National Biofilms Innovation Centre

# Biofilm Standards and Regulations in Pharma and Medical Devices Sectors

## WORKSHOP REPORT

29 APRIL 2022 – BIRMINGHAM, UK

# Contents





# Executive Summary

The National Biofilms Innovation Centre (NBIC), in partnership with the US Centre for Biofilm Engineering (CBE), organised a Workshop on Biofilm Regulations and Standardisation in Medical Devices and Pharma sectors, which took place in Birmingham, UK, on 29 April 2022.

The meeting was unique, bringing together over 40 representatives from industry, academia, metrology and standardisation and regulatory bodies to map the current landscape, needs, trends and expectations in biofilm standardisation within the UK and to establish industry and regulatory participation in a forward working group. Discussions were very candid, open and stimulating, with the aim of working together as a community to advance the field. The presence of international delegates was very useful and provided additional international context to the discussions.

The meeting was supported by the BBSRC Global Partnering Award and closely aligned to the mission of the International Biofilm Standards Task Group (of which both NBIC and CBE are co-founders): "To drive the international development and acceptance of standardised biofilm test methods in health care, the built environment and industrial systems."

As pre-work and during the workshop, we posed two questions to be considered and debated:

- What do you see as the current needs with respect to standards and regulations in your setting and business relating to biofilms?
- What do you believe should be (i) done in terms of concrete next steps by this group? and (ii) the overall long-term goals?

The participants shared a plethora of different experiences, needs, ideas and unique views on the subject. Nevertheless, several clear points emerged, both from the pre-work feedback and from the in-person discussions:

- There is both the opportunity and desire from the community to make progress in creating biofilm-related standards.
- There is a strong need for a comprehensive review of standards, methods and practices that are currently in use by the community. Such a review would provide a basis for a gap analysis and identification of a pathway for biofilm standards development.
- It is clear that 'one size will not fit all' due to diverse sectors and applications and the complexity of the biofilms themselves. It would be more practical to build a 'component approach', consisting of a base set of standards and guidance on how and when to use them.
- It is crucial that regulators are part of the standardisation activities and engaged from the beginning.

# Background

## BIOFILMS IN CONTEXT

Microbial biofilms and communities collectively represent the largest biomass and activity centre on the planet playing a major role in the biology of the environment, both natural and engineered.

Compared to unbound bacteria of the same species, biofilms are typically resilient to biocides and so can be challenging to control. They can present risks to human and animal health, introduce food safety problems, disrupt production from oil and gas wells and contaminate potable water supplies. They can also be useful. Waste-water treatment processes make extensive use of biofilms, they can increase the bioavailability of nutrients in the soil and seal cracks in borehole casings. Our estimate is that biofilms impact about $5,000bn of economic activity, approximately twice the Gross domestic product (GDP) of the UK.

## NATIONAL BIOFILMS INNOVATION CENTRE (NBIC)

NBIC was formed in December 2017 as an Innovation Knowledge Centre (IKC) funded by BBSRC, Innovate UK and the Hartree Centre.

NBIC's mission is to harness the UK's industrial and academic strength in biofilms.

NBIC is the UK's recognised hub for accessing biofilm expertise, capability, science and innovation capacity. Its aim is to catalyse the growth in the UK's scientific, technological, and industrial expertise in biofilms with the goal of delivering:

- World-class science and scientists,
- Breakthrough innovations,
- Economic and societal value.

NBIC is working to create a network and community of researchers and industrial/commercial partners across the UK and internationally who together are working to progress all of these elements.



## CENTER FOR BIOFILM ENGINEERING (CBE)

Montana State University's Center for Biofilm Engineering has been a world leader in biofilm research for 32 years. A prestigious 11-year National Science Foundation Engineering Research Center grant awarded in 1990 paved the way for the CBE's influence in the emerging field of biofilm research.

The center's three-fold emphasis in research, education, and industry continues to produce results and exciting opportunities for students, staff, and faculty as well as industrial partners. The mission of the Center for Biofilm Engineering is to advance the frontiers of health, energy, industry, and the environment through biofilm research, education, and outreach.

### PREVENT

Knowledge-based design of surfaces, interfaces and materials

### DETECT

Innovative sensing, tracking and diagnostic technologies

### MANAGE

Kill, remove or control established biofilms from exploiting their life cycle dynamics

### ENGINEER

Control and direct complex microbial communities in process applications

# Addressing the need for biofilm standards

## THE PROBLEM WITH BIOFILM STANDARDS

A critical unmet need for innovation across many industry sectors affected by biofilms is the infrastructure and support needed to demonstrate alignment to relevant standards and the associated analytical competencies.

Our national and international academic-industry roadmapping has consistently identified the establishment of global standards in biofilms as a priority need. As a key example, the burden of chronic infections caused by biofilms, e.g. non-healing wounds or biomedical device-associated infection, is a major problem faced by the UK's NHS and globally, particularly in relation to the increasing cost and long-term care requirements associated with ageing population demographics. Yet, a major block to innovation is that there are no validated standards for the measurement or definitive diagnosis of biofilms. Availability of such standards would facilitate translational innovation, stimulate business growth, and support global societal and healthcare challenges.

## INTERNATIONAL BIOFILM STANDARDS TASK GROUP (IBSTG)

In February 2020, NBIC along with the US Center for Biofilm Engineering, the Singapore Centre for Environmental Life Sciences Engineering (SCELSE), and an EU Cooperation in Science and Technology (COST) action group AMICI, formed the International Biofilms Standards Task Group (IBSTG).

The group has published its purpose and mission across all partner websites and forums:

**MISSION:**

To guide the international development and acceptance of standardised biofilm test methods in health care, the built environment, and industrial systems.

**GOAL:**

Enable informed and consistent decision making on the international regulation of anti-biofilm products.

**AIMS:**

- Educate regulatory decision makers on the importance of using biofilm methods for biofilm-specific label claims.
- Promote to public officials the need to set global biofilm standards through a consortium of established and recognised regional expert organisations.
- Standardise and validate biofilm test methods that are referenced in regulatory guidance documents.
- Promote the use of statistically validated biofilm methods when regulating products with a "kills" or "prevents" biofilm label claim.
- Leverage the global nature of the consortium to adapt testing methods across geographies.
- Engage industry, research institutions, and academic stakeholders in the method development process.
- Champion biofilm methods in country and industry-specific standard setting committees.
- Promote international consensus in the biofilm methods recognised in regulatory guidance documents.

## STAKEHOLDER CONSULTATION AND WORKSHOP

This workshop resulted directly from the activities of the IBSTG and was closely aligned to the mission of the task group. The meeting was supported by the BBSRC Global Partnering Award aimed at "Building a globally leading partnership in biofilm standardisation between USA and UK biofilm innovation centres".

The main objective was to bring together complementary expertise (academic, industrial, metrology, standardisation and regulatory) in order to address the need for standardisation in the biofilm field. The meeting concentrated on the UK landscape with the focus on the health sector.

It was preceded by industry consultation; on 17 January 2022 NBIC held an online meeting with a subset of industry representatives to better inform the planning of the workshop. The discussion helped to define the session. The key findings from the session are summarised in Appendix 1.

# Workshop on Biofilm Standards and Regulations in Pharma and Medical Devices Sectors

## SETTING AND AIMS

The workshop was held in Birmingham on 29 April 2022.

Representatives from industry, academia, metrology and standardisation and regulatory bodies were brought together to map the current landscape, the needs, trends and expectations in biofilm standardisation in medical devices and pharma sectors within the UK, and to and establish industry and regulatory participation in a forward task/working group.

The intended outputs of the day were:

- To create discussion summary notes for distribution to all attendees and for wider dissemination.
- To agree a set of next steps for the community to undertake to ensure progress in biofilm standardisation.

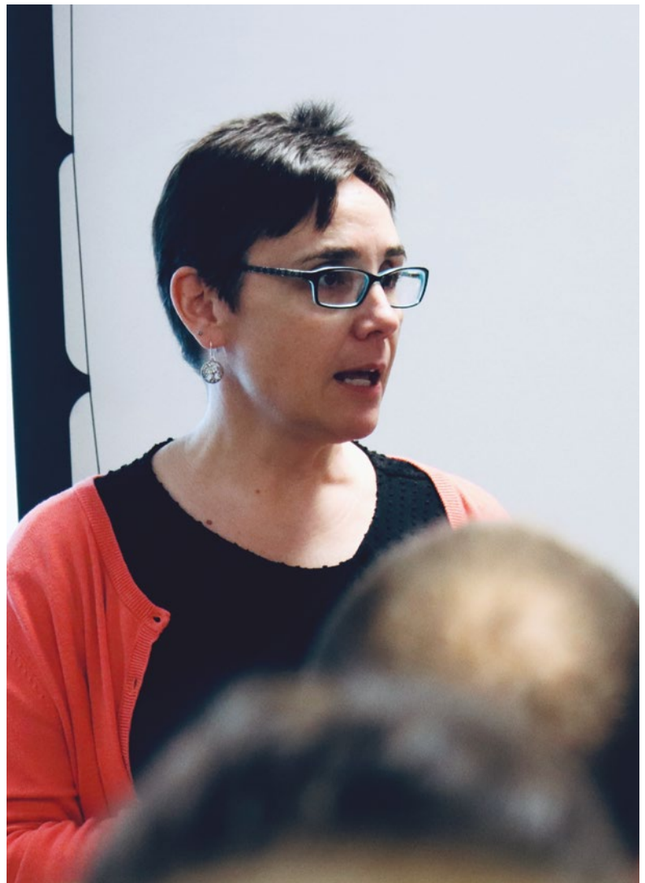
The workshop organisers invited experts from diverse sectors concerned with biofilm standardisation and regulations. 39 delegates attended the workshop, including 11 from industry, representing 9 companies, 22 from academic institutions and 6 from government institutions and agencies. To provide input to the meeting (pre-workshop questionnaire (Appendix 2)) and to ensure candid and informative discussions during the meeting (Appendix 3) all delegates were asked to consider and debate two questions:

- What do you see as the current needs with respect to standards and regulations in your setting and business relating to biofilms?
- What do you believe should be (i) done in terms of concrete next steps by this group and (ii) the overall long-term goals?

Following a welcome and introduction by Dr Mark Richardson and Dr Paulina Rakowska, there was a presentation from Professor Darla Goeres from the Center of Biofilm Engineering (CBE), who shared her experiences with biofilm standardisation and regulation in the US, in her talk entitled: 'The USA journey to establishing dialogue with regulators and gaining approval for biofilm related tests allowing product performance claims to be made'.

## WORKSHOP OUTPUTS

The delegates were then divided into 7 groups, each having a mix of representatives from different sectors (industry, academia, metrology, regulations), for focused discussions around the two predefined questions and to identify the main priorities and next steps. The NBIC team collected the outputs (Appendix 3) which along with the pre-submissions (Appendix 2), form the basis of this summary report.





## DISCUSSION

The main themes that emerged from the pre-submissions and from the discussions at the workshop were:

**What are the current challenges?**

**Regulations:**

- There is lack of clarity on how to develop and progress claims for products. Different methods are often used to support claims for different products even if the products/claims are similar.
- Regulatory processes and requirements differ between different countries. For example, the same type of product claims can fall under different regulatory pathways in the UK/EU and the USA. There is a distinct lack of harmonisation in terms of terminology or methods to be used to support the claims.

**Standards:**

- Where there are no standards to follow, companies tend to turn to testing laboratories to use their expertise and experience for methodology. Established companies who often have larger resources or budgets can afford to develop a plethora of tests and measurements to support their product claims. This can set a high bar for regulatory expectations, putting smaller companies at disadvantage as they may not be able to afford the same extent of testing.
- There are very few existing standards (ASTM standards mentioned) that are used to consider claims against biofilm(s). Moreover, methodologies within each standard come with the advantage of being adaptable, but equally all have limitations.
- Standards can be seen by academics as an inhibitor of innovation as they do not allow deviation from the agreed method.

**Biofilm Awareness:**

- The economic burden of biofilms and economic impact of having industry standards were discussed. Several sectors were highlighted during discussion that are adjacent to human drugs and devices and can have overlapping needs. For example, biofilms present a considerable issue in veterinary and animal farming settings. The recognition of biofilms as a problem is growing in that sector with novel approaches to a possible solution being based on promoting cleaning (reduce and control rather than eliminate). This also creates a need for adequate cleaning products with a biofilm reduction or removal claim.
- In the medical devices sector, biofilms do not seem to be of first concern when it comes to product claims (except where one purpose of the device is to reduce or remove biofilms e.g. wound healing topical antimicrobials). This calls for awareness of the implications of biofilm colonisation of tissue or devices to be increased, not only for regulators but also for the wider user community.

**Fundamental research:**

- It is unclear/there is no consensus of what constitutes a biofilm.
- Lack of fundamental research in biofilms and a lack of mechanisms to transform fundamental research into standard methods were mentioned repeatedly as blockers preventing development of reproducible models and methods.
- Lack of knowledge of behaviours of multispecies biofilms was voiced as a significant problem:
  - In disinfection, multispecies biofilms are important and there is a need for reproducible multispecies biofilm models. It is unclear how multispecies models would affect the effectiveness and value of tests in comparison to tests done on monospecies biofilms.
  - In pharma, monospecies biofilm models are used and are considered more robust and easier to handle. However, they do not offer appropriate challenge (e.g. single organism, no immune cell involvement) and may perpetuate the cycle of promising products failing further along the drug development pipeline.
- Fit for purpose detection methods are lacking.
  - In the context of disinfection and cleaning, it is unclear what is 'left behind' and how much this matters in different contexts and settings?
  - In the pharma industry, there is no method for the routine detection of biofilms. Currently tests are based on the limit for microbes in a water sample. A lack of detection inhibits a regulatory standard for detection and compliance.

### Reporting and information guidelines:

- There is a need for consensus and wide adoption of minimum information/reporting guidelines to ensure sufficient information is provided in published work. The guidelines would be specifically useful to the scientist, permitting them to learn and source from already published results.

### Understanding of standardisation:

- Some academics and researchers expressed strong interest in gaining an understanding of what is required to develop standard methods as well as the exact requirements for turning a method into a standard.

## What is needed to address the challenges?

### Regulations:

- The importance of engaging with regulators was repeatedly stressed. A dialogue needs to be established with regulators not only in the UK but also other countries, across the sectors.
- Regulations and the regulatory bodies' views on biofilms will differ across specific geographic regions. For this group it is important to gain an understanding of both the awareness and position that the UK regulators have in terms of biofilms and their impact. A better understanding of what regulators expect from industry, metrologists and academics will aid faster standardisation of methods.

### Biofilm Awareness:

- There is a need for general change of the mindset and culture in the field. We need to consider what would encourage collaboration, transparency and build awareness of biofilms and the pressing need for relevant standards and regulations. Educational awareness was suggested to bring end-users on board.

### Research:

- There is a need to identify the fundamental research required to develop standards and to achieve an appropriate level of simplification without compromising successful outputs.
- Concrete, basic science is needed to provide the fundamental research and to carry out the development of methods and models resembling the appropriate real environments in a reproducible manner.

### Portfolio of current standards/gap analysis:

- There is a strong need for a review/collation of the current standards, methods, guidelines, and practices that are used by researchers, industry, and regulators both in the UK and internationally. Such a review, when widely disseminated, would create a base for not only standards development but also aid dialogue with regulators, policy makers and funding bodies. The proposed aims of the review would be to:
  - Provide a basis for gap analysis between what is already available, accepted and in use and what is required to be developed.
  - Provide insight into UK regulatory requirements and constraints with respect to existing biofilm methods.
  - Provide an understanding of what methodologies are already used and accepted and which could form the basis of standard(s).
  - Create on overview of currently available methodologies alongside an indication of their robustness, application area, and type of product claims they could be used to support.
  - Identify the degree of commonality between different methodologies but also industries. This could possibly allow creation of more general standards, suited to a wider group, and reduce the individuality of product claims. An example could be antibiofilm claims focusing on the generation of a standardised biofilm on surfaces prior to treatment/exposure.
  - Create an opportunity for cross-sectoral sourcing and adaptation of methods already used by different sectors.
- It was suggested that the review should initially concentrate on specific defined biofilms areas, as each sector would cover a wide field of applications and needs. To cover more sectors, the review could be either staged, with other sectors analysed later, or segmented, with reviews focused on different sectors being carried out in parallel.

### Industry/end user consensus:

- Standardisation should be driven by the stakeholder needs: we need to understand from industry the real type of standard tests they require to respond to their specific needs.

### Interdisciplinary approach and wide collaborative effort:

- Development of standards requires the establishment of collaborations and networks as well as dedicated co-ordination of projects and initiatives at national and international levels.
- Bringing together stakeholders across different areas of industry, regulation and academia will be crucial to success and to providing an agreed, cross-sector approach.
- It should be remembered that a huge amount of work and validation has already taken place within specific sectors e.g. testing laboratories, or US's CBE. That experience and expertise should be built on while developing standards.
- Engagement with standardisation bodies e.g. BSI in the UK, is critical as they can provide guidance and support. In addition, for standards to be developed, the actual work will have to be done through the standards setting organisations. Standards developed through e.g. BSI become accessible to any industry groups.
- From a global perspective, regulators across the world should be brought into dialogue with industry and academics to prioritise the standards that need developing, and which regulators across countries will accept.
- Focus/working groups should be created that can develop standards, and through their networks, test these with industry leaders who require the models/methods. "Round robin" studies will be required for methods validation and reproducibility testing of the selected and accepted for standardisation methods. These will require coordination and engagement of laboratories that have an interest and the capacity to support method validation. The focus/working groups should have the capacity to bring these validated methods to appropriate bodies.

### Component approach:

- It is clear that 'one size will not fit all' due to diverse sectors and applications and the complexity of the biofilms themselves.
- There is a need for harmonised, general methods, which could be used by different sectors e.g. to predict the performance of a product for its desired application. There is also a need for application specific methods. Here, creation of a tier system was proposed: Tier 1 - general methods and Tier 2 – application specific methods.
- A 'component approach' was proposed as a practical solution in a form of a 'claims toolkit' - a collection of a base set of methodologies/standards, an indication of how robust they are and guidance on how and when to use them (what claims they can be used to support). The collection could be continuously reviewed and updated to include novel applications of products or novel experimental methods that have been created.

### Developing standards:

- The choice of standard to develop requires identifying the most pressing need and context for the standard.
- It would be sensible to start with one or two standards, to set an example for future developments.
- Creation of generic platforms that would aid either new standards development or modification of existing ones for specific applications should be considered.
- It was proposed that a roadmap should be created. The roadmap needs to include a plan with timeline for the engagement with regulators and end users to develop the standard that is appropriate for the point of use. The plan should also establish resources required to develop a standard.

**‘Standards for developing Standards’:**

- It was suggested that the group (workshop attendees) could ‘set standards for developing standards’. The group could help build a guideline, as to how to perform reproducible measurements in this area. The group could provide insight into the best use of reference materials within the field, driving their development as well as their use. The guideline should encompass four fundamental parts:
  - Toolbox of measurands
  - Toolbox of microbiological systems
  - Toolbox of calibration surfaces and materials
  - Universal terminology (across academia, industry and regulators)

**Reporting and information:**

- There is a need for consensus and wide adoption of minimum information/reporting guidelines to ensure sufficient information is provided on published work. The guidelines would be specifically useful to scientist permitting to learn and source from the already published results.
- Reporting on negative results should be promoted and encouraged by the community.
- It was suggested that creation of a platform to discuss the requirements, opportunities, and hurdles for developing fit-for-purpose standards would be beneficial to the community and progress being made.

**Wish list for the future**

- A portfolio of biofilm-specific standards, which would complement the current database of standards as an essential tool for industry and research in navigating the often-complex regulatory framework surrounding biofilm research.
- Creation and publication of a framework of all relevant methods that can be used, where no published biofilm standard exists.
- The wish would be to have the regulator requesting a particular standard method and a particular standard claim in device/pharma product developments.
- Independently-developed standards that are widely accepted and used over the long-term.



# CONCLUSIONS AND NEXT STEPS

The participants shared a plethora of different experiences, needs and ideas and many unique views on the subject. Nevertheless, several clear points emerged:

- There is both the opportunity and desire from the community to make progress in creating biofilm-related standards.
- There is a strong need for a comprehensive review of standards, methods and practices that are already in use by the community. Such review would provide a base for gap analysis and identification of standards most needed by the community.
- It is clear that ‘one size will not fit all’ due to diverse sectors and applications and the complexity of the biofilms themselves. It would be more practical to build a ‘component approach’ (claims toolkit), consisting of a base set of standards and guidance on how and when to use them.
- It is crucial that regulators are part of the standardisation activities and engaged from the beginning.

It is NBIC’s goal to support the biofilm community in addressing the need of biofilm standardisation and to ensure that progress is made. NBIC is already actively addressing the need by organising industry consultations, establishing networks and collaborations and engaging in a variety of initiatives and research projects. As an example, in June 2020 NBIC joined the BSI CH/216 - Chemical disinfectants and antiseptics committee to lobby for development of standards for assessment of these agents in the presence of biofilms.

The most logical next step, following this workshop, is to conduct a review on current biofilm methods, best practices, existing standards and regulatory requirements. NBIC is keen to take a lead on conducting such review in the areas of medical devices and pharma. This will form part of a larger project by the IBSTG, who are working to set up a central database of all current methodologies and standards that already exist across different sectors and regardless of the term(s) they use for biofilms e.g. “slime” and the “microbiome.”

In parallel the IBSTG will pursue approaches to establishing a joint programme in biofilm standardisation and prenormative activities informed by the outputs of this meeting, with the goal of progressing to normative activities and international standardisation.

## Reference

1) NBIC Workshop Reports (https://www.biofilms.ac.uk/publications-reports/)

# Appendix 1: Pre-workshop industry consultation

On 17 January 2022 NBIC held an online meeting with a subset of industry representatives to better inform the planning of the workshop.  The discussion was insightful and useful in helping to define the full day session.

Four key needs have been identified during the discussion.

**1. A better understanding of regulatory expectations.**

Main comments:

- Often it is not clear on how to put a claim for a product. Where there are no standards to adhere to, companies can tend to turn to testing laboratories for methods and established companies with larger budgets can afford a plethora of tests and measurements to support their product claims. This can set a high bar for regulatory expectations, putting smaller companies in disadvantage as they may not be able to afford the same extent of testing.
- The wish/end goal would be to have the regulator requesting a particular standard method and a particular standard claim in device/pharma product developments.
- Regulatory processes and requirements differ between the UK/EU and the USA. The same type of product claims can fall under different regulatory pathways. EU regulators seems more pragmatic with their requirements. Nevertheless, the EU regulatory burden has noticeably increased in recent years.
- It would be good to learn the US perspective, experiences and requirements and to have an FDA representative at the workshop.

**2. Relevant/fit-for-purpose standards**

Main comments:

- The lack of fit-for-purpose standards can lead to the use of inadequate methods. There are for example no agreed standards for disinfection use in clean rooms – the methods are taken and modified from other uses where standards do exist. Inappropriate or inadequate disinfection can lead to poor outcomes or unnecessary chemicals being used, rising costs and slower processes.
- Standards should account for end use scenarios. For example, they should account in many situations for mature biofilms, grown over long-time biofilms and long-time interventions.
- BSI is setting up a biofilm working group to help produce fit-for-purpose standards
- CEN/BSI divides standards into 3 areas – veterinary, medical and general purpose. It would be beneficial to see general standards applicable to/cross cutting the areas.
- Having representative tests would be beneficial with a not too narrow target. Perhaps a hierarchy of tests: from monospecies to provide reproducibility to added complexity biofilms to provide relevance to the system/application. For example, in the medical field there is a need to link lab tests to preclinical performance and then to clinical.
- The lack of standardisation in biofilm is not new and was there already decades ago. To be able to really make progress, we should not be starting  from scratch but should a) focus on priority area/standard needs; b) start from established and accepted methods, models and practices.
- Good starting points already exist and there is no need to start from scratch. E.g. ASTM CDC methods seem to be the most known and reliable method for biofilm production.

**3. Review of current practices/standards**

- It was proposed one useful starting point would be to produce a technical report, collating and summarising the current state of standardisation in the field, existing methods and standards used by the community. There is a wide choice already there: elegant models, developed by academics, as well as company offered services.

**4. An action orientation**

- There is an opportunity and a desire from the group to make progress. By staying focussed to an achievable end goal following these starting points it can be demonstrated a relevant standard can be developed.



# Appendix 2: Pre-workshop questions

| How do you see the current needs with respect to standards and regulations in your setting and business with respect to biofilms? | What do you believe should be done (i) in terms of concrete next steps by this group and (ii) what the overall long-term goals should be? |
|---|---|
| We need to have a better understanding of what is expected from regulatory bodies to enable standardisation of methods. | Detection of MIC.Std test of MIC/CR - Regulatory environment. Complexity of corrosion processes:- Mechanistic understanding.- Correlative/multi-factoral understanding. |
| We need to identify what degree of commonality these test methods and industries have so standardisation can suit the larger group and reduce the individuality of product claims. This may stem from the early stages of antitbiofilm claims focusing upon the generation of the biofilm itself on surfaces prior to treatment/exposure. | As above. |
| We, as researchers, need better understanding of what it takes to turn a method into a standard. | |
| There is no method for the routine detection of biofilm in the Pharma industry. There is only a dubious sample limit for bugs in a water sample. Treatment for biofilm can vary form hard science to wishful thinking. A lack of detection inhibits a regulatory standard for detection and compliance | For my industry I would like better tools for detection of biofilm in the first instance. i am not sure how a EN standard will help, except for disinfectant supplier label claims. |
| My expertise is on US regulations surrounding biofilm, therefore I am not sure of the needs in the UK. My first question would be how aware are the UK regulators with regards to the importance of biofilm? | Difficult question because a lot of the actual work will be done in the standard setting organizations and within the regulatory agencies. |
| – There appears to be little or no standards in the UK and Europe, and it's a matter of who shouts loudest and markets themselves best to see who adopts the models. We need a consortium/consensus group of people who work with industry to come to a defined panel of agreed models. | Developing a working group who can develop standards and through their networks test these and present them to industry leaders who require the models. |
| There needs to support for the work planned via BSI (or other standards bodies) to establish an initial biofilm standard(s).<br>We need to work out what already exists in terms of tests in other sectors. | Support for the BSI biofilm group, in terms of method review, development and validation.<br>The initial step is to identify the key biofilm areas of interest as they cover a very wide field and trying to include them all in the initial phase is not practical. |
| In academia if should suffice to have minimum information guidelines. There needs to be however a discussion on what type of standard methods are more meaningful for industry. | Creating a set of standard methods that can predict well the performance of a product for its desired application. These standards should be continuously reevaluated to include novel applications of products or novel experimental methods that have been created. |
| In academia if should suffice to have minimum information guidelines. There needs to be however a discussion on what type of standard methods are more meaningful for industry. | Creating a set of standard methods that can predict well the performance of a product for its desired application. These standards should be continuously reevaluated to include novel applications of products or novel experimental methods that have been created. |

| How do you see the current needs with respect to standards and regulations in your setting and business with respect to biofilms? | What do you believe should be done (i) in terms of concrete next steps by this group and (ii) what the overall long-term goals should be? |
|---|---|
| All of the examples are important. It would also be useful to establish how many standards are needed. Is it a one size fits all for health or for biofilms overall, or is it context dependent and how many contexts are achievable with regards to establishing a robust standard. How economical does the standard need to be. Does there need to be an educational awareness aspect, so end users are on board with the need. | Identification of the most pressing context for the standard and a plan with timeline for liaising with regulators and end users to develop the standard that is appropriate for the point of use. Need to identify a roadmap to establish the resources required to develop the standard. |
| We, as researchers, need better understanding of what it takes to turn a method into a standard.<br>We need to work out what already exists in terms of tests in other sectors.<br>There needs to be work via BSI (or other standards bodies) to establish an initial biofilm standard relevant to the medical setting.<br>We need to establish a dialogue with regulators in the UK, USA, EU across the sector. | Define applications; examine the similarities and differences<br>Set up working groups that will work toward drafts<br>Meet to discuss the drafts and then take those to BSI etc |
| – The academic researchers need a better understanding of what is required to develop standard methods<br>– We need to understand what are already used and accepted methods that could form the basis of standard(s)<br>– There need to be standard(s) developed by e.g. BSI that all industry groups can access | i. We need to know what methods are currently out there and accepted that can form the foundation of future standards. We also need to develop minimum methods reporting guidance for data produced for publication (as occurs in other areas) to ensure sufficient information is provided on published work.<br>ii. Long-term standards need to be developed that are independent and widely accepted / used |
| We need to understand from industry the real type of standard tests they need which reflect their specific needs.<br>We need to engage regulators across the world to dialogue with industry and academics to prioritise the standards that need developing and which regulators across countries will accept.<br>We need to identify the fundamental research required to develop these standards and the appropriate level of simplification that is required to avoid compromising successful outputs. | i. Need to start with one or two key sectors and engage industry from them to identify the standards they need. We then need to engage regulators across countries to agree. Finally, we need basic scientist to provide the fundamental research required to develop those standards in a reproducible manner resembling the appropriate real environments.<br>ii. (The ultimate goal is to develop biofilm standards that are accepted across the world and sectors, but we need to start one step at a time. |
| Create and issue biofilm standards in the UK for disinfectants in relevant areas (e.g. taking experience of the EPA approach and EHCA framework).<br>Ensure dialogue with all regulators is important in any work done in this area. | Agree to work towards issuing biofilm standards for disinfectants.<br>Create and publish a framework of all relevant methods that can be used where no published biofilm standard exists. |
| We need to work when biofilm assays can be best deployed during the development of an antimicrobial and what those best practice biofilm assays look like also identifying where further research into the translatability of assays is needed. | Systematic review identifying examples of successfully using biofilm assays in R&D roadmaps then input from funders and regulators followed by guidance on the use of biofilm assays in medicines discovery. Opportunity to also highlight ongoing challenge/opportunity to drive further research and investment. |



| How do you see the current needs with respect to standards and regulations in your setting and business with respect to biofilms? | What do you believe should be done (i) in terms of concrete next steps by this group and (ii) what the overall long-term goals should be? |
|---|---|
| Regulations and the regulatory bodies views on biofilm differ so the 'journey' will be geographically specific. Are we aiming to address UK / EU initially?<br>– There needs to be work via BSI (or other standards bodies) to establish an initial biofilm standard relevant to the medical setting - I agree with this but if we look to industry - Montana Biofilm and Perfectus Biomed - a huge amount of work and validation has already taken place within specific sectors. | Agree 2-3 currently available methods that could be utilised to address biofilm screening 2/3 chosen sectors.<br>Form a focus group to bring these methods to appropriate bodies with the validation packs, where they are willing to share them.<br>Use this meeting to get a list of round robin laboratories that have an intertest and the capacity to support method validation.<br>From a personal perspective (maybe the group is clearer) what do we need in order to engage BSI (or other) - how does this then relate to data that MHRA (or FDA but this is more challenging) would accept in order to gain a label claim. How do we ensure we are developing a method that will be accepted by regulatory bodies in the chosen sector? |
| – Preparing standardised tests which are also fit for use. Single species models, whilst easier to use and likely more robust, do not offer appropriate challenge and may continue the cycle of products failing further along the development drug pipeline.<br>– Establishing the validation criteria for outputs, would multi-lab studies be appropriate to help set validation ranges?<br>– Clear requirements for preparing standards, guidance on requirements from many regulatory bodies.<br>– Priorities for different models - challenges from biofilms exist in many sectors. Will standards be split by sectors i.e medical, industrial, marine or will these be general standards which can be moulded to fit. | Next steps include transparent requirements for standards and enabling a focused group discussion over current methods in use by labs to establish the best way forward.<br>Long term goals would be to establish these standards, or at least get the ball rolling with bodies which oversee standards (UK/EU/USA etc) to establish what needs to be done. |
| NPL are embedded in the development of Standards across a wide range of industries to support and enable innovation. We have research programmes focused on the development and characterisation of standardised Biofilms that can be used to support translation of research into new solutions across different sectors including and specifically healthcare. | The major block to innovation in biofilm affected sectors is the lack of validated standards for the measurements or diagnostics of biofilms, or methods incorporating advanced, state of the art biofilm analysis. A well characterised, biofilm model system that has agreed utility across the ecosystem including standards agencies and regulators, academia, solution providers and testing service laboratories is a key step in the development of an innovation ecosystem<br>To address this need requires the establishment of networks and collaborations and co-ordination of research projects at the national and international level.<br>The development of Standard analytical methods that can be used to enable and drive the investment required for innovation in development of Biofilm solutions is a key goal of NPL's metrology based research. The development of an initially UK approved Standard that can be utilised as an exemplar for international standardisation is vital to underpin innovation. Bringing together stakeholders from across different areas of industry, regulation, academia and will be crucial to success and providing an agreed, cross sector approach to the solution. |

| How do you see the current needs with respect to standards and regulations in your setting and business with respect to biofilms? | What do you believe should be done (i) in terms of concrete next steps by this group and (ii) what the overall long-term goals should be? |
|---|---|
| From my academic viewpoint, I can see the real need for such methods, but that they are lacking (from a UK/EU perspective at least) due in part to the complexities of modelling biofilm in different environments, and acknowledging that such standards would probably be more 'involved' than other microbiology standards. That being said, lots of great methods/models already exist, so there are some standards that could be moved forward quicker. Initially it would be useful to get an idea of what already exists (ASTM, SIAA, ISO, BSI, OECD, IBRG) and what requirements exist from industry and the competent authorities/regulators. | Establish academic network for ring trials, developing methods, pre-normative/normative work.<br>Identify what requirements exist for standards.<br>Identify what challenges might exist? Do methods already exist? Are current best practice realistic in terms of intended end-use? Tier 1/2 methods?<br>Identify particular standards to start with and move forward.<br>A particular piece of work that would be useful is to review UK regulatory constraints with respect to existing biofilm methods and assess what is needed but is missing. |
| All of the above | i. Identify one or two standards as exemplars to improve.<br>ii. Generic platforms that enable to new standards to be established or for existing ones to be finessed for specific applications. |
| We need to be driven by the stakeholder needs in this field to understand how we can best support them. Develop a reference measurement framework to support the area. | The group needs to come up with priorities in terms of what is going to help the field. The group needs to be engaged with regulators/relevant accreditation bodies to help them determine how they will meet the requirements for method validation. Overall the group could provide insight into the best use of reference materials within the field, driving their development as well as their use. The group could help set out a system by which could set an exemplar in the field as to how to perform reproducible measurements in this area. |
| There certainly has to be a dialogue with regulators - however first there needs to be a framework of what to discuss. The is not just about the biofilm but how the product and the biofilm interact - via the claim. A 'Claims Matrix' would be a very helpful tool. | Firstly a pulling together of what methodologies are currently available, an indication of how robust they are and an indication of what claims they can be used to support. There then needs to be a gap analysis between what is available and what is required. |
| A portfolio of biofilm specific standards would complement the current database of standards and essential for industry and research in navigating the often-complex regulatory framework surrounding biofilm research. When considering claims against biofilm, the only current standards I am aware of are ASTM 08/17/19/20. The methodologies adapted within each standard come with the advantage of being highly adaptable but equally all have limitations. Aiding in developing standards and gaining an understanding of the exact requirements of turning a method into a standard would be of great interest to me as a Research Scientist. | Concrete steps<br>• Open a platform to discuss the requirements, opportunities, and hurdles for developing fit-for-purpose standards<br>• Develop a working document of most relevant and required standards<br>• Develop a peer group with working expertise to oversee research and development of standards<br><br>Long term<br>• Produce a portfolio of internationally accepted fit-for-purpose standards |
| All the examples are relevant. Also, I collaborate with the additive manufacturing industry, which will benefit from biofilm standards and regulations in applications such as 3D printing of biomaterials. | From measurement perspective: I believe pre-normative tests to identify what is necessary to move onto normative activities |



# Appendix 3: Output (notes) form breakout sessions (Groups 1 – 7)

| Group | Issues | Next steps |
|---|---|---|
| 1 | Lack of harmonisation. Different Claims – different methods.<br>Regulators are not aligned in different countries in terms of making claims, terminology or methods to be used.<br>Medical Devices Regulations is a pain.<br>Standards / guidelines inhibit innovation. For academics it would be easier to turn to testing labs.<br>Need for generalised approaches but application focused. Create a tier system.<br>Tier approach – E.g. general antimicrobial test followed by specific application one.<br>Need for funding into standards | Create a report to capture needs and requirements<br>Change the mindset and the culture in the field to encourage collaboration, transparency and to build awareness |
| 2. | Testing stats sensitive to surface.<br>Vet, animal growths and farming recognise more how biofilms can be a problem: Solutions proposal – promote cleaning (reduce and control rather than eliminate).<br>Product with biofilm claim?<br>Oil and gas biofilms: Industry lead. Economic issue. One of the biggest cost of biofilms.<br>Cost of biofilms in farming.<br>Med/dev: biofilms not first concern/focus. Awareness needs to be increased.<br>Multi organism biofilms important as well.<br>Disinfectant, how to target multispecies biofilms: Multispecies biofilms need to have models that are reproducible. Efficacy vs cost of testing. How lack of multispecies models will affect the effectiveness and value of the test.<br>Lack of knowledge of behaviours of multispecies biofilms, how predictive? Basic research lacking.<br>Representative species of acceptance concern/ regional focuses differ.<br>Minimum reporting/ information guidelines - Useful for science (worked for ring trial). Standard useful for industry.<br>Reporting what did not work/fail: Data management.<br>Consolidating available methods. | Segment down to areas.<br>Standards for different areas.<br>Like coupon of bacteria to have a coupon of biofilms.<br>Standards of standards like EDA system.<br>Different species and tests. Run tests at different times.<br>Standards WG.<br>How to create biofilm model.<br>Any current biofilms standard?<br>Control.<br>Surface. |

| Group | Issues | Next steps |
|---|---|---|
| 3 | What is needed?<br>Cross discipline agreement of defining parameters (What is a biofilm, total bacterial load for each medical device etc)<br>Agreement on what to measure. Removal, Prevention, Biomarkers? Current use of log reductions and CFU are not useful measurements in most sectors.<br>Further understanding of what is happening within the biofilm in any model will allow metrologists to better define what to measure to prove efficacy.<br>Reproducible methods which are specific without using methods and equipment which would be prescriptive for smaller companies or testing houses<br>Establishing minimum model criteria across all sectors with specific extra tests depending on application. | Harmonisation of methods needed.<br>Equipment, facilities and training required.<br>NO MOLECULAR ENDPOINTS.<br>Dossier/ body of evidence: can be non standard testing. Claim supported by its matrix SPC.<br>Use instructions e.g. temporal.<br>Polymicrobial. |
| 4 | What does the medical device from scope?<br>What is left behind and how much does this matter in different contexts?<br>Shallow staircase: barriers to entry following previous claims set.<br>Without standards – don't know what you're working to.<br>In one standard, perhaps can have strands for different areas/ media?<br>Lack of clarity in the industry and lack of confidence to commission work due to this.<br>Having standards = barriers to trade, macro economic benefits.<br>Existing methods can be transferable i.e. dental waterline (prevent/ remove) ISO standard (6 years ago). Grey area as must be a 'device'.<br>Having specifics reduces the interpretation of a weight of evidence approach.<br>Have you got something to benchmark your method against?<br><u>Microbiological models:</u><br>Cytocompatability (ISO 10993), biofilms (few standards) Planktonic (standards exist). What can we mirror from the US? What needs to be done on both sides?<br>Which biofilm? Application ⟷ Application. Complexity ⟷ Complexity. In vivo.<br><u>Technology:</u><br>Surface, interface or material ⟶ What is a suitable control? And How do we test? (model system, actual device?) | Harmonisation of methods needed.<br>Equipment, facilities and training required.<br>NO MOLECULAR ENDPOINTS.<br>Dossier/ body of evidence: can be non standard testing. Claim supported by its matrix SPC.<br>Use instructions e.g. temporal.<br>Polymicrobial.<br>Create 'champions' for particular test (e.g. company with expertise/ interest), with outputs being shared into a larger group.<br><u>Technology:</u><br>Research techniques – what's traceable? – What can be used in a standard?<br><u>Setting standards for creating standards:</u><br>Toolbox of measurands.<br>Toolbox of microbiological systems.<br>Toolbox of calibration surfaces and materials.<br>Creating a universal language across academia, industry and regulators. |



| Group | Issues | Next steps |
|---|---|---|
| 5 | Physical characterisation methods. Research methods – (working groups to determine what is required e.g. imaging, spectroscopy) – reference materials ⟶ Performance and stats ⟶ Method traceability e.g. SI traceable ⟶ Sufficiently defined to use in standard ⟶ If possible calibrate against existing methods (for industry). | <u>Microbiological models:</u><br>Pick exemplar standard tests (look at protocol timeline and roadmap) e.g. EN standards (surface tests).<br>Bring in regulators (e.g. BSI) and researchers and range of industries. |
| 6 | Metrology (NPL): Create standards in biofilms. Make innovation and use metrology expertise to do that.<br>CBE 32 years (pioneering) across all sectors. Transdisciplinary. Standards and relevance of systems to the field of what you are trying to reciprocate. Broad biofilm definition.<br>SME/ Consultant: Focus perspective to standardise methods. Help progress useful activities for the UK. Consolidate knowledge. Product claims vs manufacturing challenge important.<br>Academic: UK behind US. Focus on making real world impact/ save life/ Transdisciplinary: Develop meaningful/ reliable standards for product claims / consensus group. Minimum reporting standards for biofilms.<br>Testing: All sectors/ Based on experience not to be stale – steering consensus. Which way to go? Industry specific. Seek regulator approval for own methods/ clients.<br>Tough problems:<br>Easier to develop standard to kill/ remove than in 'a closed' system.<br>A detection issue.<br>Root cause investigation – guidance principles for industry.<br>The biggest need?<br>Bespoke site dependent?<br>Wound care: skin surface. | UK roadmap:<br>1) (???) versus test group/ EU.<br>2) Scope what we have learnt (UK). (EPA/ FDA / US analogue EU/ Florian)<br>3) UK guidance language.<br>4) EPA/ ECHA framework biocide sector guidance.<br>5) PDA guideline (drug association). Aseptic manufacturing.<br>6) Bring guidance from different sectors together.<br>Define area(s) to focus on:<br>e.g. urinary catheter, endoscopes, specific industry and would dressings.<br>Start with a) where are the biggest problems, b) ontology (expand NBIC tree for regulator systems), c) impacts, d) industry and regulators involved early on (insurance USA) and e) funding important.<br>Scope a) Methods currently used across the globe (learn lessons), b) collect and review 'standards' and 'guidelines'.<br>Team: Technology (industry specific), Regulators (MHRA, Health and Safety Executive), CE (BSI, notified body), academics active in the field. Narrow group plus wider consultation).<br>Prioritise wound dressings, catheters, health medical devices.<br>Ease of execution.<br>NOTE: OECD supersedes other regulations.<br>Too complicated?<br>Define how: Area, model, validate analytical method – regulatory discussion.<br>End point 1: BSI (consult with EN). (5 years to standards).<br>End point 2: ISO standard. Vs MHRA, same with FDA.<br>Rather than single species.<br>NBIC in the UK to become the 'go to' for biofilms standards: Is it a viable route? Similar to CBE (taken stance. Not set priority. EPA/ FDA decide! Cannot lobby but provide data and guidance). NBIC like CBE?<br>Industry can validate guidance.<br>Ontology define what we want to do around PDME (kill): 1) Urinary catheters (big impact and appreciable biofilm sampling ongoing), 2) Endoscope and 3) Wounds. |

| Group | Issues | Next steps |
|---|---|---|
| 7 | Identify the most appropriate regulatory body (regulatory strategy), the relevant model to the context and standardisation of detection.<br><br>Medical devices: Making a biofilm claim 1) pharma and 2) introduction to regulatory body (to lead in the UK). Parallel set of data?<br><br>Use a system that is in place. Bring in relevant data (detection biofilm) for the context of the product. Surface claim. Multispecies.<br><br>Standard resources 'best practice'. Regulators decide. Important that regulators are part of the discussion (standard development).<br><br>Need the claim ⟷ Presents investment in innovation. | 1) Bring regulators together (which ones?)<br><br>2) Provide regulators with choices on standard(s).<br><br>3) Industry regulators – agreement on parameters and end users.<br><br>4) Broad or focused? Specific application needed 'low hanging fruit'. Not wounds. Hard surfaces? Low risk, high benefit. Method device process a) easily measured, b) low risk to health/ high benefit, c) Water systems? D) flow dynamics/ physiochemical properties significance.<br><br>Method selection guidance ⟶ Decision tree ⟶ choices for regulators ⟶ dependent on application (flow dynamics, physiochemical properties, device, species, regulatory – where to start?) ⟶ Method selection guidance. |



# Useful Resources

Hartree Centre
hartree.stfc.ac.uk/

Innovate UK
gov.uk/government/organisations/innovate-uk

Biotechnology and Biological Sciences Research Council
bbsrc.ukri.org/

University of Edinburgh (NBIC - Research Partner)
biofilms.ac.uk/research-partners/university-of-edinburgh

University of Liverpool: Open Innovation Hub for Antimicrobial Surfaces
liverpool.ac.uk/antimicrobial-surfaces/the-team

University of Liverpool (NBIC - Research Partner)
biofilms.ac.uk/research-partners/university-of-liverpool

University of Nottingham (NBIC - Research Partner)
biofilms.ac.uk/research-partners/university-of-nottingham

University of Southampton (NBIC - Research Partner)
biofilms.ac.uk/research-partners/university-of-southampton

# Links to NBIC

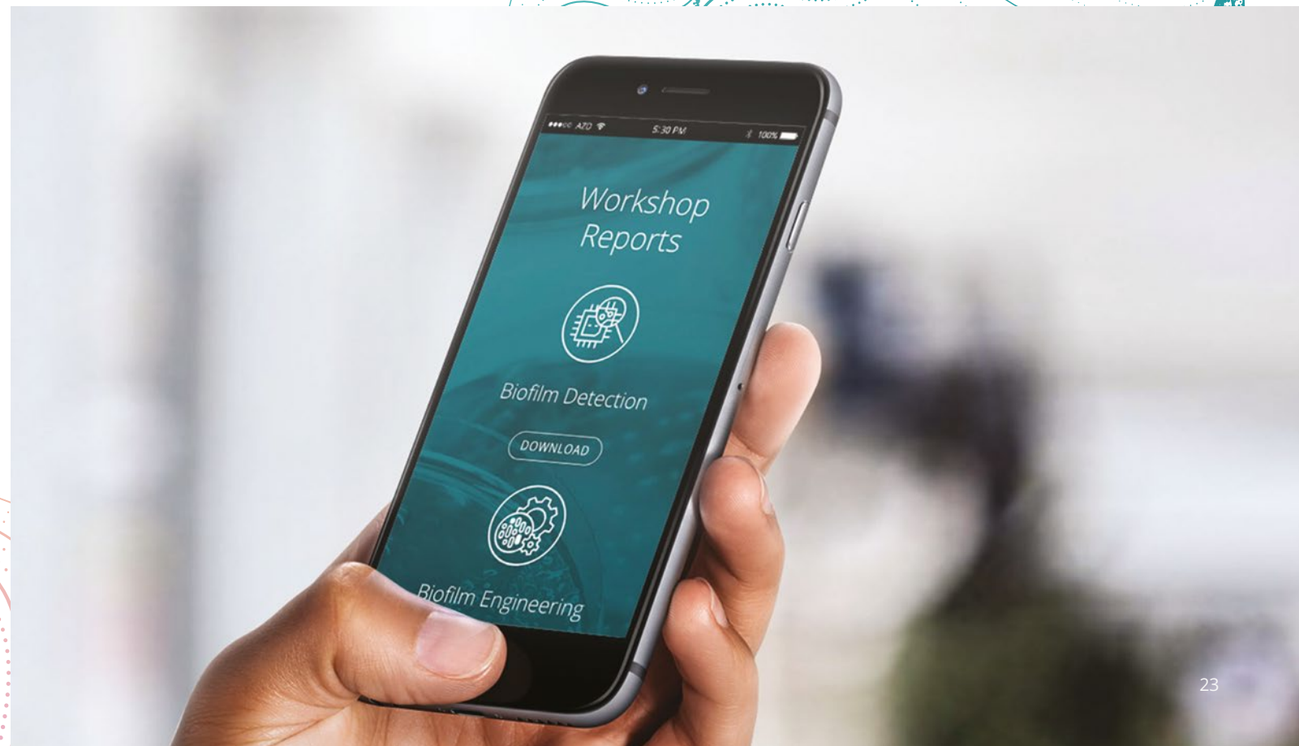
NBIC website
biofilms.ac.uk

NBIC Marketplace Portal
https://nbic.innogetcloud.com/

Our Co-Directors and Operational Management Team
biofilms.ac.uk/directors-staff

Our Research Fellows
biofilms.ac.uk/research-fellows

Our current BITE students
biofilms.ac.uk/doctoral-training-centre



# Thank you

For further information please contact nbic@biofilms.ac.uk