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:
The marketing authorisation holders of cellular blood products and fresh frozen plasma and the holders of authorisations for stem cell preparations pursuant to Section 21a AMG

CC:
Persons involved in the graduated plan

Der Präsident

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15 June 2012

Instruction to implement measures for risk minimisation in using HIV-1 NAT test systems

Dear Sir or Madam,

Subsequent to the written hearing by the Paul-Ehrlich-Institut of 2 November 2011, the following

notification

is issued.

HIV-1 NAT (nucleic acid amplification technique) tests for donor screening, used in the manufacture of cellular blood components, therapeutic individual plasma, and stem cell preparations for haematopoetic reconstitution released for marketing after 1 January 2015, must be suitable to rule out or compensate for any possible under-detection and/or non-detection of a target region. A possible approach could be the use of dual-target NAT tests in which two (or more) different sections of the HIV genome are amplified and detected. The method must be conceived in such a way that it fulfils the PEI's requirements for the minimum sensitivity for all amplified gene regions. This minimum sensitivity currently involves the reliable detection of an HIV-1-RNA concentration of 10,000 IU/mL minimum, referred to a single donation; reference material: 2nd WHO International Standard for HIV-1-NAT assays; NIBSC code 97/650; 5.56 $\log_{10}$ HIV-1-RNA IU/vial or 3rd WHO

International Standard for HIV-1-NAT assays; NIBSC code 10/152; 5.27 $\log_{10}$ HIV-1-RNA IU/vial), whichever applies.

This notification does not apply to blood components which have been manufactured before 1 January 2015 but have not been released for marketing because the quarantine storage period has not yet expired. These products may be released for marketing if the result of the examination of a subsequent donation or blood sample of the same donor using an HIV-1 NAT test system fulfilling the requirements set forth in this notification was negative.

Reasons:

In the past few years, several cases from the field of blood donor screening were reported to the PEI in which, despite high viral RNA concentrations, HIV-1-RNA positive donors were not detected by the NAT test. In this context, two confirmed transmissions of the virus to the recipients of blood products were reported. It could be shown that due to a limited binding capacity of one of the primers ("mismatch") present in the test systems used, the target viral nucleic acid was not sufficiently amplified and therefore not detected. These cases were due to new HIV-1 variants unknown at the time of designing these test systems. The design of all inadequately performing HIV-NAT test systems was conceived in such a way that only one region of the HIV-1 genome was targeted (so-called mono-target NAT tests). To enable a systematic assessment of potential problems blood donor centres involved were requested within an exchange of information procedure (graduated plan procedure, step I) to document all cases of false-negative or under-detecting HIV NAT. The questionnaires of the PEI were answered by altogether 51 blood donor centres by early 2011.

Between 2007 and the end of 2010 a total of 17 cases were reported to have shown negative results in an HIV-NAT test for donors who were proved to be HIV infected (3 to 5 cases per year). In 14 of the 17 cases, the serological screening test was positive, and the donations were not released for further processing. In two cases of negative NAT and negative serological screening testing, blood products were released and caused HIV transmissions to the recipients. In another case, no transmission of the virus occurred despite the transfusion of the blood component from an HIV infected donor. With regard to the donors tested and the reports for the period from 2007 to 2010, the frequency of HIV transmissions is one per 9.64 million donations.

A meeting at PEI was performed on 8 June 2011 with experts from blood donor centres, virological institutes, manufacturers of tests, and the PEI concluded the consensus that a very high safety standard has already been achieved by the combination of serological and NAT donor testing. The above-described cases, however, raise the question of a potential increase in the risk of HIV-1 variants by new mutations which cannot be reliably detected by means of the currently used NAT screening tests. In the event of unfavourable circumstances, both an under-detection of the virus concentration and a non-detection of the HIV genomes may occur. According to assessments of experts from virological institutes who take care of HIV infected patients, virus variants are observed detected insufficiently by CE-marked HIV-NAT tests. Both under-detection of virus concentration and non-detection of the HIV genomes tested were observed. According to the virological institutes the significance of these test results for blood donor screening is still open. It must be assumed that HIV variants characterized by new mutations will enter donor populations, too. A regular assessment of public sequence databases (such as the "Los Alamos National Laboratory HIV Sequence Database") is only of limited benefit for the determination of future risks. Publication of viral sequence data follows current epidemiologic developments with considerable delay. Besides, in many studies of nucleic acid sequences, the scientific interest focuses more on therapy relevant HIV genome areas and less on new NAT relevant mutations. In addition, a statement concerning future epidemiological developments of HIV or virus genome sections particularly affected by mutations would not be possible, even with the aid of sequence databases.

Strategies for improving the safety in NAT testing

Strategies were discussed with the background of the 17 documented NAT false-negative cases despite proven HIV infection. It should be taken into account that based on the positive serological result, an HIV infection was recognised in 14 out of the 17 donors, and blood components subsequently not released for transfusion. Thus, in several cases, no follow-up testing with other NAT test systems was performed and additional test results are not available to the PEI.
In three cases, follow-up testing showed a virus RNA concentration of > 2,000 IU/mL at the time of the blood donation, which is still below the minimum detection limit currently required by the PEI. In five cases, a concentration of > 10,000 IU/mL was determined by an alternative mono-target NAT test. In the case of a so-called "elite controller", no HIV-1-RNA was detected using several sensitive HIV-NAT test systems. In six cases, HIV-1-RNA was detected in the follow-up test with the pool size maintained and using a so-called dual-target NAT test.

One of the possible activities discussed to improve viral safety included higher minimum sensitivity in NAT testing. The appropriate increase in the minimum sensitivity of currently 10,000 IU HIV1 RNA/mL to for instance 1,000 I/mL would reduce the diagnostic window by only 2.2 days (corresponding to the doubling period for HIV-1 of 17 h in the diagnostic window). Documented cases can be used to show that this measure would have led to a favourable result in only three of the 17 cases addressed. Even though this measure would have a possible benefit, it would also involve a marked increase in the cost of NAT testing caused by the increase in sensitivity, e.g. by reducing the pool-size. Furthermore, HIV positive donors with the target region not detected by a mono-target NAT test due to a "mismatch" could not be safely recognised using this method.

Since an improved level of sensitivity could be established with most serological combination tests (detectingHIV1/2 antibodies and p24-antigen), when compared to antiHIV1/2 tests, the strict use of HIV combination tests was discussed as another possible option for donor screening. However, the analysis of the 17 documented cases was unable to provide proof of an additional benefit of this measure. In 14 of 17 cases, HIV-positive donors could already be detected using an anti-HIV1/2 test. For two HIV transmissions, however, an HIV infection was detected neither by means of an HIV1/2 antibody test nor an HIV antigen/antibody test.

The documented cases turned out to represent predominantly male donors aged between 18 and 44 years, giving rise to the assumption that some of the donors may show certain risk behaviour. The benefit of extensive interviewing of donors with regard to risk behaviour was therefore discussed as a third possible intervention. However, it was agreed that even by means of extensive interviewing, possible risk behaviour will not be established with certainty, since it cannot be ruled out that some donors obviously withhold consciously information on their risk behaviour.

From the point of view of the PEI, the use of dual-target HIV NAT tests is a feasible strategy, the efficacy of which can be proven for part of the cases documented (for the period from 2007 – 2010). Several IVDmanufacturers already have dual-target HIV-NAT tests at their disposal and/or are in a position to market or will be marketing the appropriate test systems in the foreseeable future. A disproportionate rise in the costs is not expected in the event of a change in the method with the sensitivity requirement remaining constant, since pool sizes would remain unaltered. A possible disadvantage of a "dual target strategy" being defined as binding is above all seen in the fact that this would tie users down to just one technological solution. Thus, this measure could limit or even prevent any other possible approaches.

In this context, the PEI sees a justified concern and invites all parties involved to suggest other concepts of test systems as possible options which could be suitable to rule out or compensate for a possible under- or non-detection of a target region.

Besides, concern has been raised that the benefit of a dual-target NAT test has up to now only been established in theory, but that the appropriate proof cannot be provided, e.g. by using suitable test panels. The data available to the PEI, however, show a benefit of the dual-target test in six of the 17 cases reported. Furthermore, the measure shall serve as risk prevention and thus refers to a potential and therefore future risk. The efficacy of the measure can therefore only be reliably assessed within the framework of further epidemiological developments.

Feasibility of the dual-target strategy

Considering development and CE marking of the NAT tests required as well as the implementation of the tests in blood donor screening, an implementation period of 30 months has been defined for the measure.

Analogous with existing procedures in Germany, PEI accepts both CE marked qualitative NAT screening tests and correspondingly validated quantitative NAT tests or in-house developments. The requirements defined in this graduated plan concern all tests alike.

PEI defines those NAT tests as dual-target tests in which two different amplicons are created and detected for the identification of a target structure (here: HIV-1-RNA). In this definition, PEI has refrained consciously from detailed specifications, e.g. with regard to separated or non-separated (multiplex) amplification and detection approaches or with regard to the selection of target regions. In the validation studies proof must be provided that the failure of one region can be compensated for. Since respective naturally occurring virus variants will be available only for few cases, validation studies may use in vitro transcribed RNA fragments or a an unlabelled probe (for one of the target regions).

Adherence to the Common Technical Specifications pursuant to 98/79/EC concerning qualitative HIV-NAT following the dual-target approach should be proven, e.g. using international reference preparations. The validation of tests manufactured and used in-house shall be performed accordingly. For dual-target HIV NAT test systems based on distinct approaches, proof of fulfilment of the requirements shall be provided for each target region.

Information on legal remedies available:

This administrative act is considered as published within two weeks after publication in the federal law gazette.

Protest can be lodged against this notification within a month after its announcement. The protest 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.

Professor Dr K. Cichutek

Note:

If the requirement has been implemented, the Paul-Ehrlich-Institut shall be informed on this by means of a variation concerning the donation master file or concerning the individual medicinal products, as the case may be, pursuant to Section 29 (1) sentence 1 German Medicines Act (Arzneimittelgesetz AMG) before 1 January 2015.