Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Paul-Ehrlich-Institut P.O. Box 63207 Langen, Germany

To:
All marketing authorisation holders of cellular blood products and therapeutic single plasma as well as holders of an authorisation for stem cells for haematopoetic reconstitution

For information only:
all participants in the graduated plan procedure

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Following the written hearing of the pharmaceutical companies by the Paul-Ehrlich-Institut (PEI) in the letters of 20 January 2010 and 21 December 2011 the following notification is issued:

Notification

Prevention of adverse effects of medicinal products

Imposition of conditions on the marketing authorisations for cellular blood components and fresh frozen plasma

Subject: **Imposition of conditions pursuant to Section 28 (3) c AMG (Arzneimittelgesetz, German Medicines Act) for the purpose of risk prevention to assure the safety of blood components for transfusion and of stem cell products for haematopoetic reconstitution: Testing for HIV, HBV and HCV**

1. Test methods for the examination of donors for the infection markers HIV, HBV and HCV (so-called donor screening) may be used in the manufacture of cellular blood components, therapeutic individual plasmas, and stem cell preparations for haematopoetic reconstitution, released onto the marketing after 01.10. 2013, only if proof has been provided by submitting the appropriate documents that they fulfil the requirements defined in Annex 1 of this notification, and if a batch test in conformity with Annex 2 has been performed for these methods.

2. All test methods used in the manufacture of cellular blood components, therapeutic individual plasmas, and stem cell preparations for haematopoetic reconstitution for the testing of donors for infection markers must be transmitted electronically by the pharmaceutical company to the "donor testing" database of the Paul-Ehrlich-Institut available on this web address: www.pei.de/ivd.

3. Other screening tests for HIV, HBV and HCV than those accepted by the Paul-Ehrlich-Institut and submitted to the "donor testing" databank may be used in the manufacture of blood and stem cell preparations only after prior consent from the Paul-Ehrlich-Institut.

4. Documents on the above mentioned screening tests currently used must be submitted to the Paul-Ehrlich-Institut by 1 July 2013. These shall provide proof that the requirements for determination of sensitivity and specificity (Annex 1) as well as batch-specific testing (Annex 2) have been fulfilled. After completion of the assessment with favourable results, the tests will be included in the "donor testing" database, and the applicants will receive a written confirmation that the above mentioned conditions have been fulfilled.

5. This notification does not apply to blood components which have been manufactured before 1 October 2013 but have not been released onto the market because the quarantine storage period has not yet expired. These products may be released onto the market if the result of the examination of a subsequent donation or blood sample of the same donor using a screening test fulfilling the requirements set forth in Sections 1 to 4 was negative.

Reasons

The measures ordered are based on Section 28 (3) c of the German Medicines Act (Arzneimittelgesetz, AMG). According to the AMG, the Paul-Ehrlich-Institut can decide among other things that in the control of the starting material of biological medicinal products, specific requirements be fulfilled if this is necessary for safeguarding the appropriate quality or for risk prevention.

The measure serves to ascertain that during the manufacture of blood components and stem cell products, the test methods for the detection of HIV, HBV, and HCV comply with the state of science and technology.

The Paul-Ehrlich-Institut considers this measure for the purpose of risk prevention as necessary, since it assures that the test methods used for donor screening fulfil the particular requirements for screening tests used in the manufacture of blood and stem cell preparations.

Implementation of the measure

Annex 1 lays down the requirements which test methods must fulfil if designed for donor screening during the manufacture of blood and stem cell preparations. The criteria listed take into account the current "Common Technical Specifications" (CTS) laid down in Directive 98/79/EC (Commission Decision of 27 November 2009 (2009/886/EC)) and concretise certain aspects required for a test for the medicinal products affected which meet the state of science and technology. Based on the requirements laid down in the above mentioned Directive, Annex 1 specifies how the current state of science and technology is defined and how the adherence to the requirements [specifications] can be guaranteed.

The requirements for the suitability of batches of the screening tests listed in Annex 1 are laid down in **Annex 2**.

Annex 3 concretises the requirements for the minimum sensitivity of serological screening tests using the reactivity of known seroconversion panels.

Annex 4 describes the documentation to be submitted to the PEI.

Pursuant to Section 2 of this notification, all screening tests currently used must be submitted electronically to the "donor screening" database by 1 July 2013 at the latest using the web address *www.tfg.pei.de/spendertestung*. The data are transmitted SSL encrypted and are not accessible to third parties.

The PEI checks whether the documents are available in conformity with Annexes 1 and 2, and requests the pharmaceutical manufacturer to submit any missing documents.

After checking the documents available on the notified tests, the PEI confirms the suitability of the tests pursuant to Section 1 of the regulation.

As from 1 October 2013 at the latest, only those tests for donor screening for HBV, HCV, and HIV are stored in the "donor testing" database which fulfil the requirements of this regulation.

An application must be made by the person authorised to communicate with the Paul-Ehrlich-Institut using the email address *transfusionsmedizin@pei.de* to obtain access to the "donor testing" database. For this purpose, the person authorised to communicate with the PEI must provide his/her last name and first name(s), phone number (extension) and email address in addition to the name of the pharmaceutical manufacturer.

A manual is available for the "donor testing "database. It is available for download using this internet address *www.pei.de/handbuch-spendertestung*.

Every change of the test system has to be reported electronically to the "donor testing" database. Additional documents may have to be submitted for NAT tests in conformity with the "Requirements for the validation or the routine operation of NAT for the detection of viral nucleic acids in blood donations (*www.pei.de/spendertestung).* If an institution intends to use screening tests other than those stored in the "donor testing" database, the full name of the test, the item number, and the name of the manufacturer must be entered into the databank by the person authorised (see above) for the notification of change. The person authorised will receive an email containing a template generated from the data entered for change notifications pursuant to Section 29 (2) a AMG, which must be signed and transmitted to the PEI.

The screening tests stored in the "donor testing" database are checked continuously by the Paul-Ehrlich-Institut in conformity with the current state of science and technology. The method used for this purpose and the definition of the current state of science and technology for the individual testing parameters are presented in Annex 3. The same also applies to all in-house NAT tests and CE marked quantitative NAT test systems currently used in donor screening, assessed by the Paul-Ehrlich-Institut and accepted. If a test does not fulfil the criteria defined, and if it is thus planned to remove this test from the databank of accepted tests, the graduated plan representative and the parties taking part in the graduated plan from all institutions affected will be informed that the resulting nonfulfillment of the of condition pursuant to Section 30 (2) number 2 AMG referenced here will lead to a revocation of the marketing authorisation unless the test affected is replaced by another suitable test defined pursuant to this this imposition of conditions.

Information on legal remedies available:

Formal objection against this notification can be lodged within a month after its announcement. The opposition must be addressed to the Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Paul-Ehrlich-Straße 51-59, 63225 Langen, Germany, in writing or recorded for transcription.

Langen, 1 January 2013

Prof. Dr. Klaus Cichutek

Paul-Ehrlich-Institut
– Federal Institute for Vaccines and Biomedicines -

Annexes:

Annex 1: Requirements for the determination of sensitivity and specificity of test methods used in the manufacture of blood and stem cell preparations for the donor screening for HIV-1/2, HBV and HCV

Annex 2: Requirements for the batch related documentation of the test methods listed in Annex 1

Annex 3: Requirements for the determination of the seroconversion sensitivity of serological HIV-1/2, HB, and HCV tests used as donor screening tests in the manufacture of blood and stem cell preparations

Annex 4: Requirements for the documentation to be submitted for test methods for the donor screening for HIV, HBV und HCV

Annex 1: Requirements for the determination of sensitivity of screening tests used in the manufacture of blood and stem cell preparations for the donor screening

<table>
<tr><th>Parameter</th><th>Seroconversion sensitivity</th><th>Diagnostic sensitivity</th><th>Analytical sensitivity</th><th>Genotype, subtype, mutant recognition</th></tr>
<tr><td>Anti-HIV-1/2 ab</td><td rowspan="4">The sensitivity must be determined for all HIV, HCV and HBsAg screening tests during the early infection phase (seroconversion) by testing of 30 seroconversion panels at short intervals between the blood extractions in the range in which the seroconversion takes place in comparision with a test with acceptable performance (see Annex 3).

The sensitivity detected must conform to the state of science and technology determined by the Paul-Ehrlich-Institut (see Annex 3). Besides, for anti -HCV ab and HCV ag/ab tests, a balanced recognition of anti-core and anti-NS3 must be present.</td><td rowspan="3">The diagnostic sensitivity must be tested in 400 positive samples and, in addition, for HIV in 100 anti-HIV-2 ab positive samples obtained from different stages of the disease and taking into account the variability of the pathogenic agent in accordance with CTS Table 1.

The test must show a positive result for all samples confirmed in a Western blot or line assay.</td><td>Not usable</td><td>▪ Sensitivity for HIV-1 subtype group M comparable with subtype B
▪ For HIV-1 Group O and for HIV-2, the test must be positive at least for samples serologically confirmed positive.</td></tr>
<tr><td>HIV ag/ab</td><td>HIV-1 p24 antigen ≤ 2 IE/ml referred to WHO standard (90/636)</td><td>▪ Sensitivity for HIV-1 p24 ag of subtype group M comparable with subtype B,
▪ Reactivity for HIV-1 group O should be present
▪ Detection of HIV-2 must be proved</td></tr>
<tr><td>Anti-HCV ab and HCV ag/ab</td><td>Not usable</td><td>▪ Recognition of HCV genotypes 1-6</td></tr>
<tr><td>HBsAg</td><td>For HBsAg, the test should show an overall performance which conforms to the state of technology.</td><td>< 0.1 IU/ml referred to WHO standard (00/588)</td><td>▪ Sensitivity for HBV genotypes and/or HBsAg subtypes should be comparable with genotype A
▪ Recognition of known HBsAg mutants.</td></tr>
</table>

Parameter	Seroconversion sensitivity	Diagnostic sensitivity	Analytical sensitivity	Genotype, subtype, mutant recognition
Anti-HBc Ab	Examination of several seroconversion panels with Anti-HBc ab course with appropriate informational value. The sensitivity determined must comply with the state of technology laid down by the Paul-Ehrlich-Institut (see column 4, analytical sensitivity).	The diagnostic sensitivity shall be examined on 400 positive samples pursuant to CTS Table 1. All samples which are simultaneously positive for anti-HBe ab and/or anti-HBs ab must be recognised (100% sensitivity). Isolated anti-HBc ab positive samples must be tested with at least 2 additional anti-HBc ab tests for comparison and for clarification.	< 1.40 IU/ml referred to the WHO standard (95/522)	▪ Not to be used
HCV-RNA **HIV-1-RNA** **HBV-DNA**	Samples from the pre-seroconversion phase analogous with the requirements of the CTS for qualitative NAT tests (10 seroconversion panels, each starting with a negative sample and with intervals < 7 days between the blood extractions)	Routine samples in comparison with another CE-marked procedure. No failure to detect virus genome positive samples at concentrations above the defined sensitivity limit, examination of the influence of potentially NAT inhibiting agents/substances. Regular detection of 5,000 IU HCV-RNA/ml or 10,000 IU HIV1-RNA/ml in the individual donation. For the calculation of the sensitivity, 3 x 95% LOD is used as basis.	To be determined as 95 % LOD in IU/ml (WHO standard)	Recognition of prevalent virus genotypes and subtypes with a sensitivity analogous with the appropriate WHO standards

***** With regard to the specific requirements during the manufacture of blood and stem cell preparations, the Paul-Ehrlich-Institut determines the current state of science and technology on the basis of comparable examinations of available test systems and develops the appropriate test criteria. These criteria are then published. .
ag = antigen; ab = antibody, CTS = Common Technical Specifications

Explanations for Annex 1

· Parameter HBsAg
The analytical sensitivity required from the GTS of <0.13 IU/ml corresponds to the 0.1 IU/ml required by the PEI plus an error variation of 0.03 IU/ml, involving the usual variations between batches of HBsAg tests. Since the state of technology for seroconversion sensitivity also correlates with the 0.1 IE/ml, an adjustment of the analytical sensitivity is justified.

· Parameter anti-HBc-Ab
With the early detection of anti-HBc, an overlap with the detection of HBsAg shall be guaranteed to prevent a second diagnostic window from developing. Due to the limited availability of seroconversion panels with anti-HBc course, the use of a seroconversion panel with anti-HBc course can be performed without the need of indicating the exact number of panels. > 10 panels can currently be acquired from commercial panel suppliers.
The diagnostic sensitivity shall be established on 400 positive samples. These samples must be selected in such a way that they reflect different stages of the infection (both the acute HBV stage with HBsAg detection, and the chronic stage with missing HBsAg detection; this corresponds to CTS principle 3.1.7). In general, those rules apply which are described in the CTS (Basic principle 3.1.5 Evaluation of deviating test results with the aid of the use of an alternative method or markers). The requirement for 100% sensitivity refers to samples which test positive for anti-HBe ab and/or anti-HBs ab simultaneously. This corresponds to CTS Table 1 (Diagnostic sensitivity / positive samples / including evaluation of other HBV markers).
For samples with anti-HBc as the only positive HBV marker (isolated anti-HBc Ab positive samples), which react with a result near the limit (borderline) or negative in anti-HBc tests, the result must be verified with at least 2 additional anti-HBc Ab tests. This is in keeping with CTS principle 3.1.8.2 and GTS principle 3.1.5.
In the meantime, the WHO has provided an international anti-HBc standard (NIBSC Code 95/522). The limit value specified as < 1.40 IU/ml presents an adaptation to the introduction of the new international Anti-HBc standard.

· Parameters Anti-HCV and HCV ag/ab:
The development of antibodies against HCV starts against HCV core or HCV NS3 antigen at ratios of about half each. The selection of the seroconversion panel for diagnostic testing of the anti-HCV recognition should take into account this fact. Reasons for the requirement are firstly to provide proof for sufficient sensitivity in the early phase of infection also for anti-NS3, and secondly, to prevent anti-HCV or HCV ag/ab combination tests from being used which display insufficient recognition of so-called "NS3 only samples". This is in keeping with CTS principle 3.1.7 and Table1.
The definition of the HCV genotypes was performed in derogation of the CTS, since HCV genotype 5 predominantly exists in South Africa, while genotype 6 is more widespread and shows better availability.

· Parameters anti-HIV-1/2 ab and HIV ag/ab :
The confirmation of a reactive HIV screening test by immunoblots conforms to the standard for HIV diagnostics. In conformity with CTS principle 3.1.8.3., a positive result must be shown for all samples of HIV seroconversion. For the detection of HIV p24 antigen in the case of the combined HIV antigen/antibody tests, reactivity must be tested for different HIV-1 subtypes including Group O and the detection of HIV-2 (CTS principle 3.2 and Table 5). Information shall be provided for the cross-reactivity with the HIV-2 p26 antigen.

Annex 2. Requirements for batch control testing of the donor screening tests listed in Annex 1

Requirements	**Documentation to be submitted**
Guarantee of homogenous quality by ▪ batch-related, ▪ manufacturer independent and ▪ experimental testing by involving ▪ a (contract) laboratory of the Notified Body or ▪ an ISO 17025 or ISO 15189 accredited testing laboratory or a laboratory of the manufacturer and recognised by a competent authority in conformity with the following test criteria: CTS General principle 3.4	▪ Exact description of the test methodology, samples to be tested, and test criteria ▪ Sensitivity: analytical detection limit (e.g. NAT, Ag tests) or ▪ Accuracy (e.g. for antibody tests) ▪ Precision

Annex 3: Requirements for the determination of the seroconversion sensitivity of serological HIV-1/2, HCV and HBV tests used as donor screening tests in the manufacture of blood and stem cell preparations

The sensitivity of the screening tests to be used for the blood donation in the manufacture of blood and stem cell preparations must be determined on at least 30 suitable seroconversion courses. The sensitivity must conform at least to the state of technology determined by the Paul-Ehrlich-Institut. The panels shall be selected in compliance with the requirements of the CTS (Annex 1) and should fulfil CTS requirements 3.1.8.1. For HIV CTS requirements 3.1.8.3 also apply.

1. Minimum sensitivity of HIV tests (anti-HIV-1/2- and HIV-ag/ab combination tests) with seroconversions:

Examples of suitable HIV seroconversion courses used to determine the minimum sensitivity include:

- SeraCare/BBI PRB927, PRB929, PRB930, PRB932, PRB939 Ext, PRB952, PRB965, PRB966 and ZeptoMetrix 6240, 6243, 6244, 6245, 6246, 6247, 6248, 9022, 9010, 9012, 9014, 9017, 9018, 9034, 9033, 9021, 9020, 9023, 9025, 9032, 9030 and 12007.

Altogether, these panels contain 341 single extractions. With the exception of panel PRB930, all panels at least start with an HIV-1 p24 antigen and an HIV antibody negative blood extraction. 29 panels contain HIV-1 p24- and/or antibody containing samples and are suitable for both HIV ag/ab combination tests and for anti-HIV-1/2 tests. Solely panel 9025 does not contain any antibody reactive samples. With very sensitive HIV-ag/ab tests, up to 134 samples can be detected as reactive for HIV-1 p234 antigen and/or HIV antibody for the panels listed. Sensitive anti-HIV-1/2 tests can recognise up to 89 single extractions.

An anti -HIV-1/2 test which would still be acceptable would in this panel selection have to recognise at least 65 samples as reactive (this is equivalent to 49 % of the samples detectable with HIV ag/Ab tests i.e. 73 % of the anti-HIV-1/2 ab positive samples).

The requirements for the analytical sensitivity of HIV ag/ab combination test for HIV-1 p24 antigen is described in Annex 1.

2. Minimum sensitivity of HBsAg tests with seroconversions:

Examples for suitable HBV seroconversion courses are:

- SeraCare/BBI PHM903, PHM911, PHM914, PHM916, PHM925, PHM926, PHM927, PHM928, PHM929, PHM930, PHM931, PHM932, PHM934, ZeptoMetrix 6271, 6272, 6273, 6274, 6275, 6279, 11000, 11001, 11002, 11003, 11006, 11007, 11008, 11009, 11011, 11012 and 11013.

Altogether, these panels contain 331 single extractions. With sensitive HBsAg tests, 184 samples can be detected as reactive with these panels. A test which would still be acceptable would have to recognise at least 107 samples (58 %) as positive.

The requirement for the analytical sensitivity of HBsAg tests is described in Annex 1.

3. Minimum sensitivity of anti-HCV ab tests:

To determine the minimum sensitivity of anti-HCV ab tests, seroconversion courses should be selected which show different antibody patterns (e.g. anti-NS3 first, anti-core first and mixed antibody profiles). Panels showing exclusively antibodies against NS3 in the early phase of the infection should be present in a representative number.

The following HCV seroconversion panels could be suitable:

- HCV panels which only show antibodies against core:

  SeraCare/ BBI PHV#: 909, 912, 913, 914, 918, ZeptoMetrix 6216, donor 66011

- HCV panels which only show antibodies against NS3:

SeraCare/ BBI PHV#: 904, 905, 915; ZeptoMetrix 6212, 6224, 6225, 6228, 9047, donor 65345, donor 64273

- HCV panel which show mixed antibody profiles during seroconversion:

  SeraCare/ BBI PHV#: 906 (NS3/NS4), 907 (Core/NS3), 908 (NS3/NS4), 910 (Core/NS3/NS4), 916 (NS3/NS4), 919 (Core/NS3), 920 (Core/NS3); ZeptoMetrix 6211 (NS3/NS4), 6213 (NS3/Core), 6214 (NS3/NS4), 6222 (NS3/Core), 6226 (NS3/NS4/Core), 6227 (NS3/Core/NS5/NS4), 6229 (NS3/Core/NS5), 9045 (donor 64150; Core/NS4), 9054 (donor 66626; Core/NS3), 9055 (donor 66732; Core/NS3/NS4), and donor 77890 (Core/NS3/NS4).

The determination of the antibody profiles of the seroconversion panels was performed using CHIRON RIBA HCV 3.0 SIA. The sequence of the antigens given in brackets reflects the sequence of the antibodies which occurred in the course of the seroconversion.

Altogether, all HCV panels contain 337 single extractions. With these panels, 128 samples maximum (100%) can be detected as reactive using very sensitive anti-HCV-ab tests. An anti-HCV-ab test which would still be acceptable would have to recognise at least 90 samples (70%) as positive with this panel selection.

Since there are anti-HCV tests with a weakness in the recognition of samples and seroconversions, which show only antibodies against NS-3 in the course observed, these "NS3 panels" are again observed separately here. Altogether, the so-called "NS3 panels" contain 87 single extractions out of which 37 (100%) can be recognised as positive using the most sensitive anti-HCV tests. A test acceptable for blood donations should recognise 26 (70%) tests minimum of the anti-NS3 positive samples as reactive.

A definition of the analytical sensitivity of HCV ag/ab tests is currently not possible.

The panels listed are examples of test panels with which the seroconversion sensitivity can be sufficiently accurately determined. The panels presented have been examined comparatively using a variety of available serological donor screening tests and reflect the current state of technology, i.e. they form an objective basis for the data. An important basis for providing proof that the tests fulfil the current state of technology is CTS principle 3.1.4 and 3.1.8., i.e. the direct comparison with a product which complies with the state of technology and the fact that the diagnostic sensitivity of products complies with the state of technology during seroconversion.

Annex 4: Requirements for the documentation to be submitted for test methods for donor screening for HIV, HBV, and HCV.

The central reference documentation must contain summary data on each donor screening test used in the manufacture of blood and stem cell preparations for donor screening. In particular, the documentation should include the following:

1. Manufacturer of the test procedure, and distributor in Germany, if applicable.
2. Name of test as indicated on the container and package labels, as well as instructions for use.
3. A description of the test principle which provides sufficient informational value:
   - For serological donor screening tests:
     including the precise description of the immunological components used.
   - For NAT tests:
     extraction, amplification, and detection methods must also be indicated (including optional methods)
4. A listing of equipment systems for which the test was validated.
5. A current version of the instructions for use.
6. Data and reports from the studies on performance assessment processed in conformity with the requirements of the design dossier pursuant to Annex IV of Directive 98/79/EC.

   The data should provide proof that

   - the Common Technical Specifications (CTS) are stipulated in concrete terms pursuant to Commission Decision 2009/886/EC by additional requirements pursuant to Annex 1 of this notification and
   - the underlying requirements contained in Annex I Section A 3 of Directive 98/79/EC

   are fulfilled.