to the Ministry by his authorized representative. After the establishment of a European databank, as announced by the Ministry by means of a communication in the Collection of Laws, for a manufacturer, who places in vitro diagnostic devices on the market under his own name and does not have his registered office or place of business in the Czech Republic, the data referred to in paragraph 3 above shall be notified to the Ministry by his authorized representative.

(5) The data referred to in paragraphs 1 to 3 above, including data concerning new in vitro diagnostic devices, shall be immediately entered in the Set of Data on Medical Devices Collected According to the Criteria of the European Communities (hereinafter the "Set of Data") and shall be kept pursuant to Section 13.

(6) A notification pursuant to paragraphs 1 to 5 above shall not replace compliance with the requirements for placing in vitro diagnostic devices on the market and putting them into service.

Section 12

Procedure in Prevention of Undesirable Incidents and in their Occurrence

(1) The procedure in preventing undesirable incidents and in their occurrence is subject to Section 4 (3) of the Act on Medical Devices[19]).

(2) In case of an undesirable incident related to a new in vitro diagnostic device to which a CE marking has been affixed, the manufacturer shall state this fact in the report on undesirable incident[20]).

(3) In justified cases, the State Institute for Drug Control (hereinafter the "Institute") may request, within 2 years of a report of an undesirable incident, information on experience with new in vitro diagnostic devices after their placement on the market.

Section 13

Set of Data

(1) Data

a) on in vitro diagnostic devices, authorized representative, persons performing service of in vitro diagnostic devices and in vitro diagnostic devices pursuant to Section 11 (1) to (3);

b) on issued, amended, withdrawn or, as appropriate, rejected certificates pursuant to the procedures specified in Annexes No. 3 and 7 to this Regulation; and

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[19]) Section 3 (g) and Section 32 (1) and (3) (a) of Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll. Decree No. 501/2000 Coll., stipulating the forms, manners of notification of undesirable incidents related to medical devices, their records, investigation and evaluation, documentation and its maintenance and subsequent monitoring aimed at preventing the occurrence of undesirable incidents, particularly their repeating (the Decree on Undesirable Incidents Related to Medical Devices), as amended by Decree No. 304/2003 Coll.

[20]) Annex No. 1 to Decree No. 304/2003 Coll., amending Decree No. 501/2000 Coll., with respect to item 2335 next to the code of the category of a medical device.

c) obtained in accordance with the procedure regulating notification and records of undesirable incidents[21])

shall be kept in accordance with this Regulation in the Set of Data established in the Czech Republic and kept in the framework of the information system established pursuant to the Act on Medical Devices[22]).

(2) The users of the Set of Data pursuant to paragraph 1 above include, without limitation, the Ministry, the Institute in the area of undesirable incidents related to in vitro diagnostic devices, the State Office for Nuclear Safety for in vitro diagnostic devices using nuclear energy or ionizing radiation, and the Institute of Health Information and Statistics of the Czech Republic. The data shall be provided to the Ministry on forms set forth in Annexes No. 11 to 13 to this Regulation and forms referred to in the special regulation[21]); these data shall be kept in the European databank accessible to the competent authorities of the Member States of the European Communities.

Section 14

Protective Measures and Modification of the List of In Vitro Diagnostic Devices pursuant to Annex No. 2

(1) If it is established that, in order to ensure safety or protection of health or, where appropriate, public health[23]), in vitro diagnostic devices should be prohibited or their availability limited, or in vitro diagnostic devices should be subject to special requirements, the Ministry, Institute, Czech Trade Inspection or, as appropriate, other competent authorities shall adopt appropriate temporary measures pursuant to special regulations[24]); such measures include, without limitation, limitation or prohibition of placing in vitro diagnostic devices on the market, withdrawal from the market, or limitation and prohibition of use in provision of health care. Such measures must include exact specification of the reasons on which they are based; the measures shall be notified, without delay, to the persons who are directly affected by them, together with advice on appeal and deadlines for lodging appeal.

(2) During preparation of a measure pursuant to paragraph 1 above, the manufacturer or his authorized representative may put forward his opinion on the measure, unless there is a danger of delay with respect to health protection[24]).

(3) Where the Ministry considers that

a) the list of in vitro diagnostic devices in Annex No. 2 to this Regulation should be amended or extended, or
b) the conformity of in vitro diagnostic devices or category of in vitro diagnostic devices should be established by way of derogation, by applying one or more given procedures taken from amongst those referred to in Section 8,

it shall submit a duly substantiated request for a decision to the Commission of the European Communities.

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[21]) Decree No. 501/2000 Coll., as amended by Decree No. 304/2003 Coll.
[22]) Section 41 of Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll.
[23]) Act No. 258/2000 Coll., on protection of the public health and amendment of some related laws, as amended by Act No. 254/2001 Coll., Act No. 274/2001 Coll., Act No. 13/2002 Coll., Act No. 76/2002 Coll., Act No. 86/2002 Coll., Act No. 120/2002 Coll., Act No. 309/2002 Coll., Act No. 320/2002 Coll., Act No. 274/2003 Coll., Act No. 356/2003 Coll. and Act No. 362/2003 Coll.
Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll. and Act No. 274/2003 Coll.
[24]) Act No. 102/2001 Coll., on general safety of products and amending some laws (Act on General Safety of Products), as amended by Act No. 146/2002 Coll. and Act No. 277/2003 Coll.
Act No. 123/2000 Coll., as amended.
Act No. 258/2000 Coll., as amended.

(4) Prior to submission of a request pursuant to paragraph 3 above, due consideration shall be given to:

a) any relevant information available from the procedures in the prevention undesirable incidents or in their occurrence and from external quality assessment schemes;

b) whether

1. total reliance has to be placed on the result obtained with a given in vitro diagnostic device, this result having a direct impact on subsequent medical action;
2. action taken on the basis of an incorrect result obtained using a given in vitro diagnostic device could prove to be hazardous to the patient and other persons, in particular as a consequence of false positive or false negative results; and
3. participation of the notified body would contribute to ensuring conformity of the in vitro diagnostic device.

Section 15

Notified Bodies

(1) The conditions for authorization are specified in Annex No. 9 to this Regulation; legal persons that comply with the requirements of Czech technical standards, provided that they fully transpose the requirements stipulated by a European standard or harmonization document, are presumed to comply with the relevant criteria for authorization.

(2) The notified body and the manufacturer or his authorized representative shall stipulate, on the basis of their agreement, the deadlines for completion of evaluation and verification pursuant to Annexes No. 3 and 7 to this Regulation.

(3) The notified body shall inform other notified bodies, the Czech Office for Standards, Metrology and Testing (hereinafter the “Office”) and the Ministry of withdrawal of certificates issued by it; at request, it shall inform the Office and the Ministry of issuance of a certificate or rejecting an application for issuance of certificates and provide other substantial information.

(4) Where a notified body finds that pertinent requirements of this Regulation have not been met or are no longer met by the manufacturer or where a certificate should not have been issued, it shall withdraw the certificate issued or amend it unless compliance with such requirements is ensured by the implementation of appropriate corrective measures by the manufacturer. In the case of amendment of the certificate or in cases where an intervention of the competent authority is necessary, the notified body shall inform other notified bodies, the Office and the Ministry of this fact.

(5) When providing information on certificates amended or withdrawn by the notified body pursuant to the previous paragraphs to competent authorities of other countries and the European Commission, the procedure pursuant to the Act or the Act on Medical Devices, with respect to their scope, shall apply.

(6) The notified body shall provide the Office, at its request, with substantial information and documents, including budgetary documents, in order to verify the criteria stipulated in Annex No. 9 to this Regulation.

Section 16

Transitory Provisions

(1) In vitro diagnostic devices that comply with the requirements pursuant to the former regulations[25]) may be put into service at the latest by December 7, 2005.

(2) In vitro diagnostic devices registered pursuant to Section 11 of Regulation of the Government No. 286/2001 Coll., stipulating technical requirements for in vitro diagnostic medical devices, shall be considered to be in vitro diagnostic devices notified pursuant to Section 11.

(3) In vitro diagnostic devices whose conformity has been assessed pursuant to Section 8 of Regulation of the Government No. 286/2001 Coll., stipulating technical requirements for in vitro diagnostic medical devices, may be placed on the market in the territory of the Czech Republic at the latest by December 7, 2005 for putting into service exclusively in the Czech Republic.

Section 17

Repealing Provision

Regulation of the Government No. 286/2001 Coll., stipulating technical requirements for in vitro diagnostic medical devices, is hereby repealed

Section 18

Legal Force

This Regulation enters into effect on the date of promulgation.

Prime Minister:

PhDr. **Špidla**, *signed*

Minister of Health

MUDr. **Kubinyi**, PhD., *signed*

[25]) Section 4 of Act No. 123/2000 Coll., as amended by Act No. 130/2003 Coll.

Annex No. 1 to Government Regulation No. 453/2004 Coll.

ESSENTIAL REQUIREMENTS

A. GENERAL REQUIREMENTS

1. In vitro diagnostic devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise, directly or indirectly, the clinical condition, safety or health of users or the safety of property. Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.

2. The final solution adopted by the manufacturer for the design of in vitro diagnostic devices must conform to the state of the art in science and technology at the time when the in vitro diagnostic device was manufactured. In selecting the most appropriate solution, the manufacturer must apply the following principles in the following order:
   2.1. eliminate or reduce risks as far as possible (inherently safe design and construction);
   2.2. take adequate protection measures in relation to risks that cannot be eliminated;
   2.3. inform users of the residual risks due to any shortcomings of the protection measures adopted.

3. In vitro diagnostic devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in the Act on Medical Devices, as specified by the manufacturer, taking account of the state of the art in science and technology at the time when they were manufactured. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of mutual interference, and limits of detection, stated by the manufacturer.
   The values assigned to calibrators or control materials must be traced through available reference measurement procedures and/or available reference materials of a higher order.

4. The characteristics and performances referred to in paragraphs 1 and 3 must not be adversely affected to such a degree that the health or the safety of the user are compromised during the shelf life or lifetime of the in vitro diagnostic devices as indicated by the manufacturer, even if the in vitro diagnostic device is subjected to unsuitable conditions or stresses which can occur during normal conditions of its use. When no shelf life or lifetime of an in vitro diagnostic device is stated, the same applies for the shelf life or lifetime reasonably to be expected of an in vitro diagnostic device of that kind, having regard to the intended purpose and the anticipated use of the in vitro diagnostic device.

5. In vitro diagnostic devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under storage and transport conditions (temperature, humidity, etc.) taking account of the instructions and information provided by the manufacturer.

B. DESIGN AND MANUFACTURING REQUIREMENTS

1. Chemical and physical properties.

1.1. In vitro diagnostic devices must be designed and manufactured in such a way as to achieve the characteristics and performances referred to in Part A on the "General requirements". Particular attention must be paid to the possibility of impairment of analytical performance due to incompatibility between the materials used and the specimens (such as biological tissues, cells, body fluids and micro-organisms) intended to be used with the in vitro diagnostic device, taking account of its intended purpose.

1.2. In vitro diagnostic devices must be designed, manufactured and packed in such a way as to reduce as far as possible the risk posed by product leakage, leakage of contaminants from contaminated products and other pollutants during the transport, storage and use of the devices, taking account of the instructions specified by the manufacturer.

2. Infection and microbial contamination.

2.1. In vitro diagnostic devices and their manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the users. The design must allow easy handling and reduce as far as possible contamination of, and leakage from, the device during use. In the case of specimen receptacles, the risk of contamination of the specimen must be reduced. The manufacturing processes must be appropriate for these purposes.

2.2. Where in vitro diagnostic devices incorporate biological substances, the risks of infection must be reduced as far as possible by selecting appropriate donors and appropriate substances and by using appropriate, validated inactivation, conservation, test and control procedures.

2.3. In vitro diagnostic devices labeled either as "STERILE" or as having a special microbiological state must be designed, manufactured and packed in an appropriate pack, according to procedures suitable for ensuring that they remain in the appropriate microbiological state indicated on the label when placed on the market, under the storage and transport conditions specified by the manufacturer, until the protective packaging is damaged or opened.

2.4. In vitro diagnostic devices labeled either as "STERILE" or as having a special microbiological state must have been processed by an appropriate, validated method.

2.5. Packaging systems for in vitro diagnostic devices other than those referred to in paragraph 2.3 must keep the in vitro diagnostic devices without deterioration at the level of cleanliness indicated by the manufacturer and, if the in vitro diagnostic devices are to be sterilized prior to use, minimize as far as reasonable the risk of microbial contamination.

Moreover, steps must be taken to reduce as far as possible microbial contamination during selection and handling of raw materials, manufacture, storage and distribution where the performance of the in vitro diagnostic devices can be adversely affected by such contamination.

2.6. In vitro diagnostic devices intended to be sterilized must be manufactured in appropriately controlled (e.g. environmental) conditions.

2.7. Packaging systems for non-sterile in vitro diagnostic devices must keep the in vitro diagnostic devices without deterioration at the level of cleanliness stipulated and, if the in vitro diagnostic devices are to be sterilized prior to use, minimize the risk of microbial contamination. The packaging system must be suitable taking account of the method of sterilization indicated by the manufacturer.

3. Manufacturing and environmental properties of in vitro diagnostic devices

3.1. If the in vitro diagnostic device is intended for use in combination with other in vitro diagnostic devices or equipment, the whole combination, including the connection system, must be safe and must not impair the specified performances of the in vitro diagnostic devices. Any restrictions on use must be indicated on the label and/or in the instructions for use.

3.2. In vitro diagnostic devices must be designed and manufactured in such a way as to reduce as far as possible the risks linked to their use in conjunction with materials, substances and gases with which they may come into contact during normal conditions of use.

3.3. In vitro diagnostic devices must be designed and manufactured in such a way as to remove or reduce as far as possible:

3.3.1. the risk of injury linked to their physical features (in particular aspects of volume x pressure, dimension and, where appropriate, ergonomic features);

3.3.2. risks linked to adequately foreseeable external influences, such as magnetic fields, external electrical effects, electrostatic discharge, pressure, humidity, temperature or variations in pressure or acceleration or accidental penetration of substances into the in vitro diagnostic device. In vitro diagnostic devices must be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity of electromagnetic disturbance to enable them to operate as intended.

3.4. In vitro diagnostic devices must be designed and manufactured in such a way as to reduce as far as possible the risks of fire or explosion during normal use and in fault condition. Particular attention must be paid to in vitro diagnostic devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.

3.5. In vitro diagnostic devices must be designed and manufactured in such a way as to facilitate the management of safe waste disposal.

3.6. The measuring, monitoring or display scale (including color change and other visual indicators) must be designed and manufactured in line with ergonomic principles, taking account of the intended purpose of the in vitro diagnostic device.

4. In vitro diagnostic devices which are instruments or apparatus with a measuring function

4.1. In vitro diagnostic devices which are instruments or apparatus having a primary analytical measuring function must be designed and manufactured in such a way as to provide adequate stability and accuracy of measurement within appropriate accuracy limits, taking into account the intended purpose of the device and of available and appropriate measurement procedures and materials. The accuracy limits have to be specified by the manufacturer.

4.2. When values are expressed numerically, they must be given in legal units in accordance with the applicable regulations.[26])

5. Protection against radiation

5.1. In vitro diagnostic devices must be designed and manufactured in such a way that exposure of users and other persons to the emitted radiation is minimized.

5.2. When in vitro diagnostic devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must as far as possible be:

5.2.1. designed and manufactured in such a way as to ensure that the characteristics and the quantity of radiation emitted can be controlled and/or adjusted;

5.2.2. fitted with visual displays and/or audible warnings of such emissions.

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[26]) Act No. 505/1990 Coll., on metrology, as amended by Act No. 4/1993 Coll., Act No. 20/1993 Coll., Act No. 119/2000 Coll., Act No. 13/2002 Coll., Act No. 137/2002 Coll. and Act No. 226/2003 Coll.

5.3. The operating instructions for in vitro diagnostic devices emitting radiation must give detailed information as to the nature of the emitted radiation from in vitro diagnostic devices, means of protecting the user, and on ways of avoiding misuse and of eliminating the risks inherent in installation.

6. Requirements for in vitro diagnostic devices connected to or equipped with an energy source

6.1. In vitro diagnostic devices incorporating electronic programmable systems, including software, must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use.

6.2. In vitro diagnostic devices must be designed and manufactured in such a way as to minimize the risks of creating electromagnetic perturbation which could impair the operation of other in vitro diagnostic devices or equipment in the usual environment.

6.3. In vitro diagnostic devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the in vitro diagnostic devices are installed and maintained correctly.

6.4. Protection against mechanical and thermal risks

6.4.1. In vitro diagnostic devices must be designed and manufactured in such a way as to protect the user against mechanical risks. In vitro diagnostic devices must be sufficiently stable under the foreseen operating conditions. They must be suitable to withstand stresses inherent in the foreseen working environment, and to retain this resistance during the expected life of the devices, subject to any inspection and maintenance requirements as indicated by the manufacturer.

Where there are risks due to the presence of moving parts, risks due to break-up or detachment, or leakage of substances, then appropriate protection means must be incorporated.

Any guards or other means included with the in vitro diagnostic device to provide protection, in particular against moving parts, must be secure and must not interfere with access for the normal operation of the in vitro diagnostic device, or restrict routine maintenance of the in vitro diagnostic device as intended by the manufacturer.

6.4.2. In vitro diagnostic devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the in vitro diagnostic devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.

6.4.3. In vitro diagnostic devices must be designed and manufactured in such a way as to reduce as far as possible the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.

6.4.4. Terminals and connectors to electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and manufactured in such a way as to minimize all possible risks.

6.4.5. Accessible parts of the in vitro diagnostic devices (excluding the parts of areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperatures under normal use.

7. Requirements for in vitro diagnostic devices for self-testing

In vitro diagnostic devices for self-testing must be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in users' technique and environment. The information and instructions provided by the manufacturer should be easily understood and applied by the user.

7.1. In vitro diagnostic devices for self-testing must be designed and manufactured in such a way as to:

7.1.1. ensure that they are easy to use by the users; and

7.1.2. reduce as far as practicable the risk of user error in the handling of the in vitro diagnostic device and in the interpretation of the results.

7.2. In vitro diagnostic devices for self-testing must, where reasonably possible, include user control, i.e. a procedure by which the user can verify that, at the time of use, the in vitro diagnostic device will perform as intended.

8. Information supplied by the manufacturer

8.1. Each in vitro diagnostic devices must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer. This information comprises the data on the label and in the instructions for use. As far as practicable and appropriate, the information needed to use the in vitro diagnostic device safely and properly must be set out on the in vitro diagnostic device itself and/or, where appropriate, on the sales packaging. If individual full labeling of each unit of an in vitro diagnostic device is not practicable, the information must be set out on the packaging and/or in the instructions for use supplied with one or more in vitro diagnostic devices.

Instructions for use must be provided to the user or accompany or be included in the packaging of one or more in vitro diagnostic devices.

In duly justified and exceptional cases no such instructions for use are needed for an in vitro diagnostic device if it can be used properly and safely without them.

8.2. Where appropriate, the information to be supplied should take the form of symbols.

Any symbol and identification color used must conform to the harmonized standards. In areas for which no harmonized standards exist, the symbols and color used must be described in the documentation supplied with the in vitro diagnostic device.

8.3. In the case of in vitro diagnostic devices containing a substance which may be considered as being dangerous, taking account of the nature and quantity of its constituents and the forms under which they are present, relevant danger symbols must be used and labeling requirements pursuant to the applicable regulations must be complied with.

Where there is insufficient space to put all the information on the in vitro diagnostic device itself or on its label, the relevant danger symbols shall be put on the label and the other information required by this Regulation shall be given in the instructions for use.

8.4. The label must bear the following particulars which may take the form of symbols as appropriate:

8.4.1. the name(s) and surname of the manufacturer, address of his residence and place(s) of business, if the manufacturer is a natural person; the name or business name, address of the registered office, if the manufacturer is a legal person (hereinafter “identification details”).

For in vitro diagnostic devices imported into the Member States of the European Communities with a view to their distribution in the Czech Republic, the label, the outer packaging, or the instructions for use must also contain the identification details of the authorized representative;

8.4.2. the details strictly necessary for the user to uniquely identify the in vitro diagnostic device and the contents of the packaging;

8.4.3. where appropriate, the word “STERILE” or a statement indicating any special microbiological state or state of cleanliness;

8.4.4. the batch code, preceded by the word “LOT”, or the serial number;

8.4.5. if necessary, an indication of the date by which the in vitro diagnostic device or part of it should be used, in safety, without degradation of performance, expressed in the following order: the year, the month and, where relevant, the day;

8.4.6. in case of in vitro diagnostic devices for performance evaluation, the words “for performance evaluation only”;

8.4.7. where appropriate, a statement indicating the in vitro use of the in vitro diagnostic device;

8.4.8. any particular storage and/or handling conditions;

8.4.9. where applicable, any particular operating instructions;

8.4.10. appropriate warnings and/or precautions to take;

8.4.11. if the in vitro diagnostic device is intended for self-testing, that fact must be clearly stated.

8.5. If the intended purpose of use is not obvious to the user, the manufacturer must clearly state the intended purpose in the instructions for use and, if appropriate, on the label.

8.6. Wherever reasonable and practicable, the in vitro diagnostic devices and separate components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the in vitro diagnostic devices and detachable components.

8.7. Where appropriate, the instructions for use must contain the following particulars:

8.7.1. the details referred to in paragraph 8.4, with the exception of paragraphs 8.4.4. and 8.4.5;

8.7.2. composition of the reagents (the reagent product) by nature and amount or concentration of the active ingredient(s) of the reagent(s) or kit as well as a statement, where appropriate, that the in vitro diagnostic device contains other ingredients which might influence the measurement;

8.7.3. the storage conditions and shelf life following the first opening of the primary container, together with the storage conditions and stability of working reagents;

8.7.4. the performances referred to in paragraph 3 of part A of this Annex;

8.7.5. an indication of any special equipment required including information necessary for the identification of that special equipment for proper use;

8.7.6. the type of specimen to be used, any special conditions of collection, pre-treatment and, if necessary, storage conditions and instructions for the preparation of the patient;

8.7.7. the procedure to be followed in using the in vitro diagnostic devices;

8.7.8. the measurement procedure to be followed with the in vitro diagnostic devices including as appropriate:

8.7.8.1. the principle of the method;

8.7.8.2. the specific analytical performance characteristics (e.g. sensitivity, specificity, accuracy, repeatability, reproducibility, limits of detection and measurement range, including information needed for the control of known relevant interferences), limitations of the method and information about the use of available reference measurement procedures and materials by the user,

8.7.8.3. the details of any further procedure or handling needed before the in vitro diagnostic device can be used (for example, reconstitution, incubation, dilution, instrument checks, etc.);

8.7.8.4. the indication whether any particular training is required;

8.7.9. the mathematical approach upon which the calculation of the analytical result is made;

8.7.10. measures to be taken in the event of changes in the analytical performance of the in vitro diagnostic device;

8.7.11. information appropriate to users on:

8.7.11.1. internal quality control including specific validation procedures,

8.7.11.2. the traceability of the calibration of the in vitro diagnostic device;

8.7.12. the reference intervals for the quantities being determined, including a description of the appropriate reference population;

8.7.13. if the in vitro diagnostic device must be used in combination with or installed with or connected to other in vitro diagnostic devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct in vitro diagnostic devices or equipment to use in order to obtain a safe and proper combination;

8.7.14. all the information needed to verify whether the in vitro diagnostic device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the in vitro diagnostic device operates properly and safely; information about safe waste disposal;

8.7.15. details of any further treatment or handling needed before the in vitro diagnostic device can be used (for example, sterilization, final assembly, etc.);

8.7.16. the necessary instructions in the event of damage to the protective packaging and details of appropriate methods of resterilization or decontamination;

8.7.17. if the in vitro diagnostic devices is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and resterilization or decontamination, and any restriction on the number of reuses;

8.7.18. precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, and other circumstances, if appropriate;

8.7.19. precautions to be taken against any special, unusual risks related to the use or disposal of the in vitro diagnostic device including special protective measures; where the in vitro diagnostic device includes substances of human or animal origin, attention must be drawn to their potential infectious nature;

8.7.20. specifications for in vitro diagnostic devices for self-testing:

8.7.20.1. the results need to be expressed and presented in a way that is readily understood by a lay person; information needs to be provided with advice to the user on action to be taken, in case of

positive, negative or indeterminate result, and on the possibility of false positive or false negative result; specific particulars may be omitted provided that the other information supplied by the manufacturer is sufficient to enable the user to use the in vitro diagnostic device and to understand the result(s) produced by the in vitro diagnostic device;

8.7.20.2. the information provided must include a statement clearly directing that the user should not take any decision of medical relevance without first consulting his or her medical practitioner,

8.7.20.3. the information must also specify that when the in vitro diagnostic device for self-testing is used for the monitoring of an existing disease, the patient should only adapt the treatment if he has received the appropriate training to do so;

8.7.21. date of issue or latest revision of the instructions for use.

Annex No. 2 to Government Regulation No. 453/2004 Coll.

LIST OF IN VITRO DIAGNOSTIC DEVICES REFERRED TO IN SECTION 8 (2) AND (3)

List A

1. Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups:
   ABO system,
   Rhesus (C, c, D, E, e) Kell (K),
2. reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

List B

1. Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups:
   anti - Duffy, and
   anti - Kidd,
2. Reagents and reagent products, including related calibrators and control materials, for determining:
   irregular anti-erythrocytic antibodies,
3. reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections:
   rubella, and
   toxoplasmosis,
4. reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease:
   phenylketonuria,
5. reagents and reagent products, including related calibrators and control materials, for determining the following human infections:
   cytomegalovirus,
   chlamydia,
6. reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups:
   DR, A, B,
7. reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker:
   PSA,
8. reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of:
   trisomy 21,
9. the following in vitro diagnostic device for self-diagnosis, including its related calibrators and control materials:
   in vitro diagnostic devices for measurement of blood sugar.

Annex No. 3 to Government Regulation No. 453/2004 Coll.

EC DECLARATION OF CONFORMITY

1. The EC declaration of conformity is the procedure whereby the manufacturer or his authorized representative who fulfils the obligations imposed by paragraphs 2 to 5 and additionally, in the case of in vitro diagnostic devices for self-testing, the obligations imposed by paragraph 6 of this Annex, ensures and declares that the products concerned meet the provisions of this Regulation which apply to them. The manufacturer shall affix the CE marking to in vitro diagnostic devices in accordance with Section 9.

2. The manufacturer shall prepare the technical documentation described in paragraph 3 of this Annex and ensure that the manufacturing process follows the principles of quality assurance as set out in paragraph 4.

3. The technical documentation must allow assessment of the conformity of the in vitro diagnostic devices with the requirements of the Regulation. It must include in particular:
   - 3.1. a general description of the in vitro diagnostic device, including any variants planned,
   - 3.2. the documentation on the quality system,
   - 3.3. design information, including the determination of the characteristics of the basic materials, characteristics and limitation of the performance of the in vitro diagnostic devices, methods of manufacture and, in the case of instruments, design drawings, diagrams of components, sub-assemblies, circuits,
   - 3.4. in the case of in vitro diagnostic devices containing tissues of human origin or substances derived from such tissue, information on the origin of such material and on the conditions in which it was collected,
   - 3.5. the descriptions and explanations necessary to understand the abovementioned characteristics, drawings and diagrams and the operation of the in vitro diagnostic devices,
   - 3.6. the results of the risk analysis and, where appropriate, a list of the standards referred to in Section 4, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the Regulation if the standards referred to in Section 4 have not been applied in full,
   - 3.7. in the case of sterile in vitro diagnostic devices or in vitro diagnostic devices with a special microbiological state or state of cleanliness, a description of the procedures used,
   - 3.8. the results of the design calculations and of the inspections carried out,
   - 3.9. if the in vitro diagnostic device is to be combined with other in vitro diagnostic device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when combined with any such in vitro diagnostic device(s) having the characteristics specified by the manufacturer,
   - 3.10. the test reports,
   - 3.11. adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available), with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used. Such data should originate from studies in a clinical or other appropriate environment or result from relevant biographical references,
   - 3.12. the labels and instructions for use,

3.13. the results of stability studies.

4. The manufacturer shall take necessary measures to ensure that the manufacturing process follows the principles of quality assurance as appropriate for the in vitro diagnostic devices manufactured.
The system shall address:
4.1. the organizational structure and responsibilities,
4.2. the manufacturing processes and systematic quality control of production,
4.3. the in vitro diagnostic devices to monitor the performance of the quality system.

5. The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from in vitro diagnostic devices in the phase after placement on the market and putting into service and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the in vitro diagnostic device. The manufacturer shall notify the Institute of any possibility of occurrence of an undesirable incident or an actual undesirable incident immediately on learning of it.

6. For in vitro diagnostic devices for self-testing the manufacturer shall lodge an application for examination of the design with a notified body.
6.1. The application must enable the design of the in vitro diagnostic device to be understood and must contain documents that enable conformity with the design-related requirements of this Regulation to be assessed.
The application shall include:
6.1.1. test reports including, where appropriate, results of studies carried out with lay persons,
6.1.2. data showing the handling suitability of the in vitro diagnostic device in view of its intended purpose for self-testing,
6.1.3. the information to be provided with the in vitro diagnostic device on its label and its instructions for use.
6.2. The notified body shall examine the application and, if the design conforms to the relevant provisions of this Regulation shall issue the applicant with an EC design-examination certificate. The notified body may require the application to be completed by further tests or proof to allow assessment of conformity with the design-related requirements of the Regulation.
The EC-design-examination certificate shall contain the conclusions of the examination, the conditions of validity, the data needed for the identification of the approved design and, where appropriate, a description of the intended purpose of the in vitro diagnostic device.
6.3. The applicant shall inform the notified body which issued the EC design-examination certificate of any significant change made to the approved design. Changes to the approved design must receive further approval from the notified body which issued the EC design-examination certificate wherever the changes could affect conformity with the essential requirements or could affect the conditions prescribed for use of the in vitro diagnostic device. This additional approval shall take the form of a supplement to the EC design-examination certificate.

Annex No. 4 to Government Regulation No. 453/2004 Coll.

EC DECLARATION OF CONFORMITY

(Full Quality Assurance System)

1. The manufacturer shall ensure application of the quality system approved for the design, manufacture and final inspection of the in vitro diagnostic devices concerned, as specified in paragraph 3 of this Annex, and is subject to audit as laid down in paragraph 3.3 and to the surveillance as specified in paragraph 5.
   In addition, the manufacturer must follow, for in vitro diagnostic devices covered by Annex No. 2, List A, the procedures laid down in paragraphs 4 and 6.
   The EC declaration of conformity is the procedure whereby the manufacturer who fulfils the obligations imposed by this paragraph ensures and declares that the in vitro diagnostic devices concerned meet the provisions of this Regulation which apply to them.

2. The manufacturer shall:
   2.1. mark in vitro diagnostic devices in accordance with Section 9; and
   2.2. draw up a written declaration of conformity pursuant to Section 9.

3. Quality system
   3.1. The manufacturer shall:
      3.1.1. lodge a written application for assessment (evaluation and approval) of his quality system with a notified body. The application must include:
         3.1.1.1. the name(s) and surname of the manufacturer, address of his residence and place(s) of business, if the manufacturer is a natural person; the name or business name, address of the registered office, if the manufacturer is a legal person. In both cases, this includes addresses of the manufacturing sites covered by the quality system,
         3.1.1.2. adequate information on the in vitro diagnostic device or category of in vitro diagnostic device covered by the procedure,
         3.1.1.3. a written declaration that no such application has been lodged with any other notified body for the same quality system related to the in vitro diagnostic device,
         3.1.1.4. the documentation on the quality system,
         3.1.1.5. an undertaking by the manufacturer to fulfill the obligations imposed by the quality system approved,
         3.1.1.6. an undertaking by the manufacturer to keep the approved quality system adequate and efficacious,
         3.1.1.7. an undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from in vitro diagnostic devices in the post-sales phase and to implement appropriate in vitro diagnostic devices to apply any necessary corrective action and notification as referred to in paragraph 5 of Annex No. 3 to this Regulation.
   3.2. Application of the quality system must ensure that the in vitro diagnostic devices conform to the provisions of this Regulation which apply to them at every stage, from design to final inspection.
      All the elements, requirements and provisions adopted by the manufacturer for his quality system must be documented in a systematic and orderly manner in the form

of written policies and procedures, such as quality programs, quality plans, quality manuals and quality records.

It must include in particular a description of:

3.2.1. the manufacturer's quality objectives;

3.2.2. the organization of the business of the manufacturer and in particular

3.2.2.1. the organizational structures, the responsibilities of the managerial staff and their organizational authority where quality of design and manufacture of the in vitro diagnostic devices is concerned,

3.2.2.2. the methods of monitoring the efficient operation of the quality system and in particular its ability to achieve the desired quality of design and of in vitro diagnostic devices, including control of in vitro diagnostic devices which fail to conform;

3.2.3. the procedures for monitoring and verifying the design of the in vitro diagnostic devices and in particular:

3.2.3.1. a general description of the in vitro diagnostic device, including any variants planned,

3.2.3.2. all documentation referred to in paragraphs 3.3. to 3.13. of Annex No. 3 to this Regulation,

3.2.3.3. in the case of in vitro diagnostic devices for self-testing, the information referred to in paragraph 6.1 of Annex No. 3 to this Regulation,

3.2.3.4. the techniques used to control and verify the design and the processes and systematic measures which will be used when the in vitro diagnostic devices are being designed;

3.2.4. the inspection and quality assurance techniques at the manufacturing stage and in particular:

3.2.4.1. the processes and procedures which will be used, particularly as regards sterilization,

3.2.4.2. the procedures in relation to purchasing,

3.2.4.3. the product identification procedures drawn up and kept up to date from drawings, specifications or other relevant documents at every stage of manufacture;

3.2.5. the appropriate tests and trials which will be carried out before, during and after manufacture, the frequency with which they will take place, and the test equipment used; it must be possible to trace back the calibration.

The manufacturer shall carry out the required controls and tests according to the latest state of the art in science and technology.

The controls and tests shall cover the manufacturing process including the characterization of the raw material and the individual in vitro diagnostic devices or each batch of in vitro diagnostic devices manufactured. In testing the in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation, the manufacturer shall take into account the most recent available information, in particular as regards the biological complexity and variability of the specimens to be tested with the in vitro diagnostic device concerned.

3.3. The notified body must audit the quality system to determine whether the system meets the requirements referred to in paragraph 3.2 of this Annex. It must presume that quality systems which implement the relevant harmonized standards conform to these requirements.

The assessment team must have past experience of assessments of the technology concerned.

The assessment procedure must include an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes.

After the audit, the notified person shall communicate the decision to the manufacturer, including the conclusions of the inspection and a reasoned assessment.

3.4. The manufacturer shall inform the notified body which approved the quality system of any plan for substantial changes to the quality system or the range of in vitro diagnostic devices covered.

The notified body shall assess the changes proposed and verify whether after these changes the quality system still meets the requirements referred to in paragraph 3.2 of this Annex and notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment.

4. Examination of the design of in vitro diagnostic devices

4.1. For in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation, in addition to the obligations imposed on the manufacturer by paragraph 3 of this Annex, the manufacturer must lodge with the notified body an application for examination of the design dossier relating to the in vitro diagnostic device which he plans to manufacture and which falls into the category referred to in paragraph 3.1 of this Annex.

4.2. The application must describe the design, manufacture and performances of the in vitro diagnostic device in question. It must include the documents needed to assess whether the in vitro diagnostic device conforms to the requirements pursuant to paragraph 3.2.3 of this Annex.

4.3. The notified body shall

4.3.1. examine the application and, if the in vitro diagnostic device conforms to the relevant provisions of this Regulation, it shall issue the applicant an EC design-examination certificate for the in vitro diagnostic device,

4.3.2. may require the application to be completed by further tests or proof to allow assessment of conformity of the in vitro diagnostic devices with the requirements of the Regulation,

4.3.3. state in the EC-design-examination certificate the conclusions of the examination, the conditions of validity, the data needed for the identification of the approved design and, where appropriate, a description of the intended purpose of the in vitro diagnostic device.

4.4. Changes to the approved design must receive further approval from the notified body which issued the EC design-examination certificate wherever the changes could affect conformity with the essential requirements of the Regulation or with the conditions prescribed for use of the in vitro diagnostic device.

The applicant shall inform the notified body which issued the EC design-examination certificate of all changes made to the approved design. The additional approval must take the form of a supplement to the EC design-examination certificate.

4.5. The manufacturer shall inform the notified body without delay if it has obtained information about changes to the pathogen and markers of infections to be tested, in particular as a consequence of biological complexity and variability. In this connection, the manufacturer shall inform the notified body whether any such

change is likely to affect the performance of the in vitro diagnostic device concerned.

5. Surveillance

5.1. The aim of surveillance is to ensure that the manufacturer duly fulfils the obligations imposed by the approved quality system.

5.2. The manufacturer shall authorize the notified body to carry out all the necessary inspections and supply it with all relevant information, in particular:

5.2.1. the documentation on the quality system,

5.2.2. the data stipulated in the part of the quality system relating to design, such as the results of analyses, calculation, tests,

5.2.3. the data stipulated in the part of the quality system relating to manufacture, such as inspection reports and test data, calibration data, qualification reports of the personnel concerned.

5.3. The notified body shall

5.3.1. periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system, and

5.3.2. supply the manufacturer with an assessment report,

5.3.3. pay unannounced visits to the manufacturer according to its discretion; at the time of such visits, the notified body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly.

5.3.4. provide the manufacturer with an inspection report and, if a test has been carried out, with a test report.

6. Verification of manufactured in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation

6.1. In the case of in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation, the manufacturer shall forward to the notified body without delay after the conclusion of the controls and tests the relevant reports on the tests carried out on the manufactured in vitro diagnostic devices or each batch of in vitro diagnostic devices.

Furthermore, the manufacturer shall make the samples of manufactured in vitro diagnostic devices or batches of in vitro diagnostic devices available to the notified body in accordance with pre-agreed conditions and modalities.

6.2. The manufacturer may place the in vitro diagnostic devices on the market, unless the notified body communicates to the manufacturer within the agreed time-frame, but not later than 30 days after reception of the samples, any other decision, including in particular any condition of validity of delivered certificates.

Annex No. 5 to Government Regulation No. 453/2004 Coll.

EC TYPE-EXAMINATION

1. EC type-examination of in vitro diagnostic devices is the part of the procedure whereby a notified body ascertains and certifies that a representative sample of the production assessed fulfils the relevant provisions of this Regulation.

2. The application for EC type-examination shall be lodged by the manufacturer or by his authorized representative with a notified body. It shall include:
   - 2.1. the name(s) and surname of the manufacturer, address of his residence and place(s) of business, if the manufacturer is a natural person; the name or business name, address of the registered office, if the manufacturer is a legal person,
   - 2.2. the name, surname and address of permanent residence, if the application is lodged by an authorized representative who is a natural person, or the name (business name) and address of the registered office, if the application is lodged by an authorized representative who is a legal person,
   - 2.3. the documentation described in paragraph 3 of this Annex needed to assess the conformity of the type with the requirements of this Regulation. The applicant shall submit a sample of the in vitro diagnostic device to the notified body which may request additional samples, according to its discretion,.
   - 2.4. a written declaration that no application has been lodged with any other notified body for the same type.

3. The documentation must allow an understanding of the design, the manufacture and the performances of the in vitro diagnostic device. The documentation shall contain the following items in particular:
   - 3.1. a general description of the type, including any variants planned,
   - 3.2. the documentation referred to in paragraphs 3.3. to 3.13. of Annex No. 3 to this Regulation,
   - 3.3. in the case of in vitro diagnostic devices for self-testing, the information referred to in paragraph 6.1 of Annex No. 3 to this Regulation,

4. The notified body shall
   - 4.1. examine and assess the documentation and verify that the sample of the in vitro diagnostic device has been manufactured in conformity with that documentation; it shall also record the items designed in conformity with the applicable provisions of the harmonized standards referred to in Section 4, as well as the items not designed on the basis of the relevant provisions of the abovementioned standards,
   - 4.2. perform or have performed appropriate examinations and the tests necessary to verify whether the solutions adopted by the manufacturer meet the essential requirements of this Regulation if the standards referred to in Section 4 have not been applied.

     If the in vitro diagnostic device is to be combined with other in vitro diagnostic device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when combined with any such in vitro diagnostic device(s) having the characteristics specified by the manufacturer,
   - 4.3. carry out or ask for the appropriate examinations and the tests necessary to verify whether, if the manufacturer has chosen to apply the relevant harmonized standards, these have actually been applied;

4.4. agree with the applicant on the place where the necessary examinations and tests will be carried out.

5. If the sample of the in vitro diagnostic device conforms to the provisions of this Regulation, the notified body shall issue to the applicant an EC type-examination certificate. The EC type-examination certificate must contain:

5.1. the name(s) and surname of the manufacturer, address of his residence and place(s) of business, if the manufacturer is a natural person; the name or business name, address of the registered office, if the manufacturer is a legal person,

5.2. conclusions of the examination, the conditions of validity and the data needed for the identification of the approved type.

The relevant parts of the documentation must be annexed to the EC type-examination certificate; a copy of the EC type-examination certificate and the relevant parts of the documentation annexed to the EC type-examination certificate shall be kept by the notified body.

6. The manufacturer shall inform the notified body which issued the EC type-examination certificate, without delay if it has obtained information about changes to the pathogen and markers of infections to be tested, in particular as a consequence of biological complexity and variability. In this connection, the manufacturer shall inform the notified body whether any such change is likely to affect the performance of the in vitro diagnostic device.

6.1. Changes to the approved in vitro diagnostic device must receive further approval from the notified body which issued the EC type-examination certificate wherever the changes may affect conformity with the essential requirements of this Regulation or with the conditions prescribed for use of the in vitro diagnostic device. The applicant shall inform the notified body which issued the EC type-examination certificate of any substantial change made to the approved in vitro diagnostic device. The additional approval must take the form of a supplement to the EC design-examination certificate.

7. Administrative provisions

Notified bodies may obtain a copy of the EC type-examination certificates and/or the supplements thereto. The annexes to EC type-examination certificates must be available to the other notified bodies on reasoned application, after the manufacturer has been informed.

Annex No. 6 to Government Regulation No. 453/2004 Coll.

EC VERIFICATION

1. EC verification is the procedure whereby the manufacturer or his authorized representative ensures and declares that the products which have been subject to the procedure set out in paragraph 4 of this Annex conform to the type described in the EC type-examination certificate and meet the requirements of this Regulation.

2. Procedure of the manufacturer
The manufacturer
   2.1. The manufacturer shall take all the measures necessary to ensure that the manufactured in vitro diagnostic devices conform to the type described in the EC type-examination certificate and comply with the requirements of this Regulation which apply to them,
      2.1.1. before the start of manufacture, the manufacturer shall prepare
         2.1.1.1. the manufacturing process, in particular as regards sterilization, where necessary,
         2.1.1.2. pre-established provisions which must be implemented to ensure homogeneous production,
         2.1.1.3. as required, also ensuring conformity of the in vitro diagnostic devices with the type described in the EC type-examination certificate and with the requirements of this Regulation which apply to them.
   2.2. Given the fact that certain conditions of the final testing according to paragraph 6.3 of this Annex are not appropriate, adequate process testing, monitoring and control methods shall be established by the manufacturer with the approval of the notified body. The provisions of paragraph 5 of Annex No. 4 to this Regulation shall apply accordingly in relation to the abovementioned approved procedures.

3. The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from in vitro diagnostic devices in the post-sales phase and to implement appropriate measures as referred to in paragraph 5 of Annex No. 3 to this Regulation.

4. The notified body
   4.1. The notified body shall carry out the appropriate examinations and tests pursuant to paragraph 2.2 of this Annex in order to verify the conformity of the in vitro diagnostic devices with the requirements of this Regulation, according to discretion of the manufacturer, either for
      4.1.1. every in vitro diagnostic device pursuant to paragraph 5 of this Annex, or
      4.1.2. for in vitro diagnostic devices selected on statistical basis pursuant to paragraph 6 of this Annex.
      When carrying out statistical verification according to paragraph 6 of this Annex, the notified body has to decide when statistical procedures for lot-by-lot inspection or isolated lot inspection have to be applied.
      Such decision must be taken in consultation with the manufacturer. In as far as the conduct of examinations and tests on a statistical basis is not appropriate, examinations and tests may be carried out on a random basis provided that such procedure in conjunction with the measures taken in

accordance with paragraph 2.2 of this Annex ensures an equivalent level of conformity.

5. Verification by examination and testing of every in vitro diagnostic device

The notified body shall

5.1. examine every in vitro diagnostic device individually in order to verify the conformity of every in vitro diagnostic device with the EC type described in the EC type-examination certificate and with the requirements of thus Regulation which apply to them. The notified body shall carry out the appropriate tests stipulated in the applicable harmonized standard(s) in accordance with Section 4 and, if necessary, perform equivalent tests,

5.2. affix, or have affixed, its identification number to each approved in vitro diagnostic device and draw up a written certificate of conformity relating to the tests carried out.

6. Statistical verification

6.1. The manufacturer shall present the manufactured in vitro diagnostic devices in the form of homogeneous batches;

6.2. The notified body shall take one or more random samples, as necessary from each batch. The in vitro diagnostic devices which make up the sample shall be examined and the appropriate tests defined in the relevant harmonized standard(s) referred to in Section 4 or equivalent tests shall be carried out to verify, where appropriate, the conformity of the in vitro diagnostic devices with the type described in the EC type-examination certificate and with the requirements of this Regulation which apply to them in order to determine whether to accept or reject the batch.

6.3. Statistical control of in vitro diagnostic devices shall be based on attributes and/or variables, entailing sampling schemes with operational characteristics which ensure a high level of safety and performance according to the state of the art in science and technology. The sampling scheme shall be established in accordance with the harmonized standards referred to in Section 5, taking account of the specific nature of the in vitro diagnostic devices in question.

6.4. If the notified body accepts batch, it shall affix, or have affixed, its identification number to each in vitro diagnostic device and draw up a written certificate of conformity relating to the tests carried out.

All in vitro diagnostic devices in the batch may be put on the market except any in the sample which failed to conform.

If the notified body rejects the batch, it shall take appropriate measures to prevent the batch from being placed on the market. In the event of frequent rejection of batches, the notified body may suspend the statistical verification.

The manufacturer may, on the responsibility of the notified body, affix the notified body's identification number during the manufacturing process.

Annex No. 7 to Government Regulation No. 453/2004 Coll.

EC DECLARATION OF CONFORMITY

(Production Quality Assurance)

1. The manufacturer shall ensure application of the quality system approved for the manufacture of the in vitro diagnostic devices concerned and carry out the final inspection, as specified in paragraph 3 of this Annex.
   The manufacturer is subject to the surveillance referred to in paragraph 4 of this Annex.
   The EC declaration of conformity is the part of the procedure whereby the manufacturer who fulfils the obligations imposed by this paragraph ensures and declares that the in vitro diagnostic devices concerned conform to the type described in the EC type-examination certificate and meet the provisions of this Regulation which apply to them.

2. The manufacturer shall
   2.1. affix the CE marking to in vitro diagnostic devices in accordance with Section 9, and
   2.2. draw up a declaration of conformity.

3. Quality system
   3.1. The manufacturer shall lodge an application for assessment of his quality system with a notified body. It shall include:
      3.1.1. the name(s) and surname of the manufacturer, address of his residence and place(s) of business, if the manufacturer is a natural person; the name or business name, address of the registered office, if the manufacturer is a legal person,
      3.1.2. the documentation and undertakings referred to in paragraph 3.1. of Annex No. 4 to this Regulation, and
      3.1.3. the technical documentation on the types approved and a copy of the EC type-examination certificate.
   3.2. Application of the quality system must ensure that the manufactured in vitro diagnostic devices conform to the type described in the EC type-examination certificate. All the elements, requirements and provisions adopted by the manufacturer for his quality system must be documented in a systematic and orderly manner in the form of written policy statements and procedures. This quality system documentation must permit uniform interpretation of the quality policy and procedures such as quality programs, quality plans, quality manuals and quality records.
      The documentation must include in particular an adequate description of:
      3.2.1. the manufacturer’s quality objectives;
      3.2.2. the organization of the business of the manufacturer and in particular
         3.2.2.1. the organizational structures, the responsibilities of the managerial staff and their organizational authority where quality of design and manufacture of the in vitro diagnostic devices is concerned,
         3.2.2.2. the methods of monitoring the efficient operation of the quality system and in particular its ability to achieve the desired quality of design and of in vitro diagnostic devices, including control of in vitro diagnostic devices which fail to conform;
      3.2.3. the inspection and quality assurance techniques at the manufacturing stage and in particular:

3.2.3.1. the processes and procedures which will be used, particularly as regards sterilization,

3.2.3.2. the procedures of evaluation of suppliers,

3.2.3.3. the procedures of identification of the in vitro diagnostic device drawn up and kept up to date from drawings, specifications or other relevant documents at every stage of manufacture;

3.2.4. the appropriate tests and trials to be carried out before, during and after manufacture, the frequency with which they will take place, and the test equipment used.

It must be possible to trace back the calibration.

3.3. The notified body shall

3.3.1. audit the quality system to determine whether it meets the requirements referred to in paragraph 3.2 of this Annex. It must presume that quality systems which implement the relevant harmonized standards conform to these requirements.

3.3.2. The quality system assessment team must have past experience of assessments of the technology concerned. The assessment procedure must include an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes.

3.3.3. After the audit, the notified person shall communicate the decision to the manufacturer or his authorized representative, including the conclusions of the inspection and a reasoned assessment.

3.4. The manufacturer shall inform the notified body which approved the quality system of any plan for substantial changes to the quality system.

The notified body must assess the changes proposed and verify whether after these changes the quality system still meets the requirements referred to in paragraph 3.2 of this Annex. It shall notify the manufacturer of its decision, which must contain the conclusions of the inspection and a reasoned assessment.

4. Surveillance

The provision of paragraph 5 of Annex No. 4 to this Regulation shall apply to surveillance.

5. Verification of manufactured in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation.

5.1. In the case of in vitro diagnostic devices covered by List A in Annex No. 2 to this Regulation, the manufacturer shall forward to the notified body without delay after the conclusion of the controls and tests the relevant reports on the tests carried out on the manufactured in vitro diagnostic devices or each batch of in vitro diagnostic devices. Furthermore, the manufacturer shall make the samples of manufactured in vitro diagnostic devices or batches of in vitro diagnostic devices available to the notified body in accordance with pre-agreed conditions and modalities.

5.2. The manufacturer may place the in vitro diagnostic devices on the market, unless the notified body communicates to the manufacturer within the agreed time-frame, but not later than 30 days after reception of the samples, any other decision, including in particular any condition of validity of delivered certificates.

Annex No. 8 to Government Regulation No. 453/2004 Coll.

STATEMENT AND PROCEDURES CONCERNING IN VITRO DIAGNOSTIC DEVICES FOR PERFORMANCE EVALUATION

1. For in vitro diagnostic devices for performance evaluation the manufacturer or his authorized representative shall draw up the statement containing the information stipulated in paragraph 2 of this Annex and ensure that the relevant provisions of this Regulation are met.

2. The statement shall contain the following information:
   - 2.1. data allowing identification of the in vitro diagnostic devices in question,
   - 2.2. an evaluation plan stating in particular the purpose, scientific, technical or medical grounds, scope of the evaluation and number of the in vitro diagnostic devices concerned,
   - 2.3. the list of laboratories or other persons taking part in the evaluation study,
   - 2.4. the starting date and scheduled duration for the evaluations and, in the case of in vitro diagnostic devices for self-testing, the location and number of (lay) persons involved,
   - 2.5. a statement that the in vitro diagnostic device in question conforms to the requirements of this Regulation, apart from the aspects covered by the evaluation and apart from those specifically itemized in the statement, and that every precaution has been taken to protect the health and safety of the users.

3. The manufacturer shall keep available for the competent authorities the documentation allowing an understanding of the design, manufacture and performances of the in vitro diagnostic device, including the expected performances, so as to allow assessment of conformity of the in vitro diagnostic devices with the requirements of this Regulation This documentation must be kept for a period ending at least 5 years after the end of the performance evaluation.
   The manufacturer shall take all the measures necessary for the manufacturing process to ensure that the in vitro diagnostic devices manufactured conform to the documentation mentioned in the first subparagraph.

4. The provisions on notifications pursuant to Section 11 shall apply to in vitro diagnostic devices intended for performance evaluation.

Annex No. 9 to Government Regulation No. 453/2004 Coll.

BASIC CRITERIA FOR NOTIFIED BODIES

The following criteria shall be used for granting authorization:

1. the notified body and the persons who are members of its statutory or other bodies, employees of the notified body, or persons who are responsible, on the basis of a contract, for evaluation and verification referred to in Annexes No. 3 to 7 to this Regulation (hereinafter "evaluation and verification") may not
   - 1.1. be the designer, manufacturer, supplier, installer or user of the evaluated and verified in vitro diagnostic devices,
   - 1.2. be the authorized representative of any of the persons referred to in paragraph 1 of this Annex,
   - 1.3. be directly involved in the design, construction, marketing or maintenance of the in vitro diagnostic devices, nor represent the parties engaged in these activities.

   The previous part of paragraph 1 of this Annex shall in no way prejudice the possibility of exchanges of technical information between the manufacturer and the body.

2. the notified body, its staff or, as appropriate, the persons who carry out, on the basis of a contract, evaluation and verification with the highest degree of professional integrity and the requisite competence in the field of in vitro diagnostic devices, must be free from all pressures and inducements, particularly financial, which might influence their judgment or the results of the inspection, especially from persons or groups of persons with an interest in the results of the verifications,

3. the notified body shall
   - 3.1. in case of subcontracting specific tasks connected with the establishment and verification of the facts, ensure that the subcontractor meets the provisions of this Regulation,
   - 3.2. keep at the disposal of the competent authorities or bodies the relevant documents assessing the subcontractor's qualifications and the work carried out by the subcontractor under this Regulation,
   - 3.3. be able to carry out all the tasks assigned to such bodies by one of Annexes No. 3 to 7 to this Regulation and for which it has been designated, whether these tasks are carried out by the body itself or on its responsibility,
   - 3.4. have the necessary staff and possess the facilities needed to perform properly the technical and administrative tasks entailed in assessment and verification.

     This includes, without limitation, the availability of sufficient scientific staff within the organization which possess adequate experience and knowledge necessary to assess the biological and medical functionality and performance of in vitro diagnostic devices for which it has been authorized, in relation to the requirements of this Regulation and, in particular, to requirements stipulated in Annex No. 1 to this Regulation,
   - 3.5. have access to the equipment necessary for the verifications required,

4. employees of the notified body or, as appropriate, the persons who are responsible, on the basis of a contract, for evaluation and verification must have
   - 4.1. due professional qualification covering all the assessment and verification operations, in the framework and within the scope of the granted authorization,

4.2. satisfactory knowledge of the rules on the inspections which they carry out and adequate experience of such inspections,

4.3. the ability required to draw up the certificates, records and reports to demonstrate that the inspections have been carried out,

5. remuneration of employees of the notified persons and, as appropriate, the persons who are responsible, on the basis of a contract, for evaluation and verification must not depend on the number of inspections carried out, nor on the results of the inspections,

6. the obligation of the notified body to conclude a third-party liability insurance policy is stipulated by the special regulation,[27])

7. the obligation of persons referred to in this Annex to maintain confidentiality of facts learnt by them in activities of the notified body is stipulated by the special regulation.[28])

[27]) Section 11 (3) of Act No. 22/1997 Coll., as amended by Act No. 71/2000 Coll.
[28]) Section 11 (2) (e) of Act No. 22/1997 Coll.

Annex No. 10 to Government Regulation No. 453/2004 Coll.

COMMON TECHNICAL SPECIFICATIONS FOR IN VITRO DIAGNOSTIC DEVICES

1. SCOPE

These Common Technical Specifications apply to the in vitro diagnostic devices referred to in List A in Annex No. 2 to this Regulation:

1.1. reagents and reagent products, including related calibrators and control materials, for determining the following blood groups:
ABO system, Rhesus (C, c, D, E, e) Kell (K),

1.2. reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

2. DEFINITIONS

For the purposes of this Annex:

Diagnostic sensitivity means the probability that the in vitro diagnostic device gives a positive result in the presence of the target marker.

A true positive specimen means a specimen known to be positive for the target marker and correctly classified by the in vitro diagnostic device.

A false negative specimen means a specimen known to be positive for the target marker and misclassified by the in vitro diagnostic device.

Diagnostic specificity means the probability that the in vitro diagnostic device gives a negative result in the absence of the target marker.

A false positive specimen means a specimen known to be negative for the target marker and misclassified by the in vitro diagnostic device.

A true negative specimen means a specimen known to be negative for the target marker and correctly classified by the in vitro diagnostic device.

Analytical sensitivity expresses, in the context of the common technical specifications, the limit of detection: i.e. the smallest amount of the target marker that can be precisely detected.

Analytical specificity expresses the ability of the method to determine solely the target marker.

Nucleic acid amplification techniques (hereinafter “NAT”) means tests for the detection and/or quantification of nucleic acids by either amplification of a target sequence, by amplification of a signal or by hybridization

Rapid test means those tests which can only be used singly or in a small series and which have been designed to give a rapid result for near patient testing.

The robustness of an analytical procedure means the measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

The whole system failure rate is the frequency of failures when the entire process is performed as prescribed by the manufacturer.

3. COMMON TECHNICAL SPECIFICATIONS FOR In vitro diagnostic devices DEFINED IN LIST A OF ANNEX NO. 2 TO THIS REGULATION

3.1. Common technical specifications for performance evaluation of reagents and reagent products for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C, D:

GENERAL PRINCIPLES

3.1.1. In vitro diagnostic devices which detect virus infections placed on the market for use as either screening and/or diagnostic tests, shall meet the same requirements for sensitivity and specificity (see Table 1).

3.1.2. In vitro diagnostic devices intended by the manufacturer for testing body fluids other than serum or plasma, e.g. urine, saliva, etc. shall meet the same requirements of the common technical specifications for sensitivity and specificity as serum or plasma tests. The performance evaluation must test samples from the same individuals in both the tests to be approved and in a respective serum or plasma assay.

3.1.3. In vitro diagnostic devices intended by the manufacturer for self-testing, must meet the same requirements of common technical specifications for sensitivity and specificity as respective in vitro diagnostic devices for professional use. Relevant parts of the performance evaluation shall be carried out (or repeated) by appropriate lay users to validate the operation of the in vitro diagnostic device and the instructions for use.

3.1.4. All performance evaluations shall be carried out in direct comparison with an established in vitro diagnostic device with acceptable performance. Once the CE marking of in vitro diagnostic devices is established, the in vitro diagnostic device used for comparison must be CE marked, if on the market at the time of the performance evaluation.

3.1.5. If discrepant test results are identified as part of an evaluation, these results shall be resolved as far as possible, for example:

3.1.5.1. by evaluation of the discrepant sample in further test systems,

3.1.5.2. by use of an alternative method or marker,

3.1.5.3. by a review of the clinical status and diagnosis of the patient, and by the testing of follow-up-samples.

3.1.6. Performance evaluations shall be performed on a population equivalent to the European population.

3.1.7. Positive specimens used in the performance evaluation shall be selected to reflect different stages of the respective disease(s), different antibody patterns, different genotypes, different subtypes.

3.1.8. For blood screening in vitro diagnostic devices (with the exception of HBsAg tests), all true positive samples shall be identified as positive by the in vitro diagnostic device to be CE marked (Table 1).
For HBsAg tests, the new in vitro diagnostic device must have an overall performance at least equivalent to that of the established in vitro diagnostic device (see paragraph 3.1.4). Diagnostic test sensitivity during the early infection phase (sero-conversion) has to represent the state of the art. Whether further testing of the same or additional sero-conversion panels is conducted by the notified body or by the manufacturer the results shall confirm the initial performance evaluation data (see Table 1).

3.1.9. Negative specimens used in a performance evaluation shall be defined so as to reflect the target population for which the test is intended, for example blood donors, hospitalized patients, pregnant women.

3.1.10. For performance evaluations for screening assays (Table 1), blood donor populations shall be investigated from at least two blood donation centers and consist of consecutive blood donations, which have not been selected to exclude first time donors.

3.1.11. In vitro diagnostic devices shall have a specificity of at least 99.5 % on blood donations, unless otherwise indicated in the accompanying tables. Specificity shall be calculated using the frequency of repeatedly false positive results in blood donors negative for the target marker.

3.1.12. In vitro diagnostic devices shall be evaluated to establish the effect of potential interfering substances, as part of the performance evaluation. The potential interfering substances to be evaluated will depend to some extent on the composition of the reagent and configuration of the assay. Potential interfering substances shall be identified as part of the risk analysis required by the essential requirements for each new in vitro diagnostic device but may include, for example:

3.1.12.1. specimens representing related infections;

3.1.12.2. specimens from multipara, i.e. women who have had more than one pregnancy, or rheumatoid factor positive patients,

3.1.12.3. for recombinant antigens, human antibodies to components of the expression system, for example anti-E. coli, or anti-yeast.

3.1.13. For in vitro diagnostic devices intended by the manufacturer to be used with serum and plasma the performance evaluation must demonstrate serum to plasma equivalency. This shall be demonstrated for at least 50 donations.

3.1.14. For in vitro diagnostic devices intended for use with plasma the performance evaluation shall verify the performance of the in vitro diagnostic device using all anticoagulants which the manufacturer indicates for use with the in vitro diagnostic device. This shall be demonstrated for at least 50 donations.

3.1.15. As part of the required risk analysis the whole system failure rate leading to false-negative results shall be determined in repeat assays on low-positive specimens.

3.2. **Additional requirements for NAT**

The performance evaluation criteria for NAT assays can be found in Table 2.

3.2.1. For target sequence amplification assays, a functionality control for each test sample (internal control) shall reflect the state of the art.
This control should as far as possible be used throughout the whole process, i.e. extraction, amplification/hybridization, detection.

3.2.2. The analytical sensitivity or detection limit for NAT assays shall be expressed by the 95 % positive cut-off value. This is the analyte concentration where 95 % of test runs give positive results following serial dilutions of an international reference material for example World Health Organization standard or calibrated reference materials.

3.2.3. Genotype detection shall be demonstrated by appropriate primer or probe design validation and shall also be validated by testing characterized genotyped samples.

3.2.4. Results of quantitative NAT assays shall be traceable to international standards or calibrated reference materials, if available, and be expressed in international units utilized in the specific field of application.

3.2.5. NAT assays may be used to detect virus in antibody negative samples, i.e. pre-sero-conversion samples. Viruses within immune -complexes may behave differently in comparison to free viruses, for example during a centrifugation step. It is therefore important that during robustness studies, antibody-negative (pre-sero-conversion) samples are included.

3.2.6. For investigation of potential carry-over, at least five runs with alternating high-positive and negative specimens shall be performed during robustness studies.
The high positive samples shall comprise of samples with naturally occurring high virus titres.

3.2.7. The whole system failure rate leading to false-negative results shall be determined by testing low-positive specimens. Low positive specimens shall contain a virus concentration equivalent to 3 x the 95 % positive cut-off virus concentration.

3.3. Common technical specifications for the manufacturer's batch release testing of reagents and reagent products for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C, D (immunological assays only)

3.3.1. The manufacturer's batch release testing criteria shall ensure that every batch consistently identifies the relevant antigens, epitopes, and antibodies.

3.3.2. The manufacturer's batch release testing must include at least 100 specimens negative for the relevant analyte.

3.4. Common technical specifications for performance evaluation of reagents and reagent products for determining the blood groups: ABO system, Rhesus (C, c, D, E, e) Kell (K)

Criteria for performance evaluation of reagents and reagent products for determining the blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell, are given in Table 9.

3.4.1. All performance evaluations shall be carried out in direct comparison with an established in vitro diagnostic device with acceptable performance. Once the CE marking of in vitro diagnostic devices is established, the in

vitro diagnostic device used for comparison must be CE marked, if on the market at the time of the performance evaluation.

3.4.2. If discrepant test results are identified as part of an evaluation, these results shall be resolved as far as possible, for example:

3.4.2.1. by evaluation of the discrepant sample in further test systems,

3.4.2.2. by use of an alternative method.

3.4.3. Performance evaluations shall be performed on a population equivalent to the European population.

3.4.4. Positive specimens used in the performance evaluation shall be selected to reflect variant and weak antigen expression.

3.4.5. In vitro diagnostic devices shall be evaluated to establish the effect of potential interfering substances, as part of the performance evaluation. The potential interfering substances to be evaluated will depend to some extent on the composition of the reagent and configuration of the assay. Potential interfering substances shall be identified as part of the risk analysis required by the essential requirements for each new in vitro diagnostic device.

3.4.6. For in vitro diagnostic devices intended for use with plasma the performance evaluation shall verify the performance of the in vitro diagnostic device using all anticoagulants which the manufacturer indicates for use with the in vitro diagnostic device. This shall be demonstrated for at least 50 donations.

3.5. **Common technical specifications for the manufacturer's batch release testing of reagents and reagent products for determining the blood groups: ABO system, Rhesus (C, c, D, E, e) Kell (K)**

3.5.1. The manufacturer's batch release testing criteria shall ensure that every batch consistently identifies the relevant antigens, epitopes, and antibodies.

3.5.2. Requirements for manufacturer's batch release testing are outlined in Table 10.