ATMP: Belgian legislation at a glance by at.las, Bio.be & Bird & Bird

Webinar,9 February 2021

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Key changes to the HBM Act through the Act of 30 October 2018

Issues and challenges for ATMPs

- Clarification on the scope of the law
- The "unleashed" Intermediary Structure
- Access to human tissues and cells in Belgium
  - The allocation of HBM collected in Belgium
  - Import of HBM
- (Remaining) implementation issues

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Schematic overview

EU [pharmaceutical] legal framework applicable to biological material

Finality / Type of biological material	Scientific research	Grafts and other human applications *(incl. CTs)* w/o substantial manipulation	Medicinal products/ ATMPs *(incl. IMP)*
Human	*Possibly clinical trials legislation (Directive 2001/20/EC, to be replaced by Regulation 536/2014) - GDPR*		
Organs	Not ruled at EU level → see national legislation	Directive 2010/53/UE (quality and safety standards for organs	N/A
Blood		Directive 2002/98/EC (standards of quality and safety for blood)	Directive 2002/98/EC / EUCTD + Regulation 1394/2007 + i.a. GMO Dir. 2001/18
Other human material, including all types of stem cells		Directive 2004/23/EC (standards of quality and safety for human tissues and cells "**EUTCD**")	EUCTD + Regulation 1394/2007 + i.a. GMO Dir. 2001/18
Animal	*Possibly clinical trials legislation (Directive 2001/20/EC, to be replaced by Regulation 536/2014)*		
	Directive 2010/63/EU (animal protection)		Regulation 1394/2007

Act of 19 December 2008 on HBM

Wet inzake het verkrijgen en het gebruik van menselijk lichaamsmateriaal met het oog op de geneeskundige toepassing op de mens of het wetenschappelijk onderzoek.

Loi relative à l'obtention et à l'utilisation de matériel corporel humain destiné à des applications médicales humaines ou à des fins de recherche scientifique.

	Texte
version originale • LOI DU 22-05-2019 PUBLIE LE 21-06-2019 (ART. MODIFIE : 24)	
version originale • LOI DU 30-10-2018 PUBLIE LE 28-12-2018 (ART. MODIFIES : 2; 3; 5; 7; 8; 14; 17; 21/1; 21/2; 21/3; 22; 23; 24)	
version originale • LOI DU 11-03-2018 PUBLIE LE 26-03-2018 (ART. MODIFIE : 7)	
version originale • LOI DU 18-12-2016 PUBLIE LE 27-12-2016 (ART. MODIFIES : 2; 3; 4; 7; 8; 14; 23; 45/2)	
version originale • LOI DU 22-06-2016 PUBLIE LE 01-07-2016 (ART. MODIFIES : 2; 3; 7; 8; 10; 15; 20; 21; 22; 2)	
version originale • LOI DU 17-07-2015 PUBLIE LE 17-08-2015 (ART. MODIFIES : 1/1; 23)	
version originale • LOI DU 25-04-2014 PUBLIE LE 14-05-2014 (ART. MODIFIE : 10)	
version originale • LOI DU 10-04-2014 PUBLIE LE 30-04-2014 (ART. MODIFIES : 2; 7; 9; 10; 13; 18; 22; 45/1)	
version originale • LOI DU 10-04-2014 PUBLIE LE 30-04-2014 (ART. MODIFIE : 22) Entrée en vigueur à déterminer.	
version originale • LOI DU 19-03-2013 PUBLIE LE 29-03-2013 (ART. MODIFIES : 2; 3; 4; 7; 8; 10; 11; 12; 13; 15; 16; 17; 20; 21; 22; 24; 45/1; 46)	
version originale • LOI DU 03-07-2012 PUBLIE LE 24-08-2012 (ART. MODIFIE : 2)	
version originale • LOI DU 23-12-2009 PUBLIE LE 29-12-2009 (ART. MODIFIES : 2; 3; 4; 7; NL8; 12; F20; 21; 46) (ART. MODIFIE : 22)	
version originale • LOI DU 16-06-2009 PUBLIE LE 02-07-2009 (ART. MODIFIE : 46)	

	Tekst
originele versie • WET VAN 22-05-2019 GEPUBL. OP 21-06-2019 (GEWIJZIGD ART. : 24)	
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originele versie • WET VAN 10-04-2014 GEPUBL. OP 30-04-2014 (GEWIJZIGD ART. : 22) Inwerkingtreding nader te bepalen	
originele versie • WET VAN 19-03-2013 GEPUBL. OP 29-03-2013 (GEWIJZIGDE ART. : 2; 3; 4; 7; 8; 10; 11; 12; 13; 15; 16; 17; 20; 21; 22; 24; 45/1; 46)	
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The "unleashed" Intermediary Structure

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Belgian HBM Act

Four structures

Bank for human biological material (BHM)
Intermediary structure (IS)
Production establishment (PE)

} HBM intended for human applications

Biobanks (BB)

} HBM intended for scientific research only

All structures must be **accredited**

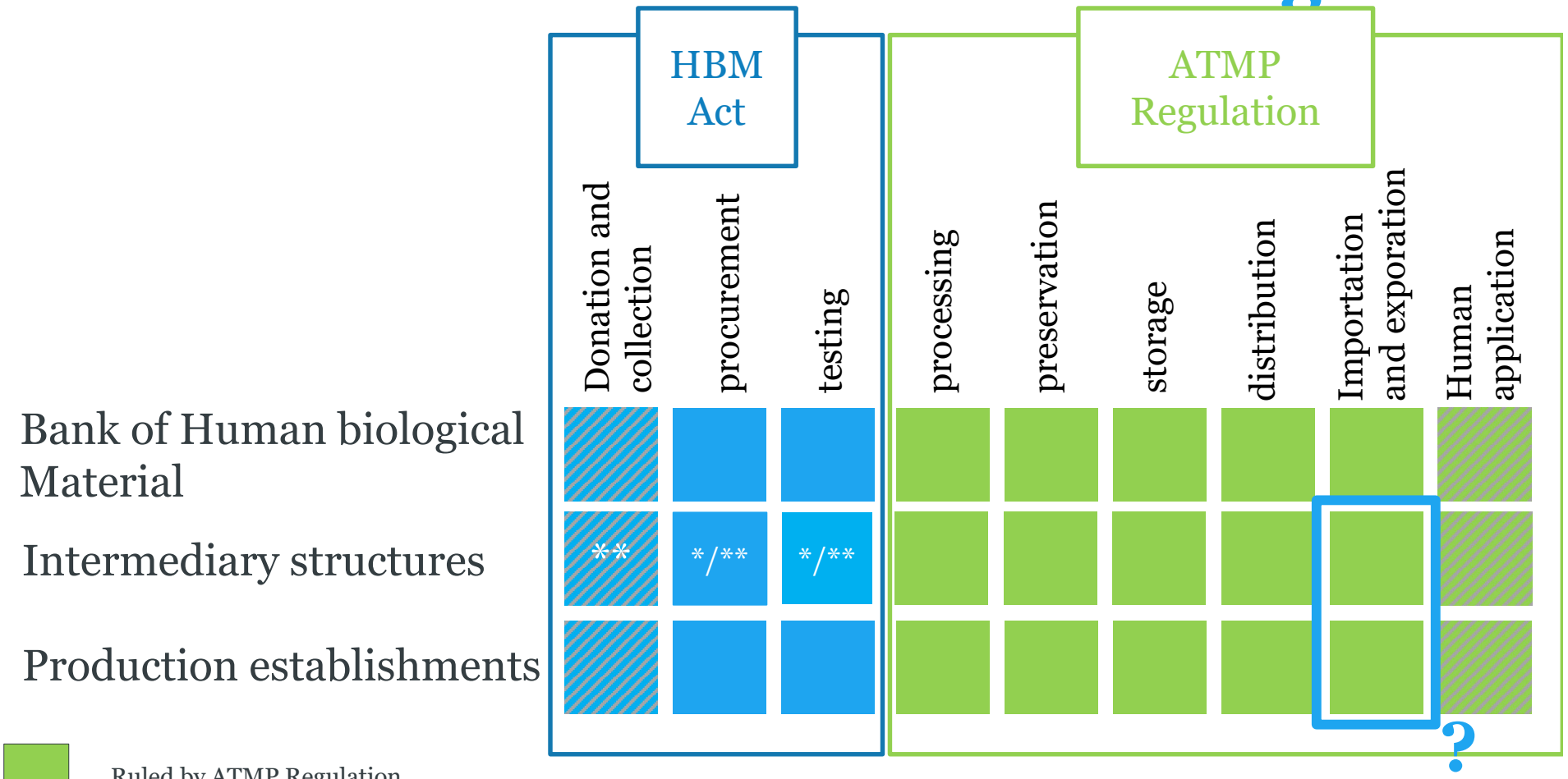
- BHMs, ISs and PEs are subject to *common requirements*
- BBs are subject to a *specific regime (notification)*

Act of 30 October 2018

Main achievements on ATMP - The "unleashed" Intermediary Structure

- **Accreditation of IS**
  - No more requirement of a collaboration agreement between IS and BHM as *prerequisite* for obtaining accreditation as IS
- **HBM collected in BE**
  - BHMs have an **obligation to contract** with any IS that seeks it
  - The law provides for mandatory **Allocation Criteria**
- **Imported HBM**
  - **Direct import** by an IS without control and responsibility of a BHM
  - **Collaboration agreement** with tissue establishments in third countries:
    - Traceability
    - Quality and safety of HCM and
    - Processing of personal data

New framework for Intermediary Structures & ATMP Manufacturing



Ruled by ATMP Regulation

Ruled by the HBM Act and/or its implementing provisions

Must be performed in a hospital

* : Stand alone (for HBM collected outside BE)

** : Subject to a collaboration agreement with a BHM for HBM collected in BE and under the responsibility of a BHM

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Access to human tissues and cells

Directive 2004/23 (Recitals 14 and 21) :

- *"The clinical use of tissues and cells of human origin for human application may be constrained by limited availability. Therefore it would be desirable that the* ***criteria for access*** *to such tissues and cells are defined in a* ***transparent*** *manner, on the basis of an* ***objective evaluation of medical needs****."*

- ***"With due regard to the principle of transparency, all tissue establishments accredited, designated, authorised or licensed under the provisions of this Directive, including those manufacturing products from human tissues and cells, whether subject or not to other Community legislation, should have access to relevant tissues and cells*** *procured in accordance with the provisions of this Directive, without prejudice to the provisions in force in Member States on the use of tissues and cells."*

New obligations for BHMs

HBM Act, Art. 21/1

Les banques de matériel corporel humain **garantissent** un accès au matériel corporel humain fondé sur des **critères d'allocation transparents** et sur la base d'une évaluation objective des besoins médicaux. Les banques de matériel corporel humain traitent tout demande de matériel corporel humain d'une façon **transparente, égale et non discriminatoire**.

Banken voor menselijk lichaamsmateriaal **waarborgen** een toegang tot het menselijk lichaamsmateriaal gebaseerd op **transparante allocatiecriteria** en op basis van een objectieve beoordeling van de medische behoeften. De banken voor menselijk lichaamsmateriaal behandelen elk verzoek voor menselijk lichaamsmateriaal op een **transparante, gelijke en non-discriminatoire wijze**.

New Principles of allocation of HBM

HBM Act, Art. 21/1 and 21/2

- BHMs have a **duty to collaborate and to contract** with any applicant (IS, BB or another BHM)

- Every request for HBM is subject to an **allocation decision** of the BHM with *statement of reasons* (motivation – met redenen omklede beslissing)

- Allocation criteria are :
  - ***Transparent*** - fixed in the collaboration agreement
  - ***Equally applied*** to all applicants (IS, BB or BHM)
  - ***Subject to changes*** by the BHM, but the changes must be notified to all applicants

Other current issues

Clarification on the Scope of application ATIMP's

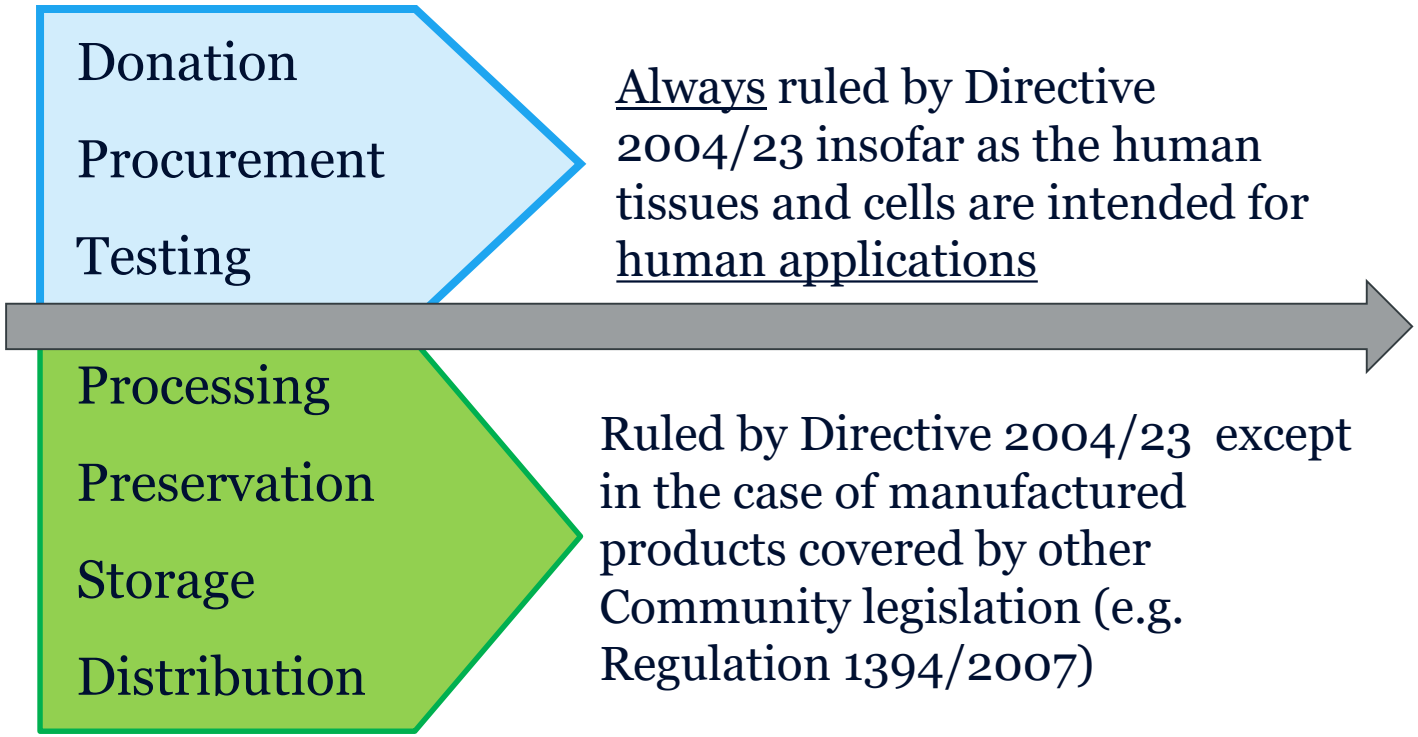
Outside the scope per HBM Act, Art 3, 3, f)

le prélèvement et les actes, visés au paragraphe 1er, effectués avec du matériel corporel humain prélevé dans le cadre d'essais cliniques, tel que visé à l'article 2, 7°, de la loi du 7 mai 2004 relative aux expérimentations sur la personne humaine ou tel que visé à l'article 2, alinéa 2, 2. du Règlement n° 536/2014 du 16 avril 2014 relatif aux essais cliniques de médicaments à usage humain et abrogeant la directive 2001/20/CE, pour autant que le matériel corporel humain ne soit pas destiné ou utilisé à d'autres fins que l'essai clinique en question. Si des actes sont effectués à une autre fin, le matériel corporel humain est distribué à une autre fin ou le matériel corporel humain est destiné à une autre fin, le matériel doit être transmis à une biobanque, telle que visée à l'article 22, qui l'obtient conformément aux dispositions de la présente loi

de wegneming en handelingen, bedoeld in paragraaf 1, verricht met menselijk lichaamsmateriaal weggenomen in het kader van klinische proeven als bedoeld in artikel 2, 7°, van de wet van 7 mei 2004 inzake experimenten op de menselijke persoon of als bedoeld in artikel 2, lid 2, 2. van de Verordening nr. 536/2014 van 16 april 2014 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik en tot intrekking van Richtlijn 2001/20/EG, voor zover het menselijk lichaamsmateriaal niet bestemd is of gebruikt wordt voor andere doeleinden dan de desbetreffende klinische proef en niet wordt toegepast op de mens. Indien handelingen verricht worden voor een ander doel, het menselijk lichaamsmateriaal gedistribueerd wordt voor een ander doel of het menselijk lichaamsmateriaal bestemd wordt voor een ander doel, dient het de materiaal te worden overgemaakt aan een biobank als bedoeld in artikel 22, die het verkrijgt overeenkomstig de bepalingen van deze wet;

Directive 2004/23 – ATMP Regulation

Scope of Application



Always ruled by Directive 2004/23 insofar as the human tissues and cells are intended for human applications

Ruled by Directive 2004/23 except in the case of manufactured products covered by other Community legislation (e.g. Regulation 1394/2007)

How is transition/ interface between regimes ruled?

Directive 2004/ 23 (Recital 6)
Tissues and cells intended to be used for industrially manufactured products, including medical devices, should be covered by this Directive ***only as far as donation, procurement and testing*** *are concerned, where the processing, preservation, storage and distribution are regulated by other Community legislation*

ATMP Regulation (Recital 14)
Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply ***only as far as donation, procurement and testing*** *are concerned, since the further aspects are covered by this Regulation.*

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Belgian HBM Act

Scope of application and definition of Intermediary Structure

Art 3, §1, al. 2 LMCH/WMLM

In afwijking van het eerste lid is deze wet ten aanzien van menselijk lichaamsmateriaal uitsluitend bestemd voor gebruik in bereide producten die onder andere wetgeving vallen, met name geneesmiddelen, geneesmiddelen voor geavanceerde therapie of medische hulpmiddelen, alleen van toepassing op het **doneren, wegnemen, verkrijgen**, **testen en invoeren** ervan

Par dérogation à l'alinéa 1er, la présente loi s'applique uniquement **au don, au prélèvement, à l'obtention, au contrôle et à l'importation** de matériel corporel humain destiné à être utilisé exclusivement dans des produits manufacturés qui tombent sous une autre législation, notamment des médicaments, des médicaments de thérapie innovante ou des dispositifs médicaux

Art 2, 25° WMLM/LMCH

"*structure intermédiaire de matériel corporel humain*": la structure organisée qui traite, conserve, stocke, distribue **et le cas échéant importe** du matériel corporel humain destiné à la fabrication de médicaments de thérapie innovante ou à d'autres applications médicales humaines;

"*intermediaire structuur voor menselijk lichaamsmateriaal*" de georganiseerde structuur die menselijk lichaamsmateriaal dat bedoeld is voor de aanmaak van geneesmiddelen voor geavanceerde therapie of voor andere geneeskundige toepassingen op de mens, bewerkt, preserveert, bewaart, distribueert **en, in voorkomend geval, invoert;**

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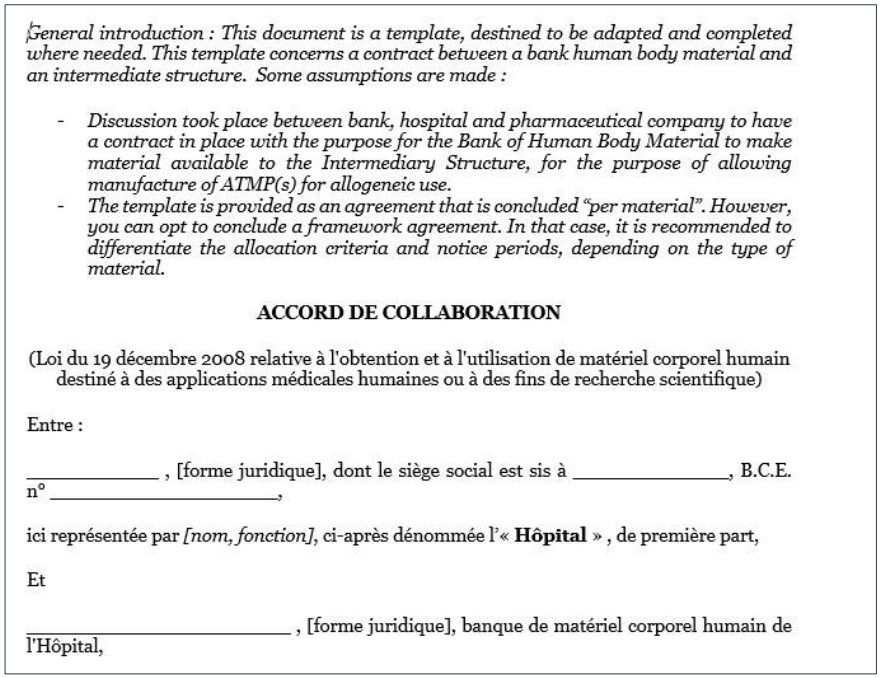
Conclusion & perspectives

Draft Template Collaboration agreement BHCM & IS

ATMP Platform

- FAMHP, Hospitals sector and Industry
- Working Group *Access*
- Working Group *Templates*



General introduction : This document is a template, destined to be adapted and completed where needed. This template concerns a contract between a bank human body material and an intermediate structure. Some assumptions are made :

- *Discussion took place between bank, hospital and pharmaceutical company to have a contract in place with the purpose for the Bank of Human Body Material to make material available to the Intermediary Structure, for the purpose of allowing manufacture of ATMP(s) for allogeneic use.*
- *The template is provided as an agreement that is concluded "per material". However, you can opt to conclude a framework agreement. In that case, it is recommended to differentiate the allocation criteria and notice periods, depending on the type of material.*

ACCORD DE COLLABORATION

(Loi du 19 décembre 2008 relative à l'obtention et à l'utilisation de matériel corporel humain destiné à des applications médicales humaines ou à des fins de recherche scientifique)

Entre :

_____ , [forme juridique], dont le siège social est sis à _____, B.C.E. n° _____,

ici représentée par *[nom, fonction]*, ci-après dénommée l'« **Hôpital** » , de première part,

Et

_____ , [forme juridique], banque de matériel corporel humain de l'Hôpital,

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Action Plan on ATMP's

European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Commission-DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs

- Contains several actions for the European Commission and EMA.
- The action plan considers the ideas collected at an EMA-hosted multi-stakeholder workshop to explore solutions to challenges in the development of ATMPs.

ANNEX — List of proposed actions to improve the regulatory framework for ATMPs.

	Action	Objectives	Deadline *(timelines are indicative and may be subject to change)*	Status update: November 2018
1	EC Guideline on GMP for ATMPs.	To reduce administrative burden and adapt the manufacturing requirements to the specific characteristics of ATMPs. Subsequently to the adoption of the Guideline, EMA will organise specific training to inspectors with a view to achieve more harmonisation.	Q4 2017	Final guideline adopted by EC on 22/11/17. In effect as of 22/05/18. ▸ Guideline A training session of GMP inspectors and assessors took place 27-28 September 2018.
2	Exchange of information on GMP inspections within the network.	IWG meetings are being used as a platform for exchange of information and experience on the application of GMP to ATMPs.	Ongoing	Ongoing.
3	The European Commission services will initiate a dialogue with national competent authorities to address the interplay between the GMO and the medicines legislation.	To reduce discrepancies across the EU regarding the application of GMO rules (Directives on deliberate release or contained use) to ATMPs containing or consisting of GMOs. Issues relevant for both clinical trials and marketing authorisation will be addressed. The aim is to help create coherent approaches for the assessment of these novel products without changing the basic legislation.	Q3 2018	A repository of national requirements has been published in the European Commission's website: ▸ EC webpage Other agreed actions can be consulted at the Commission's website on ATMPs: ▸ EC webpage Applicants are invited to check this website for further updates.

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Thank you & Bird & Bird

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