Regulatory Engagement Plan

Deliverable 7.5

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Abstract	The regulatory engagement plan describes the target setting for regulatory engagement as well as the activities planned within TraceBot.

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Versioning and Contribution History

Version	Date	Modified by	Modification reason
v.01	18,11,2021	C. Coulon (INV)	First version
v.02	01.12.2021	C. Coulon	Integrated comments and refinement
v.03	08.12.2021	C. Coulon	First complete version ready for first review
V.04	08.12.2021	Courtney & Royall	Revised version
V.05	13.12.2021	Courtney & Royall	Revised version
v.06	14.12.2021	C. Coulon	Revised version ready for internal revision
v.07	15.12.2021	A. Remazeilles (TECN) C. Lange-Prollius	Internal review
v.1.0	20.12.2021	Finalized version	Finalized version Rework based on internal review

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1 Executive Summary

TraceBot started regulatory engagement at the Kick-Off of our industrial advisory board on the 21st of September 2021. Following the approach described in the project proposal we are starting into a continuous exchange with industrial partners and regulatory authorities described in this document including stakeholder workshops and a whitepaper. The target of these activities is finally to ensure the acceptability of the results of TraceBot regarding verification and audit trail from the point of view of regulatory requirements and the pharmaceutical industry.

This report links the regulatory needs and expectation to the capability of the TraceBot, specifically self-awareness around the status of process materials and process execution. Significant activities are identified and described that connect and engage with stakeholders and individuals within. In particular, plans for the proposed white paper and communication workshop are given in some detail, including objectives, means, content and target sufficient of effective execution in the course of the project.

2 Introduction

As TraceBot is focussing on robotics in pharmaceutical industry we have to make sure, that our results will be acceptable for regulatory authorities. The outputs from regulatory engagement (task 7.5) will be used to enhance current procedures in the host laboratories which form the consortia and where appropriate short pilots of the TraceBot technology will be conducted.

Taken our application, the target group of our project and currently known requirements into account we describe in chapter 3 why, who and when we will engage with regulatory authorities/bodies.

3 Description of work & main achievements

The regulatory engagement plan describes the target setting for regulatory engagement as well as the activities planned within TraceBot to fulfil these targets. Section 3.1 describes the target setting focussing on pharmaceutical requirements and the linkage to verification and audit-trail. Section 3.2 describes the current and future activities to ensure the applicability of our results within the pharmaceutical results from the regulatory point of view.

3.1 Target Setting

Sterility testing is the process of measuring the presence or absence of contaminating microorganisms in drug products or medicines for human use. Sterility testing presents an essential but also challenging set of operations to form the architecture framework, requirements management design space and verification of the TraceBot initiative. All drug products, i.e., medicines, administered to man require sterility testing to gain regulatory approval. Thus, there is a wide range of products that require sterility testing and many things which can go wrong.

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Through regulatory engagement we want to make sure that the results in traceability and verification researched in TraceBot are pharmaceutically acceptable and find their way into implementation in pharmaceutical companies and are accepted by the regulatory authorities.

For this purpose, we plan to coordinate with pharmaceutical users as well as with regulatory authorities in Europe on the alignment of objectives, technical implementation, and final evaluation.

With TraceBot we develop an adaptive self-aware automated approach which learns and documents the successful execution of the sterility testing process in an audit trail within the regulatory framework.

3.1.1 Pharmaceutical Requirements

USP<71> (United States Pharmacopeial)expectations: Sterility testing of drug and pharmaceutical products is covered by all medical and medicines regulatory organizations worldwide. Through the drive towards international harmonization, the corresponding parts of the United States Pharmacopoeia, (USP), European (EP-2.6.1) and Japanese pharmacopoeias align. Thus, USP document 71 which outlines sterility testing covers all the required procedures. The expectation and aims of the methods outlined within USP<71> is to provide applicable and reproducible approaches for the detection of microbial contamination of drug products. The methods cover a large range of products and potential contamination, but common themes are apparent. These are essentially consideration and preparation of appropriate growth media for the microbial contamination, tests for sterility which involves inoculation of a sample taken from the product into an appropriate growth media, and an observation and interpretation of the results. The check steps are the appropriate selection of a test sample group from the main batch, quality assurance for the preparation of the media, appropriate sampling, incubation and counting of the number of contaminating colonies. A typical example is a batch of ampoules for injection, these have been aseptically manufactured or terminally sterilized, then a small sample is selected for sterility testing. Failure modes are: 1) inappropriate batch selection; 2) inappropriate selection of media; 3) contamination of media before sterility testing; 4) non representative sampling; 5) Incorrect incubation; 6) Errors in colony counting. All these failure modes require continuous feedback, that require robotic self-awareness.

3.1.2 Linking Design Space to Self-awareness

To both manage and verify sterility testing, in TraceBot the robot conducts procedures, collects trusted data of sufficient quality to meet regulatory requirements and uses this information as learning feedback to become self-aware and thus improve operations.

The Steritest System by Merck will be used as a first exemplar technology to launch this approach. There are several check points that are associated with validation and quality assurance, but these processes are very readily transferrable to other sterilization and pharmaceutical methods.

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In order to decide if sterility testing was executed successfully a design space (figure 1) will be designed in detail, such that different pathways within this design space may achieve an acceptable result in the sterility test.

The self-awareness element will be for the paths to sterility acceptance to be mapped in the different combinations of measured input variables. Thus, a broken ampoule will be rejected, but one with a mis-aligned label or an acceptable but slight increase in mass will be added to the design space.

	Status of process **Self-awareness that process was followed correctly following check points**	**Status of process** **Self -awareness of process step failure**
Status of materials (quality, assembly within specification)	**in scope**	**Out of scope** Process failure Report and recover
Status of materials (missing, damaged)	**Out of scope** Materials failure report and recover	**Out of scope** Process and material failure Report and stop

Figure 1. Design space and self-awareness matrix of TraceBot system.

3.1.3 Audit trail leading to regulator acceptance

Within the sterility testing process there is a high number of process steps which involve the opening of ampoules, canisters, application of needles, placement of bottles within ascribed locations, measurement of time, temperature, recording of barcodes, locating septa, and draining of liquids. Thus, the amount of positional and feedback data will be immense, and the only way to correlate and show that combinations of different variables may lead to similar passing of sterility tests is to document the traceable findings in an audit trail and present it in the design space matrix, as mapped in figure 1. The medicines regulators, like the European Medicines Agency, expect such presentation of the data, showing in-specification zones and where the edge of failure is approached. The findings from this will be validated by invited qualified persons and from members of advisory boards associated with medical devices and medicines regulations for example the Medical Devices Testing and Evaluation Centre in Birmingham and the NICE Interventional Procedures Advisory Committee, along with European equivalents.

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3.1.4 Adoption of technology within Pharmaceutical Regulated Operations.

The outputs from task 7.5 will be used to enhance current procedures in the host laboratories which form the consortia and where appropriate short pilots of the TraceBot technology will be conducted. Recommended auditors and qualified persons from the AstraZeneca, MHRA, NHS and USP (figure 2) will be invited to review these amendments and engage with the documentation required for approval of the technology and incorporation within the investigational brochures associated with new and pre-approved medicines and within the licenses associated with the manufacture of established medicines currently used by patients.

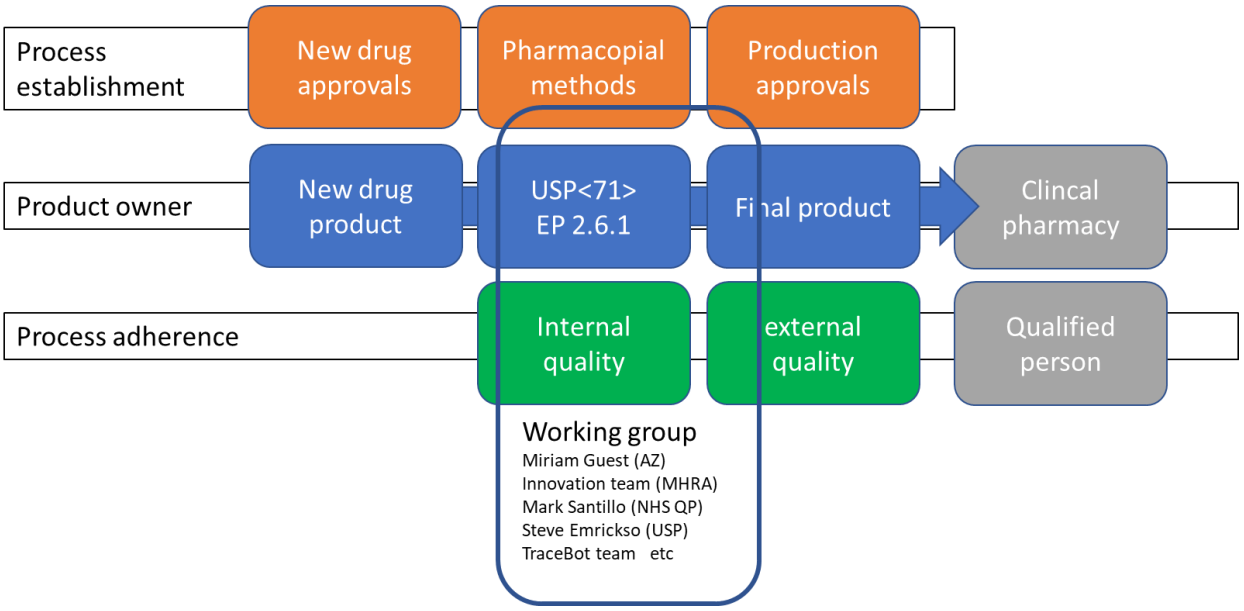

Figure 2 Stakeholder map and outline for adoption of technology,

The findings from the demonstrators within the project will be disseminated through a white paper which will lead to a peer-reviewed publication. In addition, consultation with healthcare organizations for example the NHS Pharmaceutical Quality Assurance Committee, and presentations to pharmaceutical manufacturers will be conducted for further review, engagement and then adoption. Such opportunities will be a regulatory conference ISPE (International Society for Pharmaceutical Engineering) and international events.

3.2 Core activities of the planned regulatory engagement

We scheduled regulatory engagement within TraceBot to start right from the beginning. The results to be shared and discussed with regulatory bodies/authorities are delivered by other tasks and work-packages starting nearly throughout the whole run-time of the project. While concepts are developed within the first years the different components of the demonstrator are delivered within the last years.

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Within task 7.5 we have five major activities:

1. Presentation of the target-setting to the Advisory Board (AB) and collect feedback
2. Inform regulatory authority (RA) up-front and collect feedback
3. Present the concept to AB and RA, collect feedback, and align on concept starting with the verification plan (D1.4) in month 14.
4. Demonstrate the components of the demonstrator to AB and RA and collect feedback starting end of the second year until end of the project
5. Exploit the concept within the last two years
    1. Plan and deliver communication workshop with broader audience
    2. Plan draft review and publish white paper

period	activity
1H2022	closed focus sessions
2H2022	stakeholder workshops
1H2023	drafting of adoption guidelines
2H2023	peer-reviewed paper
1H2024	communication workshop
2H2024	white paper
1H2025	end of project

Table 3 Timeline for TraceBot regulatory engagement (1H first half of year / 2H second half of year).

3.3 Description of current and future activities

While we target singular activities for the last activity (see section 3.3.1), the first four will consist of:

- utilizing our industrial advisory board for discussion and feedback, and
- target regulatory authorities (RA) one by one.

We presented our target setting to AB on the 21st of September 2021 and discussed our approach with a first RA (Paul-Ehrlich-Institut (PEI)) on the 22nd of November 2021. They:

1. confirmed the need for new approaches to verification and audit trail in automated projects
2. requested further alignment as soon as our development and research advances
3. pointed us to further regulatory authorities to be included.

3.3.1 Exploit the concept

3.3.1.1 Plan and deliver communication workshop with broader audience

Aim: improve acceptance and application of robotics technology in pharmaceutical manufacturing

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Objectives:

1. to educate practitioners about progress in trusted robotics
2. to educate on the validation progress

Audience: professionals involved in implementing and approving sterility testing solutions users (day-to-day): lab manager, implementation project leaders, quality function user (strategic) strategic leaders in biopharma (heads of innovation, digitalization)

Regulation: including PEI (DE), MHRA (UK regulator), EMA (European Regulator); US Pharmacopeia (USP), European Pharmacopeia (EP), British Pharmacopeia (BP)

Suppliers: robotics, services

Target: aiming an audience of 40 people

Content:

short (2 hour) workshop structure

- Introduction from friend-of-project, advisory board
- Keynote on problem and challenge: current practice and digitalization
- Presentation of TraceBot approach: user oriented with short video and validation approach
- Panel: regulators, a user, a qualified person, moderator
- Discussion: audience involvement

Follow-up: satisfaction survey, further action expected outcomes: 4 new contacts to engage with on pilots and facilitate take up

Location, event:

1st choice: face to face Europe ISPE Europe conference

2nd choice face to face US: ISPE conference

3rd choice online American Assoc Pharma Scientists US

Marketing: friends-of-project list, BioLAGO mailing list, DIH-Hero, ISPE-SIG contacts, personal invites, LinkedIn, TraceBot Newsletter

3.3.1.2 Plan, draft, review and publish white paper

Scope: validation of digitalization in a regulatory environment

Objective: educate audience to progress and process to validation

Audience: Professionals involved in implementing and approving sterility testing solutions users (day-to-day): lab manager, implementation project leaders, quality function user (strategic) strategic leaders in biopharma (heads of innovation, digitalization)

Regulation: including PEI (DE), MHRA (UK), EMA; US Pharmacopeia (US), EP, BP

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Suppliers: robotics, services

Structure: 5 pages

- Introduction of scope
- Challenge and burden in production
- Approaches and solution, user quotes
- Broader picture and outlook
- other relevant tasks
- Conclusion and call to action

Impact: curate website, view video, further engagement

Channel: trade press, peer-reviewed paper

- 1st choice European Pharmaceutical review
- 2nd peer reviewed, longer piece, slower to appear (J.Pharma science and technology /J.Pharma innovation / Pharma.J.)
- 3rd Pharmaceutical Engineering Magazine
- 4th Pharma Technology Focus Magazine

Marketing: friends of project list, BioLAGO mailing list, DIH-Hero, ISPE-SIG contacts, personal invites, LinkedIn

4 Deviations from the workplan

No deviation.

5 Conclusion

As expected, we started the regulatory engagement within the first year with our first meeting of our industrial advisory board. Industrial partners and regulatory authorities support our target setting and are interested to help us to deliver an approach which is acceptable from the point of view of the quality assurance of companies operating laboratories for sterility testing as well as from the point of view of regulatory requirements.

Following our regulatory engagement plan we will take the feedback and integrate it back into the development of the concepts and demonstrators within TraceBot to ensure usability of the results of TraceBot within the pharmaceutical industry.

The work within the regulator engagement task will advantageously interact with the technical tasks to ensure an appropriate level of cross-fertilization. This is particularly important as the technology develops since the regulatory stakeholders will benefit from the exposure to the new possibility (digital twin, robotic audit trails etc.) and the technical teams will benefit from the critical aspects of the regulatory world (process adherence, control of scope etc.).

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The closed working sessions will liaise closely with the technical team leaders (as indicated by the presence of TraceBot team members in figure 2). If there are some significant details which should occur during e.g., year 2 this will ensure that it will be captured and can be acted upon.

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