CENTRO NAZIONALE SANGUE

Istituto Superiore di Sanità

Key EU initiatives: GAPP-PRO

Ursula La Rocca

Italian National Blood Center,

Rome, April 8th 2025

Toward a common approach for authorizing novel BTC

- The **development of new treatments derived from substances of human origin (SoHO)** has rapidly **evolved** in recent years. Despite the **great benefits for patients**, significant **difficulties** have arisen in making **them equitably and widely accessible**.

- **Innovative uses of SoHO and SoHO-derived products** should demonstrate **quality, safety, and clinical benefits** to recipients before incorporating these products into healthcare practice.

- An **assessment of the risks and clinical benefits in terms of efficacy** (effects under ideal circumstances or clinical trials) **or effectiveness** (effects under "real-world" clinical settings) is needed before such innovation reaches the bedside.

Cuende et al. 2025

Toward a common approach for authorizing novel BTC

EuroGTP II

EURO GTP II Good Tissue & cell Practices

1. VISTART Joint Action (2015-2018)

"Principles for Competent Authorities for the **evaluation and approval of clinical follow-up protocols** for blood, tissues and cells prepared with newly developed and validated processing methodologies"

2. EuroGTP (2014-2020)

"Good Tissue and cell practice"

GAPP

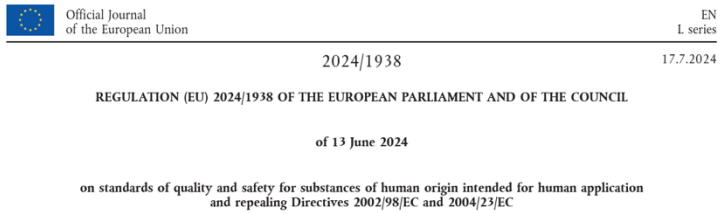
3. GAPP Joint Action (2018-2021)

"Facilitating the authorization of preparation process for blood, tissues and cells"

4. GAPP-PRO Joint Action (2024-2027)

GAPP PRO

Piloting GAPP model approach for assessing and authorizing novel substances of human origin preparation PROcesses



Official Journal of the European Union — EN L series

2024/1938 — 17.7.2024

REGULATION (EU) 2024/1938 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 June 2024

on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

An early access for patients to new Blood Tissues and Cells (BTC) products addressing **unmet clinical needs, and/or providing potentially improved safety and** efficacy, requires **adapted regulatory tools** and **concepts using risk-based approaches** to evaluate **quality, safety, and effectiveness/efficacy of BTC products.**

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SoHO oversight system:

the implementation of the new EU regulation with a focus on the obligations for competent authorities

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CHAPTER III SOHO SUPERVISORY ACTIVITIES

Article 18

SoHO preparation authorisation system

1. SoHO competent authorities shall establish and maintain a system for granting SoHO preparation authorisations to SoHO entities located in their territory. Such a system shall include the reception and processing of applications and the approval of clinical-outcome monitoring plans to generate the evidence required for authorisation, where necessary, and shall allow for the suspension or withdrawal of authorisations.

2. SoHO competent authorities shall authorise SoHO preparations in accordance with Articles 19, 20 and 21 and, where applicable, Article 22.

3. The requirement of SoHO preparation authorisation shall be waived for SoHO that are intended to be distributed for the manufacture of products regulated by other Union legislation, as referred to in Article 2(6).

4. SoHO preparation authorisations shall be valid throughout the Union for the period set out in the authorisation granted pursuant to Article 19(2), point (e), or until the SoHO competent authority has suspended or withdrawn the authorisation. Where a Member State has adopted a more stringent measure in accordance with Article 4, which relates to a specific SoHO preparation, that Member State may decline to recognise the validity of the SoHO preparation authorisation of another Member State until the SoHO entity authorised for that SoHO preparation has demonstrated to that Member State compliance with that more stringent measure.

GAPP Joint Action 2018-2021

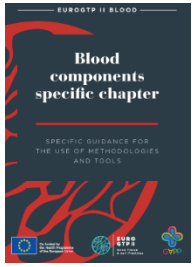
A large consortium of BTC Competent Authorities aiming at facilitating the development of a common and optimal approach to assess and authorize preparation processes in blood and tissues establishments

- **17 European Countries**
  - 16 EU MS
  - 1 non-EU MS
- **24 partners**
  - 1 coordinator
  - 23 beneficiaries (+ 2 affiliated entities)
- **15 collaborating stakeholders**
  (NHSBT, SALAR, JPAC, Fundatia Renale, ESHRE, EBMT, ECDC, SOHO Consortium, ANSM, EFS, Hellenic National Blood Transfusion Centre, Croatian Institute for Transplantation and Biomedicine, Latvian State Agency of Medicine, EDQM, EHA)

GAPP

The **guide** developed provides **useful tools for the evaluation of novelty**, identification of **risk factors**, identification of risk **consequences**, **quantification** of risk by determining the **probability of its occurrence, its severity and detectability, assessment of risk reduction, and definition of the extent of studies needed** on the basis of the risks quantified.

Risk-based approach



Methodology and Interactive assessment tool, to provide recommendations and to improve the quality of healthcare delivery within the field of blood components

FACILITATING THE AUTHORISATION OF GAPP PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

GOOD PRACTICE GUIDELINE TO AUTHORISATION ON PREPARATION PROCESSES IN BLOOD, TISSUES AND CELLS ESTABLISHMENTS

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GAPP methodology: preparation process dossier (PPD)

Module 1: Applicant information

- BE/TE data.
- Data of the responsible person for the PPD.

Modules 2 and 3: Novelty and risk assessment

- Description of BTC.
- Novelty Questions.
- Activity information.
- Risk Assessment.

Module 4: Quality

- Updated SOPs.
- Validation.

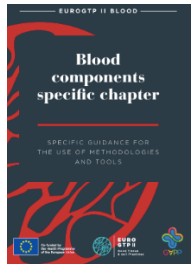
Module 5: Preclinical studies

- *In-vitro/In-vivo* studies
- Performed studies.
- Bibliography.

Module 6: Clinical information

- General clinical information.
- Clinical indication.
- CIP.
- CFUpP

Preparation of a dossier (PREPARATION PROCESS DOSSIER - PPD) for the process to be authorised, which includes 6 modules, aimed at evaluating the CHANGES that imply a NOVELTY (according to EuroGTPII) and the related risks.



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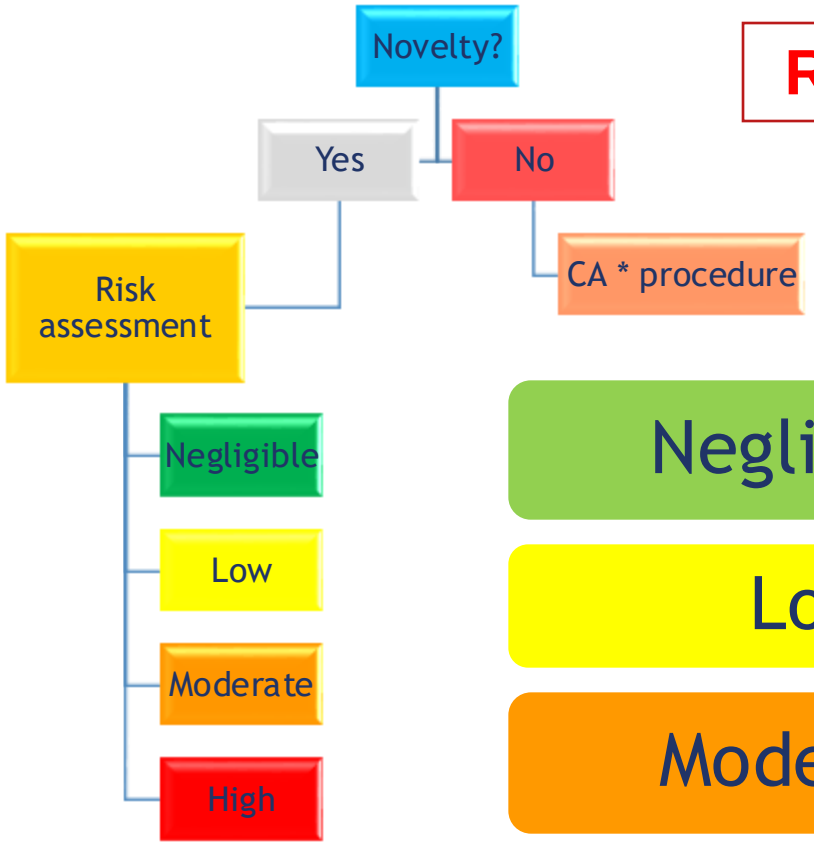
GAPP methodology: application process

Applicant information	BTCE information and data of person responsible for the dossier.
BTC novelty	Information of the BTC where the novelty will be applied as well as the description of the novelty.
Risk Assessment	Using EUROGTP II tool.
Quality	Information of the new related SOPs, quality control procedure, validation, stability and evaluation.
Preclinical studies	Information of non-clinical (in vitro or/and in vivo) studies.
Clinical information	To support the implementation of the novelty.

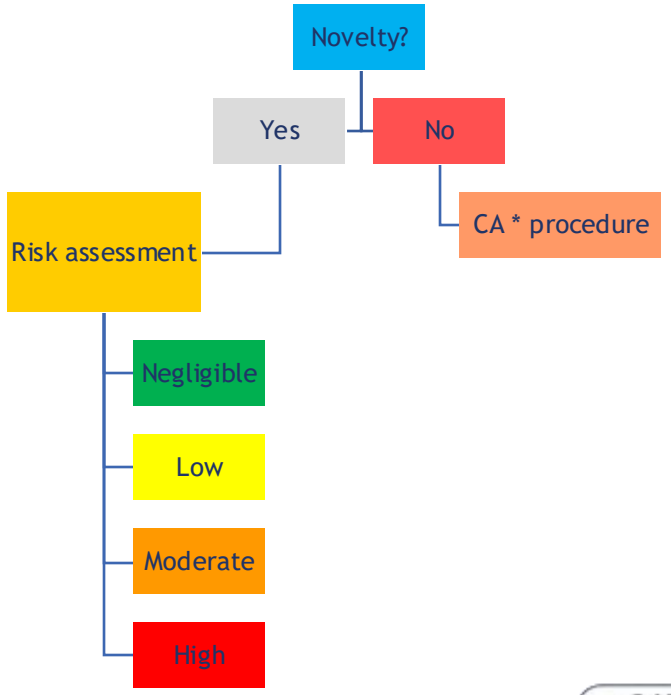
Preparation Process Authorization (PPA)



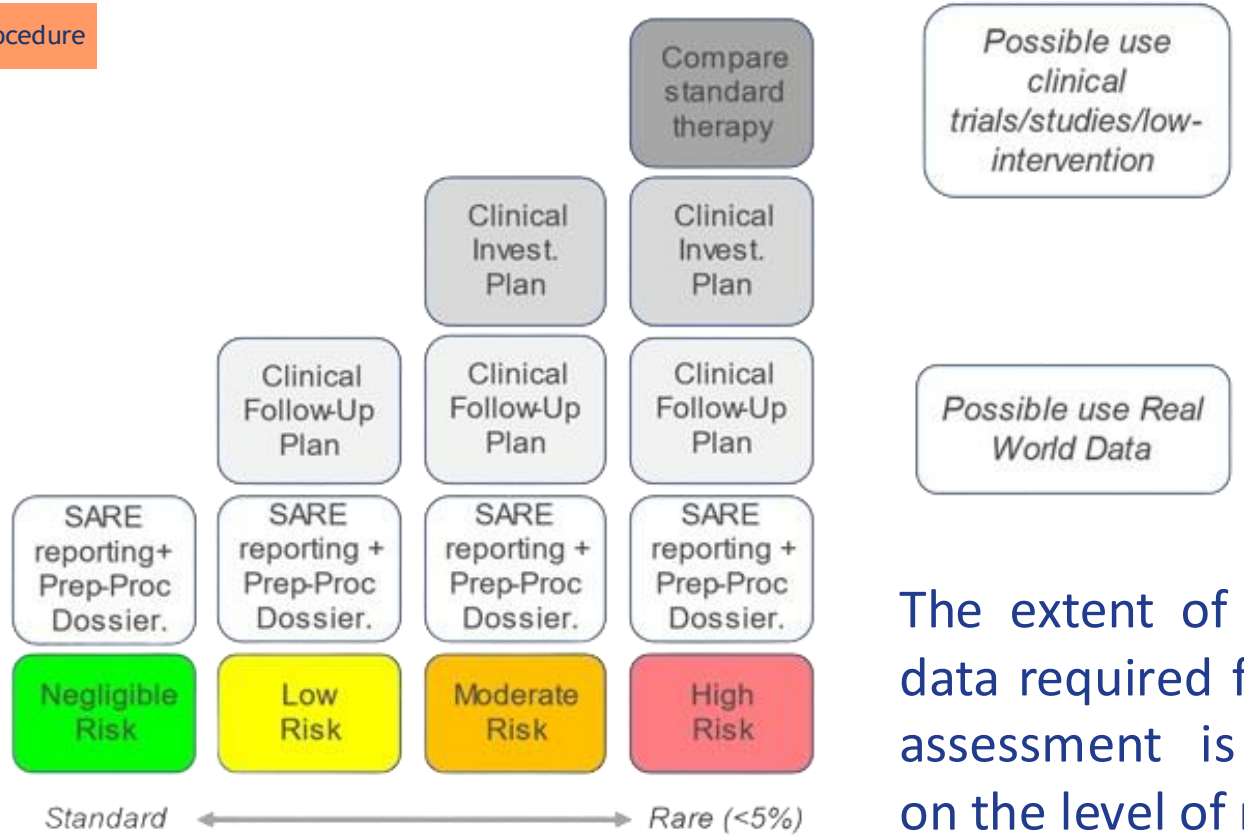
Risk-based approach

Negligible	• Novelty questions, risk assessment, PPD (only the information regarding the novelty).
Low	• Novelty questions, risk assessment, PPD (only the information regarding the novelty) and the proposal of follow up.
Moderate	• Novelty questions, risk assessment, PPD (only the information regarding the novelty) the proposal of follow up and the clinical investigational plan.
High	• Novelty questions, risk assessment, PPD (only the information regarding the novelty) the proposal of follow up, the clinical investigational plan and the comparison to the standard therapy.

Evidence requested for level of risks

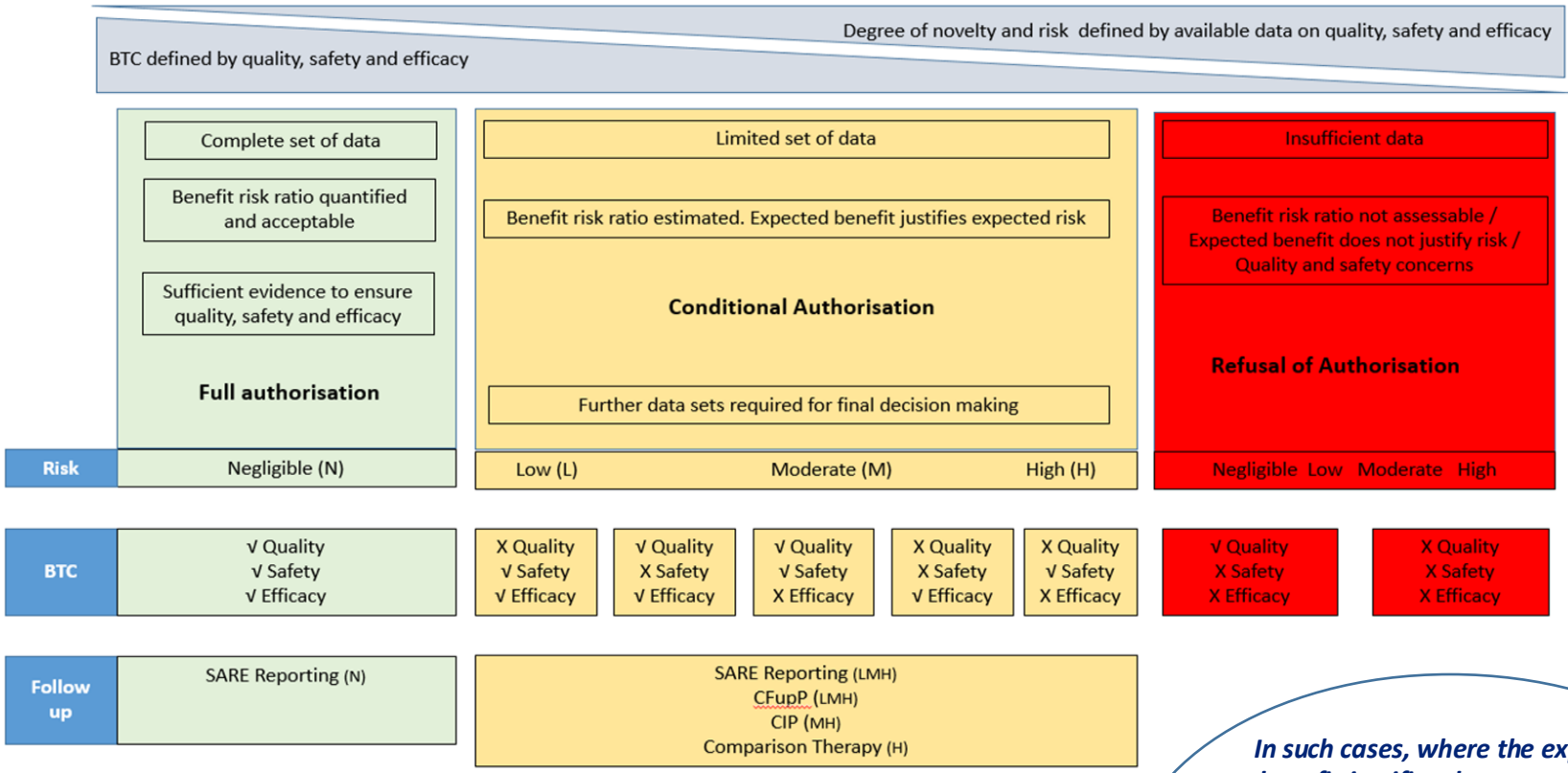


Different levels of risk



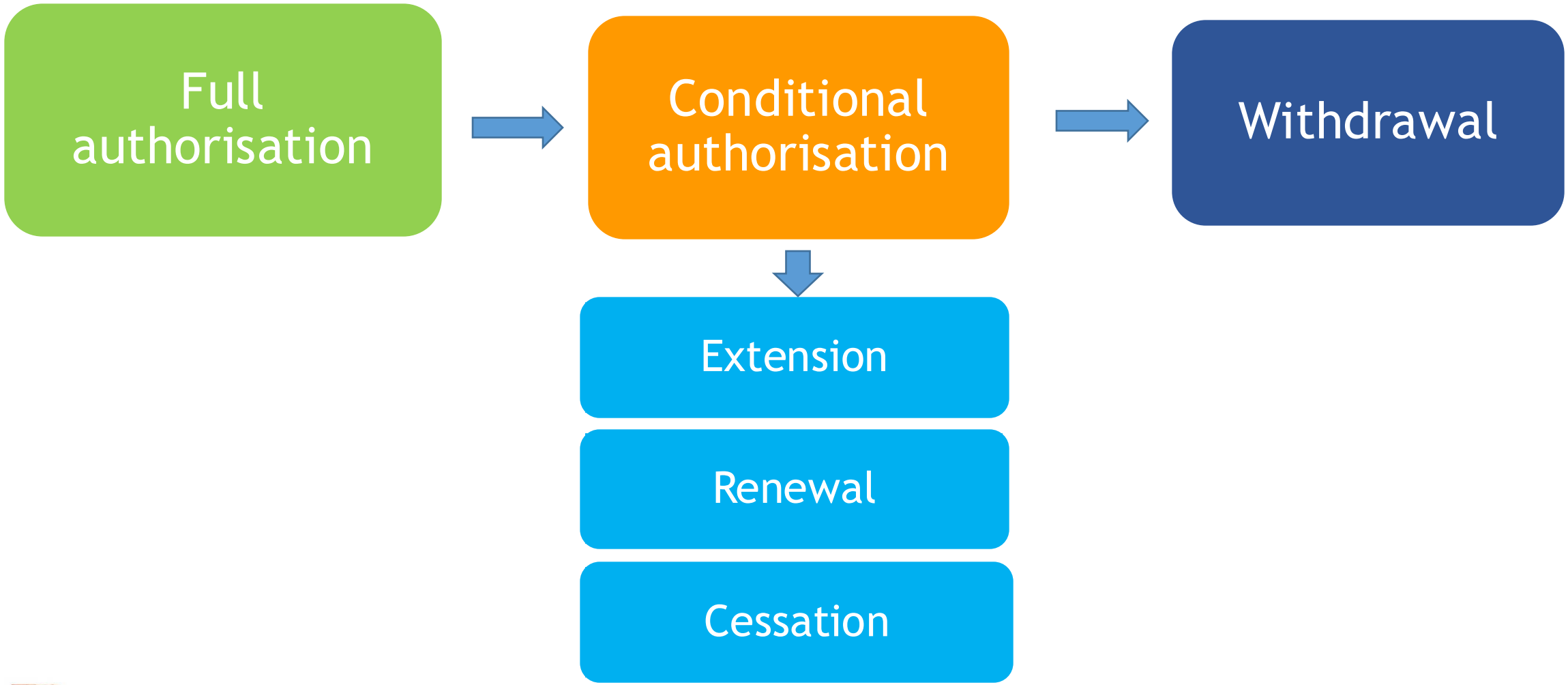
The extent of clinical data required for PPD assessment is based on the level of risk

Risk/benefit balance

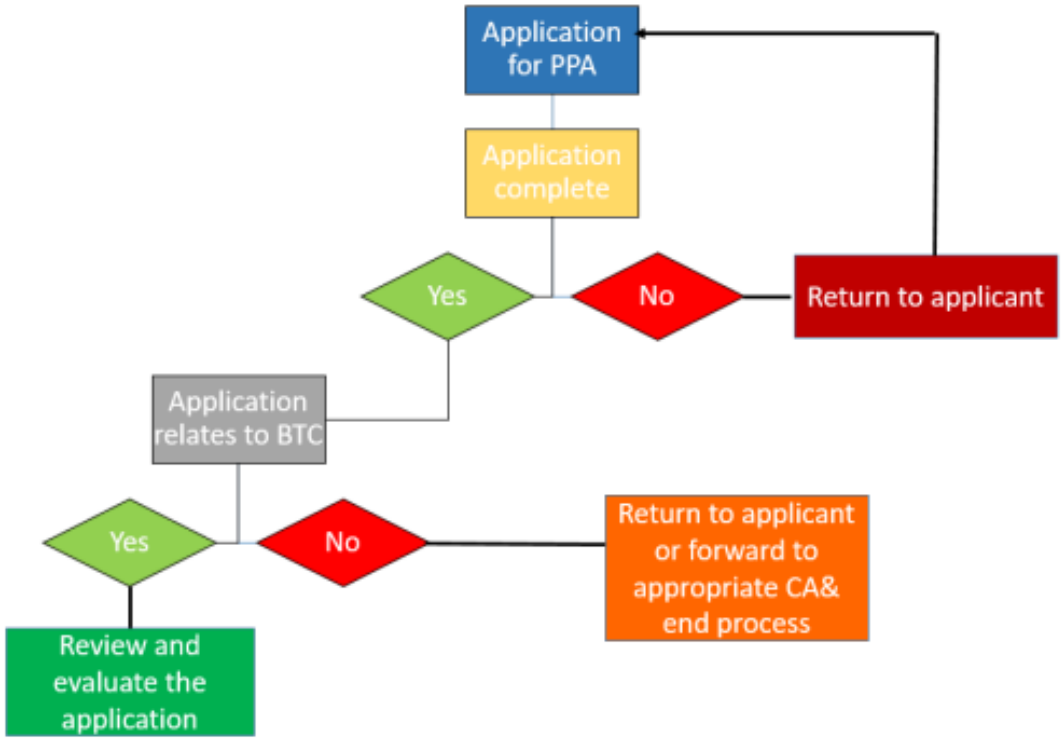


In such cases, where the expected benefit justifies the expected risk and no alternative options are available, a conditional authorisation may be granted, defining the further data sets that are required for further assessment and for final decision-making (full authorisation or refusal).

Preparation Process Authorization (PPA)



An application whenever a new SoHO or a change indicating novelty



If the file is incomplete, the applicant is informed and asked to send the missing documents / information and the technical / regulatory evaluation does not proceed until the application is complete.

If during initial review of the PPD, the CA confirms that the application does not relate to a BTC which falls under the EUBTCDs, they will return the application to the applicant or forward to the appropriate CA, and the assessment process for the BTC CA will end.

https://www.gapp-ja.eu/

GAPP-PRO will pilot and roll-out approach by 2027

14 Main beneficiaries

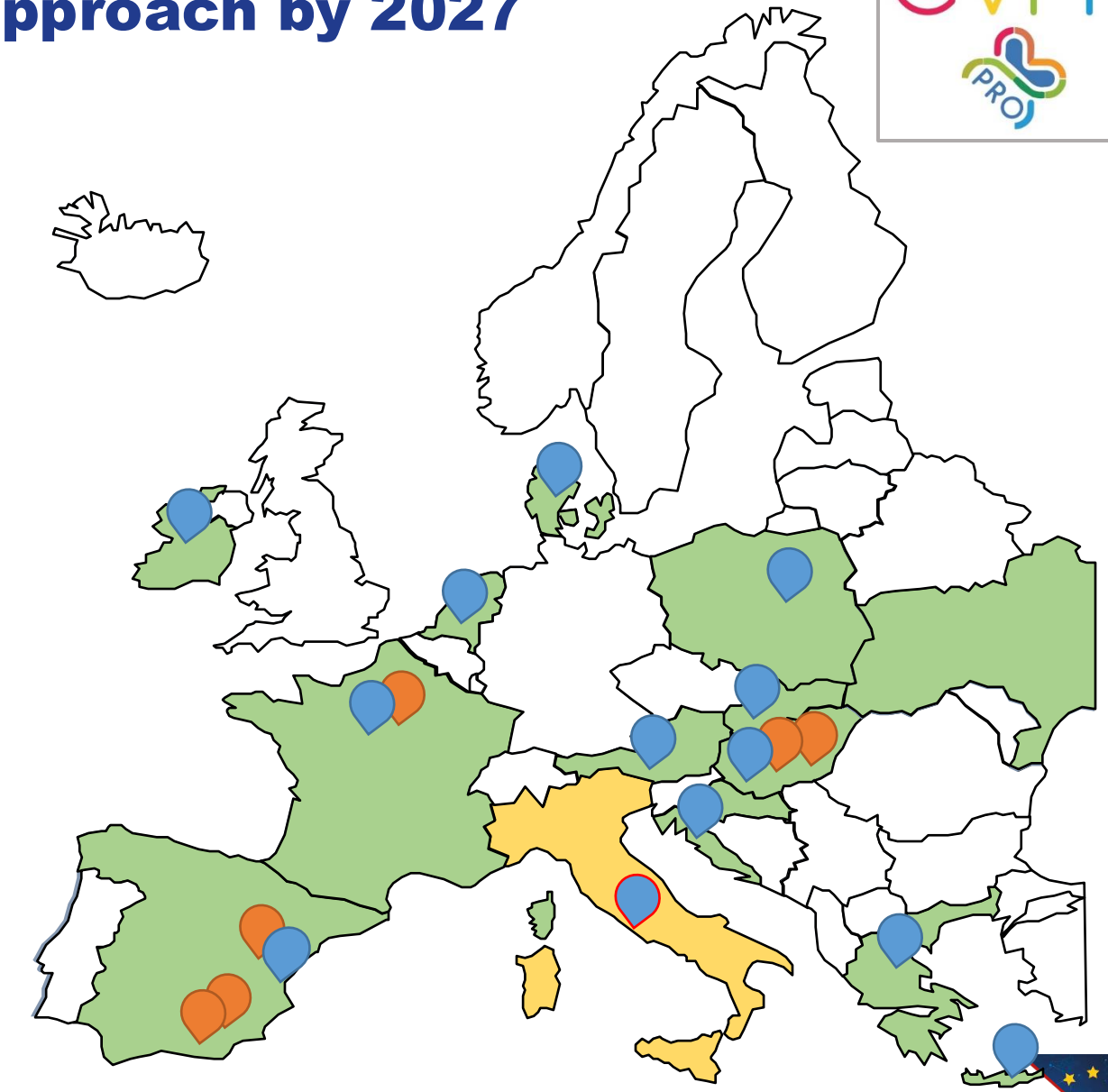
7 Affiliated entities

from 13 EU countries and 1 non-EU country

Project start date: 15/02/2024

Project duration: 40 months (14/06/2027)

- Map current status of authorised SoHO preparations and inherent risks
- Pilot GAPP methodology: test, assess and improve
- Test cross-entity/country applications and assessments
- Test cross-sector collaboration for SoHO preparations entailing medical devices
- Refine and update the methodology



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SoHO oversight system:
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GAPP-PRO: main objectives

GAPP-PRO aims at **testing and perfecting GAPP JA** (GA 785269) **methodology**

- **piloting authorization processes for substances of human origin** (eg: faecal microbiota, breast milk, platelet lysate eye drops), including **bedside preparations;**
- verifying the **capability to implement the GAPP model in the different Member States** (MS), with **a common assessment of risk levels**;
- **testing the methodology** in a **perspective of multi-country assessment**;
- testing the **feasibility of joint assessments**, **including** interactions with **stakeholders from medical devices and pharmaceutical fields**;
- **Updating the EuroGTPII risk assessment tool** extending the already available platform to other **Substances of Human Origin (SoHO), namely faecal microbiota and breast milk**.

GAPP PRO WP activities

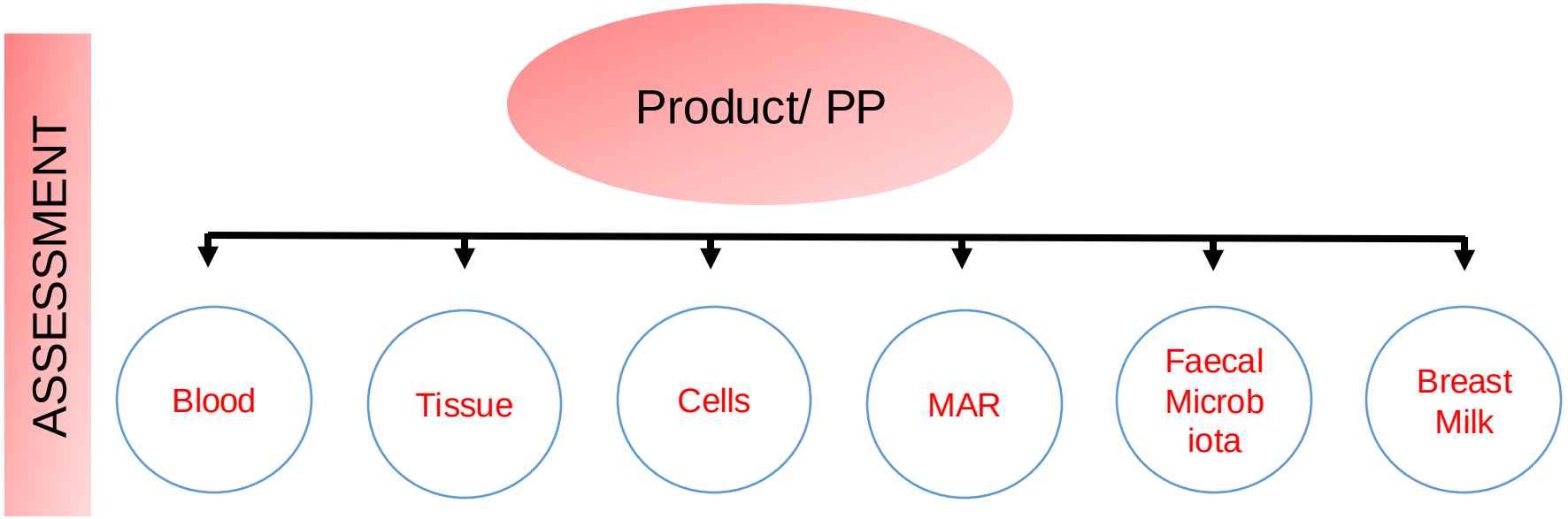
WP4	Snapshot of SOHO preparation processes in Europe grouped by different risk level, including bed-side preparations	The main goal of this WP is to gain clear insight into the current European authorization of SoHO preparation processes, including bed-side preparations, grouped by different risk level. In particular it will: • investigate the presence of ongoing evaluation of new SoHO preparation processes; • investigate the presence of **already authorised SoHO preparation processes in relation to identified risk level**
WP5	**Pilot-test of GAPP methodology on SoHO**	**To perform the test to assess the GAPP methodology applicability on selected SoHO (including at least 2 autologous bedside preparations), from application to final assessment in order to:** • **Test the evaluation of different levels of risk (negligible, low, medium, high);** • **Detect strengths and weaknesses of GAPP methodology through the performance of a SWOT analysis.**
WP6	**Pilot-test of GAPP methodology for cross country and joint country assessments**	**To organise and perform cross-country applications and joint-country assessments involving a group of Member States and experts (inspectors and assessors) in order to test and prove its feasibility and added value.**
WP7	**Analysis of pilot tests results**	**This WP will perform a thorough analysis of pilot outcomes, including interactions in the assessments and authorisation process with those of other regulatory frameworks, for example, where a new SOHO preparation process relies on the use of a new medical device.**
WP8	Refine of GAPP Guideline	**The aim of this WP is to refine/update the GAPP Guidelines on the basis of the pilot-tests results. Moreover, within this WP, the existing EUROGTP II platform will be extended to other SoHO (i.e. breast milk and faecal microbiota) so to provide European professionals with the opportunity to perform risk assessment also for other products.**

GAPP-PRO: technical work packages

WP5 **Assessment of the GAPP methodology applicability on selected SoHO, from application to final assessment.**

The WP5 objective is to assess the GAPP methodology for different risk levels. The desired aim is the improvement of the method that will be standardized for all EU members:

- Test the evaluation of different levels of risk (negligible, low, medium, high);
- Detect strengths and weaknesses of GAPP methodology through the performance of a SWOT analysis.



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GAPP-PRO: technical work packages

ASSESSMENT

Blood | Tissue | Cells | MAR | Faecal Microbiota | Breast Milk

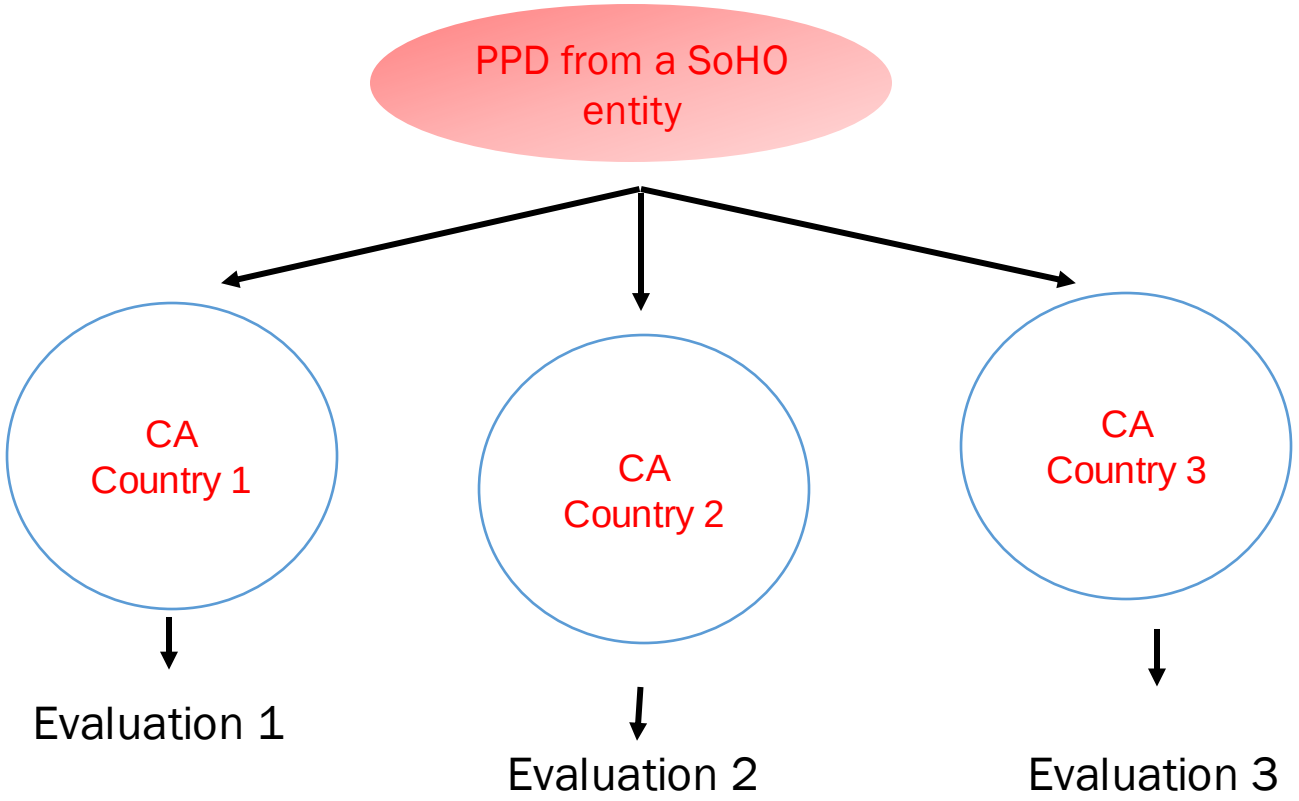
NAME OF PILOTS DOSSIER	CONTACT POINT FOR DOSSIER
Non-DEHP Blood Bags  	Luciana Teofili / Claudio Pellegrino (Italy) P. Universitario A. Gemelli Luciana Labanca (Italy) AOU Città del Sole Torino
Blood Derived Eye drops 	Marina Buzzi / Piera Versura (Italy)
PRP from cord blood 	Stathis Michalopoulos, BRFAA (Greece)
Lower titer 0 whole blood 	Silvano Rossini / Elisabetta Volpato (Italy) Ospedale Niguarda
Red blood cells from cord blood for transfusion of premature neonates	Luciana Teofilli (Italy) P. Universitario A. Gemelli

GAPP-PRO: technical work packages

The WP6 goal is to test that methodology and to see if with a standardized methodology, the assessment's result is similar, regardless of the country.

WP6

- Each PPD will be evaluated by at least 3 CAs using the GAPP Methodology. Evaluations will be done separately.



Expectations from GAPP-PRO

CAs

- Member States know how to manage SoHO preparation authorisations
  - Awareness building, preparation, training
  - Organisation of national pathway for SPA
  - Leverage cross-country collaboration, bringing all MS to high/similar level of SPA
  - Trust building with other sector authorities (in particular medical devices)

- Link to SoHO digital platform
  - Compendium (application/authorisation module)
  - EuroGTP-II tool

BEs

Taking into account any relevant EDQM monograph

- Systematic Benefit/Risk Assessment to determine the evidence available on safety, quality and effectiveness

- Submission of an application, including laboratory validation and other safety, quality and effectiveness data and, where relevant, a clinical outcome monitoring plan proportionate to risk


THANK
YOU