REPORTING AND INTERPRETING BIOLOGICAL TESTS CARRIED OUT ON SAMPLES FROM DONORS OF HUMAN BODY MATERIAL.

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In this scientific advisory report on public health policy, the Superior Health Council of Belgium issues recommendations on how to interpret (optional and mandatory) biological tests that are carried out as part of the selection of donors of human body material as well as on how to report the results of these tests.
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1. INTRODUCTION

The Royal Decree (RD) of 28 September 2009 setting standards of quality and safety for the donation, harvesting, procurement, testing, processing, storage and distribution of human body material that the banks for human body material, the intermediary structures and the production establishments must comply with, describes, among other things, the biological tests that need to be carried out among living and deceased donors.

For some serological parameters, interpreting their results may turn out to be a complex issue, giving rise to doubts and/or uncertainties.

Uncertainty about the interpretation of serological test results currently leads to the sometimes unjustified cancelling of planned donations or the rejection of harvested HBM, whilst more sophisticated diagnostic algorithms would still allow the use of organs or tissues that would otherwise have been rejected.
In this advisory report, the Superior Health Council (SHC) has decided to examine both the mandatory serological tests (anti-HIV-1,2, HBsAg3, anti-HBc4, anti-HCV5 and the syphilis screening test) as well as the optional serological tests (CMV6, toxoplasmosis, EBV7, HTLV8). The Council also drew up practical recommendations for the interpretation of test results in the form of diagnostic tables. A second goal is to provide recommendations as regards the reporting of serological test results.

Viruses such as the West Nile virus, Chikungunya, Ebola, Zika etc. will not be discussed in this advisory report. Indeed, having already issued advisory reports on these subjects, the SHC refers to the latter documents as well as to the circulars of the Federal Agency for Medicines and Health Products (FAMHP), which set out the measures that need to be implemented in relation to these infectious agents as well as the relevant biological tests to be carried out by HBM banks when selecting donors. In all cases, this concerns optional tests, which are often only relevant during a specific period of time, i.e. when there is an increased prevalence of the infection in question.

This advisory report does not deal with any other tests than those mentioned above. It focusses on the interpretation and reporting of serological tests carried out within the legal framework of the Royal Decree of 28 September 2009. It does not consider these tests for any other diagnostic purposes, and therefore does not look at tests performed in the context of e.g. organ donation.

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2 Anti-HIV-1,2: antibodies to the human immunodeficiency virus 1,2
3 HBsAg: hepatitis B surface antigen
4 Anti-HBc: antibodies to hepatitis B core antigen
5 Anti-HCV: antibodies to hepatitis C virus
6 CMV: cytomegalovirus
7 EBV: Epstein-Barr virus
8 HTLV: Human T cell leukemia/lymphoma virus type
2. CONCLUSION

General discussion:

- The HBM bank concerned and the laboratory must have signed an agreement which, among other things, describes the tests used, turnaround time and reporting.

- In vitro diagnostic tests are generally validated for use on serum or plasma. If they are run on other biological fluids or on the tissues themselves, they must have been validated for the material in question. The blood samples may come from deceased or living donors and can be obtained via the venous, arterial or intracardiac route. As regards deceased donors, the samples available should, ideally, be ante-mortem samples or post-mortem samples taken within 24 hours after death. If post-mortem samples are used, the test needs to have been validated for post-mortem blood samples. If the potential donor suffered massive blood loss shortly before the donation and received a transfusion of donor blood, blood components, colloids or crystalloids, an algorithm should be used to assess the degree of haemodilution. If plasma dilution turns out to exceed 50%, the tests used must have been validated for this type of plasma or a pre-transfusion sample must be used. Pooling should be avoided.

- In addition to the mandatory tests, additional tests can be carried out depending on the donor, the type of tissue and the prevalence of the infection concerned.

- If the test results are positive, the HBM will usually be rejected. In some cases (e.g. past HBV\(^9\) infection, autologous donation or donation between partners), HBM from donors with positive test results can still be released. Once confirmed positive, the general practitioner or attending physician informs the donor or their survivors about the results of the tests.

- Given the fact that the risk of HBM-donor-derived transmission of infection cannot be ruled out entirely, it is advisable to mention this when providing information to the potential recipient.

Anti-HIV-1,2:

- The use of 4\(^{th}\) generation anti-HIV-1,2 immunoassays, which have a shorter "window period", is recommended. These 4\(^{th}\) generation immunoassays not only detect antibodies to HIV-1,2, but also the HIV-1\(^{10}\) p24 antigen. These 4\(^{th}\) generation tests are already being commonly used.

- In the event of non-negative (borderline or positive) results, the results report must clearly state whether this concerns a screening or a confirmatory test.

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\(^9\) HBV : Hepatitis B virus  
\(^{10}\) HIV : human Immunodeficiency Virus
HBV-serology:
- In the event of a positive anti-HBc test, it is of paramount importance to carry out a quantitative interpretation of anti-HBs\textsuperscript{11} antibody screening results for its final interpretation and hence for releasing the tissues.

Anti-HCV:
- If HCV antibody testing has yielded positive results but screening for HCV RNA\textsuperscript{12} has yielded negative results, further evidence in support of considering the initial result of the anti-HCV test as false-positive can be obtained on the basis of a specific additional serological assay performed with a different technique and/or the analytical result of some initial anti-HCV tests.

Syphilis:
- In the serological diagnosis of syphilis and independently of the screening algorithm used, a confirmatory test will always need to be carried out if the screening test is positive.

- To maximise the safety of HBM intended for donation, it is advisable to combine treponemal and non-treponemal tests.

\textsuperscript{11} Anti-HBs : antibodies to hepatitis B surface antigen
\textsuperscript{12} RNA: ribonucleic acid
Keywords and MeSH terms

<table>
<thead>
<tr>
<th>Mesh terms*</th>
<th>Keywords</th>
<th>Sleutelwoorden</th>
<th>Mots clés</th>
<th>Schlüsselwörter</th>
</tr>
</thead>
<tbody>
<tr>
<td>human&quot; &quot;cells&quot; &quot;tissues&quot;</td>
<td>Human body material</td>
<td>Menselijk lichaamsmateriaal</td>
<td>Matériel corporel humain</td>
<td>Menschliches Körpermaterial</td>
</tr>
<tr>
<td>Biological test</td>
<td>Biologische test</td>
<td>Test biologique</td>
<td>biologischer Test</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>HIV</td>
<td>HIV</td>
<td>HIV</td>
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</tr>
<tr>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>HCV</td>
<td>HCV</td>
<td>HCV</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>syphilis</td>
<td>syphilis</td>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>CMV</td>
<td>CMV</td>
<td>CMV</td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Toxoplasmosis</td>
<td>Toxoplasmosis</td>
<td>Toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>EBV</td>
<td>EBV</td>
<td>EBV</td>
<td></td>
</tr>
<tr>
<td>HTLV</td>
<td>HTLV</td>
<td>HTLV</td>
<td>HTLV</td>
<td></td>
</tr>
</tbody>
</table>


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13 The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".
3. METHODOLOGY

After analysing the request, the Board and working group Chair identified the necessary areas of expertise. An ad hoc working group was then set up which included experts in infection serology, HBM banking, QA/QC. The experts of this working group provided a general and an ad hoc declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in scientific journals and in reports from relevant national and international organisations, as well as on the opinion of the experts.

Once the advisory report was approved by the ad hoc working group and by the standing working group tasked with "Cells, tissues and organs of human and animal origin", it was ultimately validated by the Board.
4. ELABORATION AND ARGUMENTATION

List of abbreviations used

- Anti-CMV: Antibodies to cytomegalovirus
- Anti-EBV: Antibodies to Epstein-Barr virus
- Anti-HBc: Antibodies to hepatitis B core antigen
- Anti-HBs: Antibodies to hepatitis B surface antigen
- Anti-HCV: Antibodies to hepatitis C virus
- Anti-HIV-1,2: Antibodies to human immunodeficiency virus 1,2
- ARL: AIDS Reference Laboratory
- CDC: Centers for Disease Control and Prevention
- CLIA: Chemiluminescence immunoassays
- CMV: Cytomegalovirus
- DNA: Deoxyribonucleic acid
- EA: Early antigen
- EASL: European Association for the Study of the Liver
- EBNA: Epstein-Barr nuclear antigen
- EBV: Epstein-Barr virus
- EIA: Enzyme immunoassay
- EQA: External Quality Assessment
- FAMHP: Federal Agency for Medicines and Health Products
- HA: Heterophile antibodies
- HBM: Human Body Material
- HBsAg: Hepatitis B surface antigen
- HBV: Hepatitis B virus
- HCV: Hepatitis C virus
- HIV: Human Immunodeficiency Virus
- HTLV: Human T cell leukaemia/lymphoma virus type
- IgG: Immunoglobulin G
- IgM: Immunoglobulin M
- IPH: Scientific Institute of Public Health
- IVF: In vitro fertilisation
- MAP: Medically assisted procreation
- NAT: Nucleic acid testing
- PTLD: Posttransplant lymphoproliferative disease
- RD: Royal Decree
- RNA: Ribonucleic acid
- RPR: Rapid plasma regain
- S/CO: Signal to cut-off ratio
- SHC: Superior Health Council
- TPHA: Treponema pallidum haemagglutination assay
- TPPA: Treponema pallidum particle agglutination assay
- VCA: Viral capsid antigen
- VDRL: Venereal disease research laboratory
- VZV: Varicella-Zoster virus
1 General discussion

- Agreement between the HBM establishment and the laboratory
Prior to transferring the samples to the laboratory that will undertake the biological testing as part of the HBM donation process, an agreement needs to be signed between the HBM bank concerned and the laboratory. At the very least, the latter should clarify the methodology of the tests used by the laboratory, the expected turnaround time for the assays and the agreements relating to the reporting of the results.

- Source material
Blood samples may come from deceased or living donors. In the case of a living donor, a new sample may be taken at a later stage, if necessary. In the case of a deceased donor, this is not an option, with the only remaining possibility being that of using a sample that might have been stored in the serum bank. There is no difference between blood samples taken via the arterial, venous or intracardiac route (Baleriola et al., 2012; Kitchen et al., 2013).

The biological tests are carried out on donor serum or plasma. They are not to be performed on other fluids or secretions such as aqueous or vitreous humour, nor on the HBM itself unless clinically justified. In this case, the test that is used must have been validated for such fluids.

As regards deceased donors, the blood samples must have been taken within 48 hours prior to death. If this is not possible, the sample needs to be taken as soon as possible and in any event within 24 hours after death. The time since death may affect the reliability of the tests, hence the importance of using an ante-mortem sample whenever possible, unless the test has been validated for post-mortem blood samples.

As stated in the regulations, if a transfusion was administered shortly before donation, haemodilution may have occurred, which needs to be taken into account. In theory, a transfusion shortly before the donation can result in disease transmission. However, major dilution is also liable to lessen the detectability of the antibodies or antigens in the donor blood. Individual samples should be given preference. Pooling should be avoided.

- Choice of tests
Apart from the mandatory tests, further tests may be decided upon as well. The decision whether or not to run optional tests depends on the type of tissue (infection sites may be found in some tissues and not in others) and the type of donor.

In all cases, this concerns optional tests, which are often only relevant during a specific period of time, i.e. when there is an increased prevalence of the infection in question.

- Actual tests
The serological method used must have been validated by the producer or by the laboratory that performs it (in the event of there being no certification available from the producer) on post-mortem samples if the test is carried out on tissue samples from deceased donors. A published validation or validation of the test in another Belgian clinical diagnostic laboratory can also be used as a basis for validation, provided that it can be shown to be exactly the same test and that the same level of accuracy and precision can be guaranteed.
- Test interpretation and implications for the releasing or rejecting of HBM
If the test results are positive, the HBM will usually be rejected.
In some cases (e.g. a combination of positive results for anti-HBc and anti-HBs and negative results for HBsAg), the HBM will still be released, since this combination of results points to a past infection.
In some very specific cases, the results of a screening test may be overridden by a confirmatory test. This is only possible under certain conditions, which will be discussed below for each of the tests concerned.
In the case of autologous donations or donations between partners for medically assisted procreation (MAP) purposes, HBM from donors with positive test results may still be released. If inactivation steps are applied during processing (for example ensuring the safety of bone tissue), the serological results will always have to be negative. The tests need not be repeated when the inactivation step in question has been validated for the viruses concerned.

- Communicating the results of the tests
The "Quality" R.D. provides that the confirmed results of the donor assessment shall be communicated and clearly explained to the latter, taking into account the privacy requirements (Section 9, § 4, of the Act of 22 August 2002). The information shall preferably be transferred via the attending physician or the general practitioner. The laboratory contact information shall be sent to the attending physician or general practitioner for any questions regarding the results.

Even an optimal policy for serological and NAT testing in donors does not fully rule out residual risks. As a result, the potential recipient must be informed of this admittedly low risk. Ideally, this will be done as part of an informed consent procedure.
2 Mandatory biological tests

The R.D. of 28 September 2009 mentioned above sets out mandatory biological tests that need to be carried out on samples from tissue donors. At the very least, the following tests need to be performed:

A. As regards living donors: anti-HIV 1,2; HBsAg, anti-HBc; anti-HCV and the syphilis screening test. When HBM from living donors that is intended for allogeneic use can be stored for extensive periods of time, new blood samples should be taken and retested after a period of one hundred and eighty days. In the event of repeat testing, the donation sample can be taken within 30 days prior to and seven days following the donation. When HBM from living donors that is intended for allogeneic use cannot be stored for extensive periods of time and repeat testing is therefore not possible, NAT testing (nucleic acid amplification technique) is performed, as is the case for deceased donors, unless the processing includes an inactivation step that has been validated for the viruses in question. If, in the case of a living donor, the sample of the donation, as defined above, also undergoes NAT testing for HIV, HBV and HCV\(^{14}\), there is no need to examine a second blood sample. Similarly, there is no need to repeat the test when the processing includes an inactivation step that has been validated for the infectious agents concerned.

B. As regards deceased donors, the tests to run include, at the very least, those listed under paragraph A, as well as: NAT screening for HIV, NAT screening for HCV and NAT screening for HBV, unless the processing includes an inactivation step that has been validated for the infectious agents concerned.

Under certain circumstances, the donor history and specific features of the HBM intended for donation (e.g. malaria, CMV, toxoplasmosis) may require further testing. Some examples of such infectious agents, as well as HTLV-1 and EBV, will be discussed in Section 3, which looks at optional tests.

2.1 Biological screening tests for HIV antibodies/RNA

2.1.1 Anti-HIV 1,2

Serological screening tests for anti-HIV 1,2 are among the routine tests that are carried out in most diagnostic laboratories in Belgium. The strict regulations in place for the producers of these tests contributed to the placing on the Belgian market of high-performance and high-quality tests. As a result, there are usually no major difficulties when running or interpreting these tests.

Non-negative (grey area and reactive) screening results for anti-HIV-1, 2 need to be confirmed by one of the recognised Belgian AIDS Reference Laboratories (ARLs).

As regards HBM donations, this primarily involves interpreting and reporting the results of the screening tests, given the fact that the confirmatory tests that are currently used cannot be carried out in an emergency situation.

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\(^{14}\) HCV: hepatitis C virus
HIV 1,2-screening assays are traditionally subdivided into distinct "generations" according to the different principles on which they are based. As regards the serological immunoassays that are used for anti-HIV-1 screening, the general rule is that the higher the generation of the test (e.g. 4th generation), the shorter the serological "window period" between the infection with HIV and its detection (see Fig. 1).

Figure 1. Serological progress of the HIV-1 infection as well as the serological window periods of anti-HIV-1,2 immunoassays belonging to different generations.

Based on: Laboratory Testing for the Diagnosis of HIV Infection: Updated CDC Recommendations (27/06/2014).

In Belgium, most diagnostic laboratories use 4th generation immunoassays. According to recent data on the external quality assessment (EQA) conducted by the Quality Department of the Medical Laboratories of the Scientific Institute of Public Health (IPH), 15/163 (9 %) of Belgian laboratories that took part in the EQA-cycle for serological HIV tests still use 3rd generation immunoassays. Immunoassays belonging to these two generations (3rd and 4th generation) do not differ in terms of the detection of anti-HIV-1,2 antibodies. However, 4th generation tests can also detect p24 antigen, which means that the HIV-1 infection can be identified before seroconversion.

It follows that using 3rd generation immunoassays for serological screening in tissue donors means that the "window period" will be 3-5 days longer compared to the use of 4th generation anti-HIV-1,2 tests.
Given the fact that the generation the anti-HIV1,2 immunoassay used belongs to affects the "window period" of this test, which in turn impacts on the safety of the donation, it is of paramount importance to use the tests with the shortest "window period", i.e. 4th generation tests, for samples from tissue donors.

Samples from deceased HBM donors need to be analysed using tests that have been validated by the producer or by the laboratory performing them (in the event of there being no certification available from the producer) for use on post-mortem samples.

In the event of non-negative (borderline or positive) screening results for anti-HIV 1,2, and pending confirmation by an ARL, the report must clearly state that these screening results still need to be confirmed. In Belgium, it is the ARLs that are in charge of interpreting and reporting the confirmatory test results. The final result of the test is that obtained by an ARL on the basis of the confirmatory tests carried out.

2.1.2 HIV NAT testing

As was the case for serological assays, the analytical features of NAT tests used for HIV screening have evolved significantly over the past decade. At the methodological level, almost every analytical feature of the NAT tests for HIV has been optimised. As regards the scope of this advisory report, the main improvements concern the greater sensitivity and accuracy of the assays used, even in a low analytical range.

Carrying out additional NAT testing for HIV reduces the "window period" after a possible infection by an additional 3 to 4 days compared to the 4th generation serological anti-HIV 1,2 tests described above, which enhances the safety of tissue donations.

<table>
<thead>
<tr>
<th>Anti-HIV1,2 **</th>
<th>HIV NAT</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>positive</td>
<td>infection with a detectable viral load</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>infection with an undetectable viral load</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>acute infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>no infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
</tbody>
</table>

**This concerns a negative result from the laboratory or a negative result confirmed by an ARL.
2.2 Biological screening tests for HBV antibodies/DNA15

2.2.1 HBV serology

The diagnosis of HBV infection is grounded in serological markers. The fact that multiple markers are available and that these different markers display divergent patterns of appearance/persistence/disappearance during the period following the initial infection results in a fairly complex interpretation chart.

The R.D. of 28 September 2009 mentioned above provides that the serology for hepatitis B must, at the very least, include HBsAg and anti-HBc assays.

In addition, Annex VI, Section 1.3 of this R.D. states that if, on the one hand, the anti-HBc test is positive whilst on the other, the HBsAg and HBV NAT tests are both negative, an anti-HBs shall be carried out. If the latter test is positive, this points to a natural infection that has cleared, which means that the positive anti-HBc test is not a contraindication for releasing the HBM for human application.

If the HBsAg test is negative and the anti-HBc and anti-HBs tests are both positive, this may be due to:

- A past natural HBV infection with HBsAg clearance.
- A false-positive result for anti-HBc. This is the most likely explanation for the positive screening results for anti-HBc in areas with a low (<8%) seroprevalence of HBsAg, as is the case in Belgium.

The serological profile corresponding to negative HBsAg and anti-HBs screening results in combination with positive anti-HBc screening results ("core-only" HBV serology) is not explicitly described in the R.D. mentioned above. The reasons indicated above also apply to the positive anti-HBc test results, viz. a false-positive result or a past natural HBV infection with HBsAg clearance. Unlike the serological profile that corresponds to a positive screening result for anti-HBs, there is no serological evidence in support of there being any immunity, as there are no anti-HBs present. Despite the extremely low infectious risk associated with individuals with a "core only" serological profile, as a rule, tissue donations from these donors should nonetheless be rejected. In exceptional individual cases, the HBM administrator may derogate from this rule, but only after having consulted the laboratory virologist and after having carried out a thorough risk assessment in agreement with all the parties concerned.

2.2.2 HBV NAT testing

Carrying out additional HBV NAT testing has enhanced the safety of tissue donations, as these can yield positive results just one week after the initial infection, whilst screening based on the early serological marker for acute infection, viz. HBsAg, displays a high degree of variability and depends, among other things, on the viral inoculum, the route of transmission and host factors and usually only yields positive results at least one month after the initial infection (Workowski et al., 2015).

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15 DNA : deoxyribonucleic acid
For donated tissues, it is usually possible to wait for the results of HBV NAT testing, and it is essential to interpret the serological results in conjunction with those of HBV NAT testing. This is in fact what the R.D. provides.

Table 2. Summary table for interpreting the results of biological screening tests for serological markers for/DNA of HBV.

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>HBV NAT</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>early acute infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>recent vaccination, acute infection or false-positive</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>chronic infection¹ with undetectable viral load</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>acute/chronic infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>positive²</td>
<td>negative</td>
<td>past natural infection, immunity</td>
<td>release possible</td>
<td>no further action</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>occult infection³</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>« core only »⁴ profile</td>
<td>reject</td>
<td>no further action</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>post-vaccination immunity</td>
<td>release possible</td>
<td>no further action</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>acute infection or false-positive</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
</tbody>
</table>

¹: An acute infection can be distinguished from a chronic infection if it has been confirmed that HBsAg has been present for > 6 months.
²: ≥ 10 U/l
³: Occult infection: negative result for HBsAg but HBV DNA found in blood or tissues.
⁴: See section 2.2.1 for the interpretation of a “core only” serological profile.

Based on CDC: Sexually Transmitted Diseases Treatment Guidelines 2006/Hepatitis B
2.3 Biological screening tests for HCV antibodies/RNA

2.3.1 Anti-HCV

The most recent guidelines from both the Centers for Disease Control and Prevention (CDC) and the European Association for the Study of the Liver (EASL) favour anti-HCV screening in the first-line diagnosis of an HCV infection. In the event of positive results for anti-HCV, both international recommendations suggest to run a search for HCV RNA.

Interpretation difficulties are mainly due to the combination of a positive search result for anti-HCV and a negative result for HCV RNA: this serological profile may be attributable to a past HCV infection that has subsequently cleared or to a false-positive result.

Ideally, one of the following confirmatory strategies will be chosen in the event of a suspected false-positive result for HCV antibodies, with the second the preferred choice to confirm that this is indeed a false-positive result.

1/ the carrying-out of an additional serological assay for anti-HCV based on a different method than the original test. Repeat false-positive results are known to be rather unlikely, especially if different methods are used. Also, if additional testing yields a negative result, this indicates that the result for the initial serological assay was false-positive. Given the fact that these different serological methods also vary in terms of their specificity, the competent clinical biologist needs to be consulted.

2/ if the initial serological assay yields a low analytical value, the result will probably be false-positive. For the vast majority of serological tests for anti-HCV, the analytical results will be expressed as S/CO (Signal to cut-off ratios). For some anti-HCV tests, the CDC have suggested an analytical value below which the result can be regarded as probably false-positive. For the most recent anti-HCV tests, however, such a cut-off value for potentially false-positive results has not (yet) been verified.

2.3.2 HCV NAT testing

Given the fact that a considerable amount of time elapses between the initial infection and the appearance of anti-HCV, the use of HCV NAT testing has enhanced the safety of HBM donations. It is estimated that in about half of those with an acute HCV infection and detectable HCV RNA, the search for anti-HCV remains negative.
Table 3. Summary table for interpreting the results of biological screening tests for HCV antibodies/RNA

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV-NAT</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>positive</td>
<td>infection with a detectable viral load</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>past infection with an undetectable viral load or false-positive result for anti-HCV</td>
<td>reject*</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>early infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>no infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
</tbody>
</table>

* In the event of a low analytical value, the result will probably be false-positive. For the vast majority of serological tests for anti-HCV, the analytical results will be expressed as S/CO. For some anti-HCV tests, the CDC have suggested an analytical value below which the result can be regarded as probably false-positive. For the most recent new anti-HCV tests, however, such a cut-off value for potentially false-positive results has not (yet) been verified.

2.4 Biological screening tests for syphilis

In addition to screening for HIV, hepatitis B and C, the "Quality" R.D. also requires a syphilis screening test. However, syphilis is a disease for which treatment is available. Recent epidemiological findings confirm that syphilis is more common in people who have also contracted HIV and hepatitis C. Conversely, increasingly sophisticated serological and NAT tests have become available in recent years to screen for HIV and hepatitis B and C. This has allowed to shorten the window period to such an extent that a positive syphilis test retains but a very limited relative value as an indicator for an increased risk of HIV and hepatitis C.

2.4.1 Serological tests available for syphilis screening

The algorithms that are recommended for the serological diagnosis of syphilis are challenging due to the inherent complexity of these methods. Thus, these tests are subdivided into treponemal and non-treponemal tests and the interpretation of the results obtained is often particularly difficult, hence the need for further confirmatory testing (Morshed, 2014).

Non-treponemal tests are tests that search for IgG\(^{16}\) and IgM\(^{17}\) directed against the lipids that are released from the damaged human cells during an early stage of the disease. Their goal is therefore to search for antibodies to antigens that are not specific to an infection with species of the genus *Treponema*, as reflected in the term reaginic antibodies. The non-specific nature of this category of serological tests is also reflected in the fact that many other causes, such as advanced age, pregnancy, various types of malignant tumours, autoimmune diseases and other unrelated infections may result in the formation of anti-lipoid antibodies, thus generating false-positive results.

\(^{16}\) IgG : immunoglobulin G  
\(^{17}\) IgM : immunoglobulin M
Consequently, a positive result obtained with a non-treponemal test should always be confirmed by means of a treponemal test. Moreover, non-treponemal tests usually display a low sensitivity as regards the detection of early syphilis, whilst the first positive results are only obtained some 4-8 weeks after infection. The tests belonging to this category have mainly a diagnostic purpose as part of the therapeutic follow-up of patients with syphilis. Thus, a declining titre over a certain period of time is indicative of a favourable response to treatment. As a rule, a successful treatment leads to negative results for these tests. The Venereal Diseases Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test belong to this group of non-treponemal tests used for serological syphilis screening.

**Treponemal tests** are serological screening tests that search for specific antibodies directed against species of the genus *Treponema*. No distinction can be made between the different treponematoses due to immunological cross-reactions. These tests usually remain positive after the initial infection, which means that they cannot be used to monitor the response to treatment or diagnose reinfections. Treponemal serological tests include the *T.pallidum* haemagglutination (TPHA) test, the *T.pallidum* particle agglutination (TPPA) test, treponemal enzyme immunoassays (EIA), chemiluminescence immunoassays (CLIA) and immunoblotting.

New developments, especially as regards the optimisation of treponemal immunoassays, offer new possibilities due to the earlier detection of syphilis and the shorter diagnostic window, but do not necessarily simplify the assessment of the overall serological picture.

According to recent international recommendations (IUSTI, 2014), different screening algorithms can be used for serological syphilis screening:

- **Only the treponemal screening test.** This screening strategy is commonly used in European blood banks and laboratories due to its potential for large-scale automation. This algorithm identifies both individuals in whom syphilis has been treated successfully as well as those who have not received any treatment. It is better suited to detect the early stages of infection than the sole use of a non-treponemal test. Given the fact that this strategy is mainly used for populations with a low prevalence of syphilis, it is fraught with a considerable number of false-positive results.

- **Only the non-treponemal screening test.** Ideally, a non-treponemal test carried out for screening purposes should be quantitative in nature in order to rule out the prozone effect when using undiluted blood samples (this concerns <2 % of samples, usually during the secondary phase of syphilis. These patients display extremely high titres of antibodies that interfere with the formation of antigen-antibody complexes, which are necessary to visualise flocculation when interpreting the non-treponemal test). This algorithm can only detect active (infectious) syphilis, which means that it can miss the early stage of syphilis.

- **Treponemal and non-treponemal tests.** This algorithm is especially useful to screen high-risk populations as well as to screen for the early stages of syphilis.

In the serological diagnosis of syphilis and independently of the screening algorithm used, a confirmatory test will always need to be carried out, regardless of which of the screening tests turned out positive.
• If the initial screening test only included a treponemal test, the results should be confirmed by means of a second treponemal test based on a different analytical method as well as a quantitative non-treponemal test if this second treponemal test also turns out positive.

• If the initial screening test only included a non-treponemal test, the positive result needs to be confirmed by means of a treponemal test, whereas the non-treponemal test should be performed in a quantitative manner if this was not initially the case.

• If the initial screening was performed using a treponemal test as well as a non-treponemal test, the non-treponemal test should be performed in a quantitative manner. A second treponemal test based on a different analytical method may be used to rule out a false-positive result for the initial treponemal test only if the non-treponemal test is negative.

It seems advisable to carry out treponemal tests (alone or in combination with non-treponemal tests) during the initial screening that is carried out as part of the process of HBM donations to ensure maximum safety for the HBM intended for donation.

Table 4. Interpretation of the results of biological screening tests for syphilis

<table>
<thead>
<tr>
<th>Treponemal test</th>
<th>Non-treponemal test</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>positive¹</td>
<td>active infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>treated (past) infection or early stage of infection or false-positive²</td>
<td>reject</td>
<td>contact the attending physician²</td>
</tr>
<tr>
<td>negative</td>
<td>not carried out or negative</td>
<td>no infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>false-positive result for the non-treponemal test/false-negative result for the treponemal test</td>
<td>release potentially possible³</td>
<td>no further action</td>
</tr>
</tbody>
</table>

¹: Given the fact that in the vast majority of cases in which non-treponemal tests yielded false-positive results, the titres were ≤ 1/4, a "positive non-treponemal test" is considered to be a test with a titre ≥ 1/8.

²: In such a case, a confirmatory treponemal test needs to be carried out. If this confirmatory treponemal test yields a negative result, the initially positive result of the treponemal test is not confirmed and is therefore looked upon as false-positive, which justifies releasing the HBM intended for donation and requires no contact with the attending physician concerned.

³: The bank administrator can still accept the HBM after having consulted the clinical biologist, possibly after carrying out additional tests, and after having received the informed consent of the recipient and the medical transplant team.
3 Optional biological tests

The R.D. of 28 September 2009 mentioned above provides that further biological testing is required under specific circumstances. The criteria that are crucial when selecting possible additional tests have to do with the donor's medical history and specific features of the donated HBM. This advisory report looks at screening for HTLV-1 antibodies, CMV, toxoplasmosis and EBV as examples for such additional serological tests.

The decision to run these optional tests is made on the basis of the tissues and cells that are intended for donation as well as specific clinical and epidemiological circumstances.

Infections are transmitted most effectively via viable cells and tissues, blood, stem cells and vascularised organs, which accounts for the fact that the risk of transmission is higher in the case of an organ transplantation than non-viable fresh frozen bone grafting. In addition, the risk is greater if the recipient is immunocompromised. Another factor that needs to be taken into account is that tissues may undergo potential decontamination procedures (Fishman et al., 2012).

3.1 Biological screening tests for Toxoplasma gondii antibodies/DNA

3.1.1 Anti-Toxoplasma

Serological screening tests for anti-Toxoplasma IgG\(^{18}\) and IgM\(^{19}\) are some of the routine tests that are carried out in most diagnostic laboratories in Belgium. In general, the anti-Toxoplasma IgG assay does not pose any significant analytical problems, whereas the search for anti-Toxoplasma IgM is subject to possible cross-reactivity with other acute infectious processes (e.g. acute CMV or EBV infections) or autoimmune diseases with, as a corollary, false-positive results. In recent years, laboratories have acquired considerable expertise in the use of Toxoplasma IgG-avidity tests that are not fraught with specificity problems that are typical of IgM assays.

Molecular assays for the identification of Toxoplasma DNA are rarely, if at all, performed as part of the HBM donation process. With requests for Toxoplasma gondii genome screening very rare, this assay is not widely available in Belgian diagnostic laboratories. It is almost exclusively carried out as part of the screening/confirmatory process of ocular or congenital toxoplasmosis.

Table 5. Summary table for interpreting the results of biological screening tests for Toxoplasma antibodies

<table>
<thead>
<tr>
<th>Anti-Toxoplasma IgG</th>
<th>Anti-Toxoplasma IgM</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>positive</td>
<td>acute infection or false-positive IgM result</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>acute infection or false-positive IgM result</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>past infection</td>
<td>release possible</td>
<td>no further action*</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>no infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
</tbody>
</table>

**“No risk” of reactivation in "eye, bone, artery" donors found in the paper by Derouin et al. in CMID 2008.

\(^{18}\) IgG : immunoglobulin G

\(^{19}\) IgM : immunoglobulin M
3.2 Biological screening tests for EBV antibodies/DNA

3.2.1 Anti-EBV

Most Belgian diagnostic laboratories already routinely use serological testing to screen for both specific and non-specific antibodies to EBV. There is a broad commercial offer available that allows to search for a wide range of parameters, thus contributing to a more accurate interpretation. These parameters as well as the testing algorithms differ from one diagnostic laboratory to another. The following serological parameters can be searched for in order to establish the serological progress of the EBV infection and especially to detect/rule out an acute infection: non-specific heterophile IgM antibodies (anti-HA IgM), IgM antibodies to viral capsid antigens (anti-VCA IgM), IgG antibodies to viral capsid antigens (anti-VCA IgG), IgG antibodies to EBV nuclear antigens (anti-EBNA IgG) and IgG antibodies to EBV early antigens (anti-EA IgG) (see Figure 2). The commercially available serological tests that are commonly used to search for anti-EBV IgG do not present any significant analytical problems, whereas anti-EBV IgM screening tests have to contend with a considerable number of false-positive results, mainly as regards patients with acute infections with taxonomically related herpes viruses (e.g. CMV, Varicella Zoster virus (VZV)).

Figure 2. Serological progress of the EBV infection, taking into account the detection of antibodies to different EBV antigens

![Figure 2](image.png)

w: week; m: month

Based on Neocleous et al. 2013.

20 Anti-EBV: antibodies to Epstein-Barr virus
Table 6. Summary table for interpreting the results of biological screening tests for antibodies to EBV

<table>
<thead>
<tr>
<th>anti-VCA IgM</th>
<th>anti-VCA IgG</th>
<th>heterophile antibodies</th>
<th>anti-EBNA IgG</th>
<th>anti-EA IgG</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>early acute infection</td>
<td>reject*</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>acute infection/early recovery</td>
<td>reject*</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>early acute infection or false-positive result for HA IgM</td>
<td>reject*</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>early acute infection or false-positive result for anti-VCA IgM</td>
<td>reject*</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>recovery</td>
<td>release possible*</td>
<td>no further action</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>(past) infection</td>
<td>release possible*</td>
<td>no further action</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>positive</td>
<td>reactivation</td>
<td>release possible*</td>
<td>no further action</td>
</tr>
</tbody>
</table>

*Only for seronegative recipients

Molecular assays for the identification of EBV DNA are rarely, if ever, performed as part of the tissue donation process. The same is true for Belgian diagnostic laboratories. These assays are usually only carried out as part of the screening and follow-up process of patients who are at an increased risk of post-transplant lymphoproliferative disease (PTLD). Each individual diagnostic laboratory is responsible for determining which test combinations they will use to detect acute/past EBV infections and reactivations. The tests mentioned above do not always need to be carried out.

3.3. Biological screening tests for HTLV-1

Directive 2012/39/EU requires that HTLV-1 tests be carried out in certain circumstances: in the case of living donors who reside in or come from regions with a high incidence or whose sexual partner or parents come from such regions.

Most of the serological tests that are currently available on the market detect anti-HTLV-1 and HTLV-2 antibodies. They use recombinant antigens and/or synthetic peptides, which enhances their specificity compared to that of first generation tests. Nevertheless, the positive predictive value of these tests remains low, especially in low-prevalence populations. A confirmatory immunoblot must therefore be carried out for all positive screening tests. A positive immunoblot confirms the diagnosis, whilst a negative immunoblot rules out an HTLV-1/2 infection. In some cases, the result may be indeterminate, i.e. there is reactivity to one or several HTLV-antigens, whilst the criteria for positivity are not met.
This is a common situation (up to 50 % of cases) in endemic areas and may indicate early seroconversion. It rarely occurs in Belgium, which has a very low seroprevalence (<0.1 %), (Manaro et al., 2015 ; ECDC, 2012, Costa et al., 2011).

In this respect, molecular biology techniques (NAT tests) play only a very marginal role, as the latter do not confer any advantages in terms of sensitivity, specificity and cost.

Some studies reveal that the sensitivity of the immunoblot is superior to that of NAT testing in the diagnosis of HTLV-1/2 infection in the event of a positive screening test result. One explanation for the lower sensitivity of NAT testing in this context is the low viral load displayed by some asymptomatic individuals (Costa et al., 2011).

Table 7. Summary table for interpreting the results of biological screening tests for HTLV-1.

<table>
<thead>
<tr>
<th>Anti-HTLV-1 screening</th>
<th>Anti-HTLV-1 immunoblot</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>negative</td>
<td>no infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
<tr>
<td>positive</td>
<td>indeterminate</td>
<td>possible infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>infection</td>
<td>reject</td>
<td>contact the attending physician</td>
</tr>
</tbody>
</table>

3.4. Biological screening tests for CMV

After primary infection, the virus spreads via polymorphonuclear cells and monocytes and remains for life, mainly in endothelial cells, bone-marrow progenitor cells, and circulating monocytes. Under certain circumstances, such as the stem cell or sperm donations, serological testing for CMV is required. The tests used detect anti-CMV IgG and IgM.

Screening for anti-CMV IgG allows to identify donors carrying CMV, which is true for 50 % of the population in countries with high socio-economic standards such as Belgium. Detecting anti-CMV IgG poses few interpretation problems, except for equivocal results, i.e. in the grey zone of the test. In that case, it is possible to run a second IgG test, viz. one that is based on a different analytical method, but if any doubt remains, the donor should be considered as CMV positive.

IgM tests are less specific and their interpretation often poses problems when there is no suggestive clinical presentation. Indeed, the presence of anti-CMV IgM is not necessarily linked to a recent infection. Positive results can also be due to cross-reactions with other herpes viruses such as Epstein-Barr virus or another infection leading to non-specific polyclonal stimulation of the immune system. In addition, the use of increasingly sensitive techniques makes it possible to detect specific IgM antibodies long after the onset of primary infection (FDA, 2007 ; Kotton et al., 2013).

In case of doubt, confirmation using molecular techniques seems justified, given the fact that clinical laboratories are experienced in carrying out molecular assays on blood/plasma samples, though not as part of the diagnosis of acute infection. These findings imply that it is necessary to consult with the competent clinical biologist if the decision is made to carry out a molecular assay.

- 22 -
Table 8. Summary table for interpreting the results of biological screening tests for antibodies to CMV

<table>
<thead>
<tr>
<th>Anti-CMV IgG</th>
<th>anti-CMV IgM</th>
<th>Interpretation</th>
<th>Consequence for the donation</th>
<th>Further management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>positive</td>
<td>acute infection or false-positive IgM result</td>
<td>release possible *</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>past infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>acute infection or false-positive IgM result</td>
<td>release possible*</td>
<td>contact the attending physician</td>
</tr>
<tr>
<td>negative</td>
<td>negative</td>
<td>no infection</td>
<td>release possible</td>
<td>no further action</td>
</tr>
</tbody>
</table>

*Depending on the type of donation and the status of the recipient

3.5. Other tests

Depending on the travel history and specific current or past clinical situation of the HBM donor as well as the ongoing epidemiological situation and the nature of the HBM intended for donation, the decision can be made to carry out other optional tests, such as screening for tropical infections such as malaria, trypanosomiasis, infections with the West Nile virus, Zika virus, etc. The need to perform such assays, or even others, must be examined on a case-by-case basis. In this respect, we also refer to other advisory reports the SHC has issued on specific infections (SHC 8751, 2015; SHC 9340, 2016).
5. REFERENCES

- Kingdom of Belgium. Royal decree of 28 September 2009 setting quality and safety norms for the donation, collection, procurement, testing, processing, storage and distribution of human body material that the banks for human body material, the intermediary structures and the production establishments must comply with. Belgian Official Gazette of 23 October 2009, p. 69409.
• SHC- Superior Health Council Shorter deferral periods for blood donation following the implementation of pathogen reduction technology on platelet concentrates against the chikungunya and West-Nile viruses. Brussels: SHC ; 2015 Advisory report no 8751.
• SHC- Superior Health Council Response to the questions put by the Risk Management Group on the current Zika-virus epidemic and recommendations to the various groups of travelers visiting areas in which a Zika-virus epidemic is raging: overview of the situation on 25 April 2016. Brussels: SHC ; 2016 Advisory report no 9340.
VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the SHC website (about us).

All experts joined the working group in a private capacity. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by Hilde BEELE, the scientific secretary was Muriel BALTES.

<table>
<thead>
<tr>
<th>Expert Name</th>
<th>Specialty</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEELE Hilde</td>
<td>Medicine, dermatology</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>DELFORGE Marie-Luce</td>
<td>Microbiology, virology</td>
<td>ULB Erasme</td>
</tr>
<tr>
<td>ECTORS Nadine</td>
<td>Medicine, anatomopathology</td>
<td>KUL</td>
</tr>
<tr>
<td>GOOSSENS Dominique</td>
<td>Medicine, biology</td>
<td>Croix-Rouge</td>
</tr>
<tr>
<td>HANSSENS Geert</td>
<td>Medicine</td>
<td>Independent</td>
</tr>
<tr>
<td>JANSENS Hilde</td>
<td>Hospital hygiene, medical microbiology</td>
<td>UZA</td>
</tr>
<tr>
<td>KLYKENS Johan</td>
<td>Biochemical engineer, QA/QC</td>
<td>UZ Leuven</td>
</tr>
<tr>
<td>LIBOIS Agnès</td>
<td>Infectious diseases</td>
<td>CHU St Pierre</td>
</tr>
<tr>
<td>MATTHYS Conny</td>
<td>Medicine, cord blood banking</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>MUYLLE Ludo</td>
<td>Blood, Cells, Tissues</td>
<td>UA</td>
</tr>
<tr>
<td>PADALKO Elizaveta</td>
<td>Clinical biology, virology</td>
<td>UZ Gent</td>
</tr>
<tr>
<td>PIRNAY Jean-Paul</td>
<td>Medical sciences</td>
<td>MHKA</td>
</tr>
<tr>
<td>SOKAL Etienne</td>
<td>Medicine, visceral surgery</td>
<td>UCL</td>
</tr>
<tr>
<td>VANDERKELEN Alain</td>
<td>Medicine, general surgery</td>
<td>HMRA</td>
</tr>
<tr>
<td>VERBEKEN Gilbert</td>
<td>Biology, QA/QC/RA</td>
<td>MHKA</td>
</tr>
</tbody>
</table>

The standing working group "Cells, tissues and organs of human and animal origin" has endorsed the advisory report. The working group was chaired by Hilde BEELE, the scientific secretary was Muriel BALTES.

<table>
<thead>
<tr>
<th>Expert Name</th>
<th>Specialty</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAUDOUX Etienne</td>
<td>Medicine, cell therapy</td>
<td>ULg</td>
</tr>
<tr>
<td>DELFORGE Alain</td>
<td>Medicine, cell therapy</td>
<td>ULB</td>
</tr>
<tr>
<td>DEVREKER Fabienne</td>
<td>Medicine, reproductive medicine</td>
<td>ULB Erasme</td>
</tr>
<tr>
<td>GARRAUX Gaëtan</td>
<td>Neurology</td>
<td>CHU Liège</td>
</tr>
<tr>
<td>GUNS Johan</td>
<td>Medical-social sciences</td>
<td>UZ Brussel</td>
</tr>
<tr>
<td>JASHARI Ramadan</td>
<td>Cardiac surgery, cardiovascular tissue banking</td>
<td>Cliniques St Jean</td>
</tr>
<tr>
<td>VAN RIET Ivan</td>
<td>Medicine, cell therapy</td>
<td>UZ Brussel</td>
</tr>
<tr>
<td>VANSTEENBRUGGE Anne</td>
<td>Reproductive medicine, embryology</td>
<td>CHR Namur</td>
</tr>
</tbody>
</table>

The following administrations and/or ministerial cabinets were heard:

<table>
<thead>
<tr>
<th>Expert Name</th>
<th>Specialty</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENNEU Claire</td>
<td>Non-clinical assessor</td>
<td>AFMPS</td>
</tr>
</tbody>
</table>
About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 40 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.shc-belgium.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send a mail to info.hgr-css@health.belgium.be.