CEN Workshop “Guidelines for Blood-Brain Barrier on-Chip Models for Drug Delivery Testing”

Workshop description form

- PART A – Workshop Summary
- PART B – Project Plan

PART A – Workshop SUMMARY

1	WS details		
1.1.	**Organization**	☒ CEN ☐ CENELEC ☐ Joint with ☐ CEN lead ☐ CENELEC lead	
1.2.	**Title**	CEN/WS "Guidelines for Blood-Brain Barrier on-Chip Models for Drug Delivery Testing"	
1.3.	**Scope**	This CEN Workshop aims to define guidelines for BBB-on-chip models for the evaluation of the passage of drugs into the brain, without the need for animal testing.	
1.4.	**Does this WS stem from an EU Research project?**	☒ YES Name of the project: BiSCUIT Grant number: 101146025 End date 2025-12-31 ☐ NO	
1.5.	**Financial support**	☒ EU Research project ☐ EC/EFTA Grant reference: Type here ☐ Other Specify, if needed: Type here	
1.6.	**WS Proposed Chair**	Name: Organization: Postal address: Email: Phone: Webpage:	Attilio Marino Istituto Italiano di Tecnologia (Smart Bio-Interfaces Research Unit) attilio.marino@iit.it +393281211056 https://www.iit.it/it/people-details/-/people/attilio-marino
	WS proposer	Name: Organization: Postal address: Email: Phone: Webpage:	Gianni Ciofani Istituto Italiano di Tecnologia (Smart Bio-Interfaces Research Unit) Gianni.ciofani@iit.it +39050883481 https://www.iit.it/it/people-details/-/people/gianni-ciofani
1.7.	**WS Secretariat**	Organization: Postal address: Email: Phone: Webpage: WS Secretary name: Email: Phone:	UNI - Ente Italiano di normazione Via Sannio 2, 20137, Milano (MI), Italy uni@uni.com +39 02700241 https://www.uni.com/ Fabio Rossi fabio.rossi@uni.com +39 0270024468
1.8.	**CEN and CENELEC Management Centre (CCMC) contact**	Organization: Postal address: Webpage: CCMC Project Manager name: Email: Phone:	CEN and CENELEC Rue de la Science 23B - 1040 Brussels, Belgium https://www.cencenelec.eu/Pages/default.aspx Claire Van Thielen cwa@cencenelec.eu +3225500831

			+32478793545
1.9.	**Tentative date and place of the Kick-off Meeting**	Date: 30th June 2025	Place: Online meeting
1.10.	**Does the proposed Workshop fall within the scope of existing CEN and/or CENELEC Technical Bodies?[1]**	☒ ☐	YES Specify: CEN/TC 140 – In Vitro Diagnostic Medical Devices NO
1.11.	**Are there other Technical Bodies or Joint Advisory and Coordination Groups potentially interested in the Workshop? ?[2]**	☒ ☐	YES Specify: CEN/TC 206 – Biological Evaluation of Medical Devices, ISO/TC 276/SC 2 - Microphysiological Systems and Organ-on-Chip and ISO/TC 229 - Nanotechnologies NO
1.12.	**Are the following aspects affected?**	Safety matters Management system aspects Conformity assessment aspects Security matters	YES[3] ☐ YES[4] ☐ YES[5] ☐ YES[6] ☐
			NO ☒ [7] ☒ NO ☒ NO ☒ NO [8]
		Add information/explanations if Management System aspects and Conformity Assessment aspects are affected: Type here	
2	**WS Deliverables**		
2.1.	**CWA #1**		
2.1.1	**Title**	☒ ☐	Same as WS title (1.2) Other: Type here
2.1.2	**Scope**		This CEN Workshop Agreement defines guidelines for BBB-on-chip models for the evaluation of the passage of drugs into the brain, without the need for animal testing. The CWA is applicable in the following areas: 1. Microfluidic parameters (flow rate, shear stress, and perfusion conditions). 2. Cell sources and culture conditions (primary vs. iPSC-derived cells, endothelial co-cultures). 3. Drug permeability testing protocols (standardized TEER thresholds, permeability coefficients). 4. Validation with reference drugs (benchmarking against known human BBB permeability data).

[1] Part A and Part B of this form shall be sent by the WS secretary to the secretary of the Technical Bodies identified in this section to inform them about the creation of the WS and register any possible objection within 30 days (45 during the holiday period).

[2] Part A and Part B of this form should be sent by the WS secretary to the Bodies identified in this section to inform them about the creation of the WS.

[3] Work on the proposed CEN and/or CENELEC Workshop shall not be initiated.

[4] The CEN and/or CENELEC Workshop proposal shall be submitted to the CEN/CENELEC BT(s) for decision.

[5] CEN-CENELEC Internal Regulations - Part 3, Clause 33 applies.

[6] For projects dealing with security matters the security risk analysis provided in Annex I shall be carried out.

[7] See Note 2 in CEN-CENELEC Guide 29, Clause 3.

[8] See Note 2 in CEN-CENELEC Guide 29, Clause 3.

			5. Data reporting guidelines (ensuring reproducibility and inter-laboratory comparability).
2.1.3	**Does the proposed CWA conflict with a published EN**	☐ ☒	YES Specify: Type here NO In case the answer is 'yes', the development of the CWA shall be stopped

PART B – Project Plan

1 Status of the project plan

Draft project plan for public commenting (Version 1.0)

This draft project plan is intended to inform the public of a new Workshop. Any interested party can take part in this Workshop and/or comment on this draft project plan by sending an email to the WS secretary.

All those who have applied for participation or have commented on the project plan by the deadline will be invited to the kick-off meeting of the Workshop on **2025-06-30**.

2 Workshop proposer and potential Workshop participants

2.1 Workshop proposer

The proposer of this CEN Workshop is the BiSCUIT project, funded by Horizon Europe programme under Grant agreement n. 101146025 and coordinated by:

Gianni Ciofani

Istituto Italiano di Tecnologia (IIT) - C/O via Morego, 30 - 16163, Genoa, Italy

e-mail: gianni.ciofani@iit.it

Dr Gianni Ciofani is also the main contact point for the CEN Workshop.

The CEN/CENELEC national member holding the Workshop secretariat is:

UNI - Ente italiano di Normazione

Via Sannio n.2, Milano, Italy (20137)

(+39)0270024213

sviluppo.progetti@uni.com

2.2 Potential participants

This CWA will be developed in a Workshop (temporary body) that is open to any interested party. The participation of the following persons/organizations would be helpful and is desired. It is recommended that:

- Academic and research bodies
- Funded European Projects (i.e. Horizon 2020, Horizon Europe)
- Research/Test institutes for in vivo/in vitro applications
- CEN/CLC interested Technical Committees

take part in the development of this CWA.

3 Workshop objectives and scope

3.1 Workshop background

Brain disorders pose an enormous socioeconomic burden that can be alleviated by accelerating the development of the most suitable central nervous system (CNS) drugs for clinical trials. Nevertheless, pharmaceutical companies experience a low success rate of candidate CNS compounds during preclinical and clinical testing mainly due to the complex anatomy of the brain [1]. Specifically, the blood-brain barrier (BBB) – a natural barrier that protects the delicate brain environment from potentially harmful substances – also prevents several drugs and therapeutic agents from reaching the target sites [2]. As a result, developing and testing new drugs for brain disorders is extremely costly. Studies evaluated that the average cost for the development of a single drug is approximately €1 billion, with a €778-2814 million range [3], and preclinical testing alone account for 32% of total drug development costs [4].

Traditional *in vivo* models often yield misleading results and have limited predictive value for clinical outcomes, whereas conventional *in vitro* models, such as 2D cultures and static systems, fail to accurately replicate the BBB, making them inadequate for predicting *in vivo* responses. In this context, "barrier-on-a-chip" technology represents an intermediate step between *in vitro* and *in vivo* investigations, capable of boosting drug development in the CNS domain while reducing the elevated costs of preclinical drug testing. These devices can reliably mimic the physiological microenvironment and integrate all necessary components (e.g. cells, extracellular matrix, external stimuli, and sensors) in a precisely controlled platform [5], while maintaining a high degree of biomimetic features, that are fundamental in the obtainment of consistent results that can predict the *in vivo* behavior. By using more and more realistic "barrier-on-chip" platforms, a strong reduction of the number of animals needed to perform in vivo screenings will be possible, in conformity with the "*Three Rs*" principle (Replacement, Reduction, and Refinement) and the Directive 2010/63/EU. Therefore, these technologies represent an ethical alternative to animal testing while also offering direct economic benefits by reducing the costs associated with animal purchase, management, and treatment.

Nonetheless, the lack of standardization in BBB models for drug screening significantly limits their reproducibility, comparability, and regulatory acceptance. Current BBB models vary widely in design, cell sources (primary vs. iPSC-derived endothelial cells), culture conditions (static vs dynamic), and analytical methods (TEER measurements vs. fluorescent permeability assays), making it difficult to obtain reliable and translatable results. As a result, data from different laboratories cannot be directly or easily compared [6]. Furthermore, most BBB-on-chip studies have not been validated using well-characterized drugs with known human BBB permeability. This gap reduces their predictive power for real-world drug screening applications. Only few BBB-on-chip models have been benchmarked against human in vivo permeability data, making it difficult to assess their reliability for pharmaceutical applications [7].

For these reasons, the goal of this workshop is to establish a standardization for BBB-on-chip models for the evaluation of the passage of drugs into the brain, without the need for animal testing.

The only existing standards on micro-physiological system (MPS) are the ASTM F3570 − 22 and the ISO 10991:2023, which concern mainly the terminology relating to these systems. Other appliable standards, even if not specifically related to MPSs, are the ISO 10993-5 and ISO 11137-3 that concern non-cytotoxicity and sterilization of cell culturing devices. From the legal point of view, MPSs fall within the category of devices for

pre-clinical tests, so they must align with the Commission Directive 91/356/EEC on good manufacturing practice for medicinal products for human use. Regulatory agencies, including the FDA and EMA, have recognized the potential of organ-on-chip technology to reduce reliance on animal models. However, without standardized validation protocols, these models cannot be integrated into drug development pipelines [8]. The lack of regulatory guidance has slowed the clinical translation of BBB-on-chip models, despite their potential to accelerate drug screening and personalized medicine applications.

To conclude, standardization is essential in the following areas:

1. Microfluidic parameters (flow rate, shear stress, and perfusion conditions).
2. Cell sources and culture conditions (primary vs. iPSC-derived cells, endothelial co-cultures).
3. Drug permeability testing protocols (standardized TEER thresholds, permeability coefficients).
4. Validation with reference drugs (benchmarking against known human BBB permeability data).
5. Data reporting guidelines (ensuring reproducibility and inter-laboratory comparability).

By implementing these standards, BBB-on-chip technology can become a regulatory-accepted tool for drug permeability testing, ultimately reducing the need for animal models and improving the efficiency of drug development.

This document is based on BiSCUIT's deliverable 5, "Conformity & standardization". BiSCUIT (Grant Agreement 101146025) is an EU-funded research and innovation project which focuses on the validation of a dynamic and biomimetic blood-brain barrier model, integrating sensing features to allow a real-time evaluation of barrier formation and integrity maintenance. Task 3.5 deals with standardization, with the goal of paving the way for standardization of BBB models.

References

[1] B. Booth and R. Zemmel, "Prospects for productivity," *Nat Rev Drug Discov*, vol. 3, no. 5, pp. 451–456, May 2004, doi: 10.1038/nrd1384.

[2] A. S. Kesselheim, T. J. Hwang, and J. M. Franklin, "Two decades of new drug development for central nervous system disorders," *Nat Rev Drug Discov*, vol. 14, no. 12, pp. 815–816, Dec. 2015, doi: 10.1038/nrd4793.

[3] O. J. Wouters, M. McKee, and J. Luyten, "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018," *JAMA*, vol. 323, no. 9, p. 844, Mar. 2020, doi: 10.1001/jama.2020.1166.

[4] S. M. Paul *et al.*, "How to improve RD productivity: the pharmaceutical industry's grand challenge," *Nat Rev Drug Discov*, vol. 9, no. 3, pp. 203–214, Mar. 2010, doi: 10.1038/nrd3078.

[5] N. Kashaninejad *et al.*, "Organ-Tumor-on-a-Chip for Chemosensitivity Assay: A Critical Review," *Micromachines (Basel)*, vol. 7, no. 8, p. 130, Jul. 2016, doi: 10.3390/mi7080130.

[6] "Focus Group Organ-on-Chip Standardization Roadmap," 2024.

[7] H. C. Helms *et al.*, “In vitro models of the blood-brain barrier: An overview of commonly used brain endothelial cell culture models and guidelines for their use,” 2015, *Nature Publishing Group*. doi: 10.1177/0271678X16630991.

[8] J. J. Han, “FDA Modernization Act 2.0 allows for alternatives to animal testing,” Mar. 01, 2023, *NLM (Medline)*. doi: 10.1111/aor.14503.

4 Workshop programme

4.1 General

The kick-off meeting is planned to take place on **2025-06-30** in a virtual meeting.

The working language (language of meetings, minutes, etc.) of the WS will be **English**. The CWA will be written in **English**.

4.2 Workshop schedule

Table 1: Workshop schedule (preliminary)

CEN/CENELEC Workshop	M01	M02	M03	M04	M05	M06	M07	M8	M9	…
Initiation										
1. Workshop description form submission and TC response										
2. Open commenting period on draft project plan (mandatory)										
Operation										
3. Kick-off meeting										
4. CWA(s) development										
5. Open commenting period on draft CWA(s) (optional)										
6. CWA(s) finalized and approved by Workshop participants										
Publication										
7. CWA(s) publication										
Dissemination (see 6)										
Milestones			K	V	V	V	V	V/A	P D	

Legend

K Kick-off

M Workshop meeting

V Virtual Workshop meeting

A Adoption of CWA

P Publication of CWA

D Online distribution of CWA

5 Resource planning

The administrative costs of CEN Workshop Secretariat will be covered by resources from the H2020 project CircThread GA n° 101146025.

6 Workshop structure and rules of cooperation

The workshop will be led by a chair or vice-chair, while the project leader will support them in the organization.

The CEN Workshop Chair is responsible for ensuring that the development of the CWA follows the principles and content of the adopted project plan and the requirements of the CEN Guide 29. The CEN Workshop Chair may take decisions on the conduct of the CEN Workshop based on the comments expressed by the participants according to the CWA rules.

The workshop secretariat is responsible for the organization and management of the workshops according to the CEN Guide 29.

CEN Workshop participants draft the CWA and take in consideration the comments after the public commenting phase. CEN Workshop participants are the CWA proposers (the members of CIRCTHREAD project), plus other relevant stakeholder, identified by the proposer.

6.1 Participation in the Workshop

The Workshop will be constituted during the kick-off meeting. By approving this project plan, the interested parties declare their willingness to participate in the Workshop and will be formally named as Workshop participants, with the associated rights and duties. Participants at the kick-off meeting who do not approve the project plan are not given the status of a Workshop participant and are thus excluded from further decisions made during the kick-off meeting and from any other decisions regarding the Workshop.

As a rule, the request to participate in the Workshop is closed once it is constituted. The current Workshop participants shall decide whether any additional members will be accepted or not.

Any new participant in the Workshop at a later date is decided on by the participants making up the Workshop at that time. It is particularly important to consider these aspects:

a. expansion would be conducive to shortening the duration of the Workshop or to avoiding or averting an impending delay in the planned duration of the Workshop;
b. the expansion would not result in the Workshop taking longer to complete;
c. the new Workshop participant would not address any new or complementary issues beyond the scope defined and approved in the project plan;
d. the new Workshop participant would bring complementary expertise into the Workshop in order to incorporate the latest scientific findings and state-of-the-art knowledge;
e. the new Workshop participant would actively participate in the drafting of the manuscript by submitting concrete, not abstract, proposals and contributions;
f. the new Workshop participant would ensure wider application of the CWA.

All Workshop participants who approved the publication of the CWA or its draft will be named as authors in the European Foreword, including the organizations which they represent. All Workshop participants who did not approve the publication of the CWA will not be named in the European Foreword.

6.2 Workshop responsibilities

The Workshop Chair is responsible for content management and consensus building. The Workshop Chair is supported by the Workshop Vice-Chair (if any) and the responsible Workshop secretariat, whereby the Workshop secretariat will always remain neutral regarding the content of the CWA(s). Furthermore, the Workshop secretariat shall ensure that CEN-CENELEC's rules of procedure, rules of presentation, and the principles governing the publication of CWA(s) have been observed. Should a Workshop Chair no longer be able to carry out her/his duties, the Workshop secretariat shall initiate the election of a new Workshop Chair. The list below covers the main tasks of the Workshop Chair. It is not intended to be exhaustive.

- Content related contact point for the Workshop
- Presides at Workshop meetings
- Ensures that the development of the CWA respects the principles and content of the adopted project plan
- Manages the consensus building process, assesses when the Workshop participants have reached agreement on the final CWA, on the basis of the comments received
- Ensures due information exchange with the Workshop secretariat
- Represents the Workshop and its results to exterior

The Workshop secretariat, provided by a CEN and/or CENELEC Member, is responsible for organizing and leading the kick-off meeting, in consultation with the Workshop proposer. Further Workshop meetings and/or web conferences shall be organized by the Workshop secretariat in consultation with the Workshop Chair. The list below covers the main tasks of the Workshop secretariat. It is not intended to be exhaustive.

- Administrative and organizational contact point for the Workshop
- Ensures that the development of the CWA respects the principles and content of the adopted project plan and of the requirements of the CEN-CENELEC Guide 29
- Formally registers Workshop participants and maintains record of participating organizations and individuals
- Offers infrastructure and manages documents and their distribution through an electronic platform
- Prepares agenda and distributes information on meetings and meeting minutes as well as follow-up actions of the Workshop
- Initiates and manages CWA approval process upon decision by the Workshop Chair
- Interfaces with CEN-CENELEC Management Centre (CCMC) and Workshop Chair regarding strategic directions, problems arising, and external relationships
- Advises on CEN-CENELEC rules and brings any major problems encountered (if any) in the development of the CWA to the attention of CEN-CENELEC Management Centre (CCMC)
- Administrates the connection with relevant CEN or CENELEC/TCs

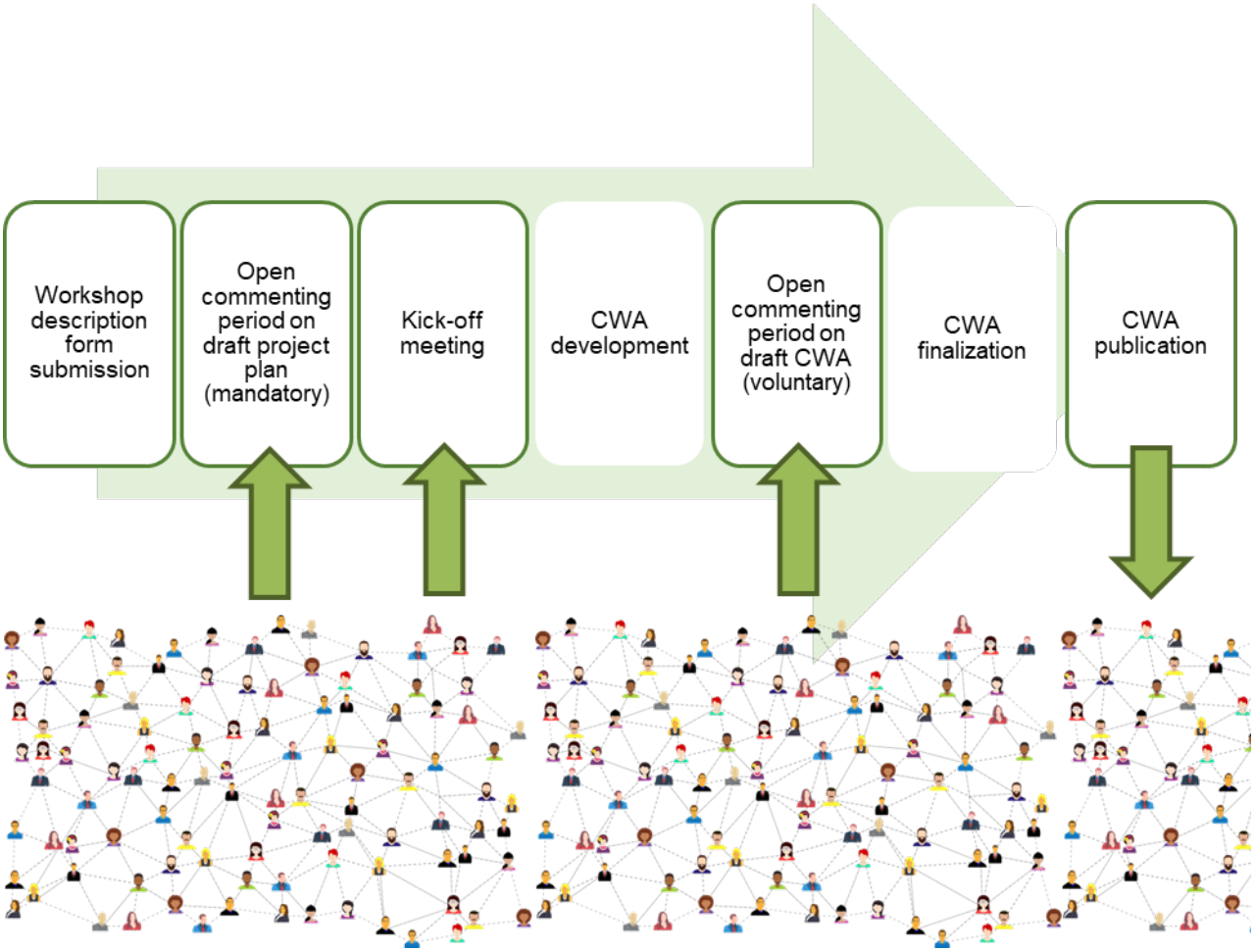
6.3 Decision making process

The CEN and/or CENELEC Workshop Chair is responsible for ensuring that the development of the CWA follows the principles and content of the project plan described in this document and the requirements of CEN-CENELEC

Guide 29. The CEN and/or CENELEC Workshop Chair may take decisions on the conduct of the CEN and/or CENELEC Workshop on the basis of the comments expressed by the participants and of CEN-CENELEC Guide 29.

If Workshop participants cannot be present in the meetings when the CWA or its draft is adopted, an alternative means of including them in the voting procedure shall be used.

7 Dissemination and participation strategy



Proposal form submission

The Workshop proposal will be disseminated to the following relevant stakeholders and bodies for consultation:

- standards committee, working group etc. In particular:
  - CEN/TC 206 – Biological Evaluation of Medical Devices
  - CEN/TC 140 – In Vitro Diagnostic Medical Devices
  - ISO/TC 276/SC 2 – Microphysiological Systems and Organ-on-Chip
  - ISO/TC 229 – Nanotechnologies
- publisher of technical rules
- sector forum
- CEN-CENELEC Focus Group on Organ-on-Chip (FGOOC)

- coordination group
- other academic / research institutions working on BBB and organ-on-chip models
- others

Open commenting period on draft project plan

The project plan will be disseminated to the following relevant stakeholders and bodies for commenting:

- standards committee, working group etc. In particular:
  - CEN/TC 140 – In Vitro Diagnostic Medical Devices
  - CEN/TC 206 – Biological Evaluation of Medical Devices
  - ISO/TC 276/SC 2 – Microphysiological Systems and Organ-on-Chip
  - ISO/TC 229 – Nanotechnologies
- publisher of technical rules
- sector forum
- CEN-CENELEC Focus Group on Organ-on-Chip (FGOOC)
- coordination group
- other academic / research institutions working on BBB and organ-on-chip models
- others

In addition to the CCMC website, the project plan and the date of the kick-off meeting will be advertised on the UNI website (https://www.uni.com/) to raise awareness. Interested parties are requested to contribute either through commenting of the project plan (short term) or through Workshop participation (long term).

Open commenting period on draft CWA

The commenting phase is not compulsory in this case and it can be added. Decision on the submission of the draft CWA to public commenting phase can be agreed at a later stage, during the works of the CEN/WS.

Considering the limited time available, the Public Consultation stage will be skipped.

CWA publication

The final CWA will be disseminated to the following relevant stakeholders and bodies:

- standards committee, working group etc. In particular:
  - CEN/TC 140 – In Vitro Diagnostic Medical Devices
  - CEN/TC 206 – Biological Evaluation of Medical Devices
  - ISO/TC 276/SC 2 – Microphysiological Systems and Organ-on-Chip
  - ISO/TC 229 – Nanotechnologies
- publisher of technical rules
- sector forum
- CEN-CENELEC Focus Group on Organ-on-Chip (FGOOC)
- coordination group
- other academic / research institutions working on BBB and organ-on-chip models
- others

In addition to the CCMC website, the final CWA will be advertised on:

- sector specific newsletter
- social media, such as
    - Facebook
    - Instagram
    - LinkedIn
    - X
- Research Gate
- Others

Annex I – Security risk analysis

This annex shall be completed if section 1.12 of Part A indicates that security aspects are addressed by the Workshop.

I.I General

Security risk analysis is a process of identifying and analyzing the main negative factors that may affect a standardization project's objectives. The following is targeted at secretariats of CEN and/or CENELEC Workshop Agreements (CWA) dealing with security issues. Its purpose is to help them identify and mitigate the risks associated with their project. It is structured around two main security threats that can affect the success of the work: major diverging interests among stakeholders and sensitive information.

I.II Risk analysis on major diverging interest among stakeholders

Diverging interests among stakeholders can impede the process in reaching agreement on the CWA and even lead to failure to deliver the planned CWA. In order to identify and possibly mitigate the risks, the following questions should be reviewed:

– Is the planned CWA expected to have a major impact on the security policy/strategy of the core stakeholders?

– Does the scope of the CWA cover products or services with a clear dual-use purpose (i.e. which can be used for military purposes)?

I.III Risk analysis on sensitive information

– In light of the scope of the CWA, is it likely that it may deal with sensitive information? If so, what is the information sensitivity level?

- Is there a need for a (non-)disclosure agreement?
- Is there any conflict of interest for stakeholders involved in the CEN and/or CENELEC Workshop, regarding especially the use they may make of any information they receive during the development of the CWA?
- What steps should be taken to manage information dissemination and storage (e.g. memory stick, emailing, storage) during the development process of the CWA?