



DEFINITION OF TECHNOLOGY READINESS LEVELS (TRL) AND APPLICATION TO BIOMEDICAL FIELD

Adriano Savoini & Alessandro Tronchin

T&B e associati S.r.l., c/o AREA Science Park, Padriciano 99, 34149 Trieste

Description of the various Levels, corresponding phase (if any) of the Product Design process according to ISO9000 rules, actors involved and scenarios.

TRL 1 BASIC PRINCIPLES OBSERVED AND REPORTED: Lowest level of technology readiness. Scientific research begins to be translated into applied research and development.

Biomedical field: Active monitoring of scientific knowledge base. Scientific findings are reviewed and assessed as a possible foundation for characterizing new technologies

ISO 9000 Project phase: preliminary phase and brain-storming

Actors: Scientist, Researcher, Technician, R&D people

Scenario: Observation might be done by operators acting in a different field / scientific area and reported in literature, congresses, blogs, etc.

TRL 2 TECHNOLOGY CONCEPT AND/OR APPLICATION FORMULATED: Invention begins. Once basic principles are observed, practical applications can be invented. Applications are speculative and there may be no proof or detailed analysis to support the assumptions.

Biomedical field: Scientific “paper studies” can generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues. Focus on practical applications based on basic principles observed. Use of computer simulation or other virtual platforms to test hypotheses

ISO 9000 Project phase: preliminary phase and brain-storming

Actors: Laboratory team leader, Scientist, Researcher, Marketing & Finance people, IP specialist, Regulatory Affairs, Opinion leaders

Scenario: It's the inventive step! Tech concepts are transferred to product/service/application hypothesis. Budget / Market forecasts / IP strategies come into play. Focus groups with opinion leaders are used to test the product concept

TRL 3 ANALYTICAL AND EXPERIMENTAL CRITICAL FUNCTION AND/OR CHARACTERISTIC

PROOF-OF-CONCEPT: Active research and development is initiated. This includes analytical studies and laboratory studies to physically validate analytical predictions of separate elements of the technology.

Biomedical field: Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components, and begin characterization of candidate. Preliminary efficacy demonstrated in vitro

ISO 9000 Project phase: Feasibility study

Actors: Research and Development (mainly), Manufacturing

Scenario: Key points (usually the most uncertain ones) are carefully examined to demonstrate the "Project" is feasible, both on the tech and financial side. Scientists provide support and guidance to solve specific problems. This step will provide a GO / NO GO result !

TRL 4 COMPONENT/SUBSYSTEM VALIDATION IN LABORATORIAL ENVIRONMENT:

Basic technological components are integrated to establish that they will work together. This is relatively "low fidelity" compared to the eventual system.

Biomedical field: Integration of critical technologies for candidate development. Initiation of animal model development. In vitro toxicity and efficacy demonstration in accordance with the product's intended use. Initiation of experiments to identify markers, correlates of protection, assays, and endpoints for further non-clinical and clinical studies.

- Animal Models: Initiate development of appropriate and relevant animal model(s) for the desired indications.
- Assays: Initiate development of appropriate and relevant assays and associated reagents for the desired indications.
- Manufacturing: Manufacture laboratory-scale, quantities of bulk product and proposed formulated product.

ISO 9000 Project phase: Prototype optimization

Actors: Research and Development (mainly)

Scenario: Prototype is developed to its full performance potential, but still in a lab environment

TRL 5 SYSTEM/SUBSYSTEM/COMPONENT VALIDATION IN RELEVANT ENVIRONMENT:

Fidelity of breadboard technology increases significantly. The basic technological components are integrated with reasonably realistic supporting elements so it can be tested in a simulated environment.

Biomedical field: Continue in vitro studies, and animal model and assay development. Establish draft Target Product Profiles. Develop a scalable and reproducible manufacturing process.

- Animal Models: Continue development of animal models for efficacy and dose-ranging studies.
- Assays: Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate.
- Manufacturing: Initiate process development for small-scale manufacturing

ISO 9000 Project phase: Prototype optimization

Actors: Research and Development (mainly), external consultants, key customers, opinion leaders

Scenario: Once lab prototypes are available and internally tested, first tests out of R&D start, so first feedback from users can be acquired.

TRL 6 SYSTEM/SUBSYSTEM MODEL OR PROTOTYPING DEMONSTRATION IN A RELEVANT END-TO-END ENVIRONMENT: Representative model or prototype system, which is well beyond that of TRL 5, is tested in a relevant environment. Represents a major step up in a technology's demonstrated readiness.

Biomedical field: Prepare and submit Investigational New Drug package to EFSA and conduct Phase 1 clinical trial to determine the safety and pharmacokinetics of the clinical test article.

- Animal Models: Continue animal model development via toxicology, pharmacology, and immunogenicity studies.
- Assays: Qualify assays for manufacturing quality control and immunogenicity, if applicable.
- Manufacturing: Manufacture, release and conduct stability test and formulated product in support of the clinical trial.

ISO 9000 Project phase: Industrialization

Actors: Research and Development, external consultants, key customers, opinion leaders, industrialisation (mainly), manufacturing

Scenario: Scale-up process begins. Precise feedback from users is required so to draft final product technical specifications. Part list and precise costing sheet is finalised

TRL 7 SYSTEM PROTOTYPING DEMONSTRATION IN AN OPERATIONAL ENVIRONMENT: Prototype near, or at, planned operational system. Represents a major step up from TRL 6, requiring demonstration of an actual system prototype in an operational environment.

Biomedical field: Scale-up and initiate validation of manufacturing process. Conduct animal efficacy studies as appropriate. Conduct Phase 2 clinical trials.

- Animal Models: Refine animal model development in preparation for pivotal animal efficacy studies.
- Assays: Validate assays for manufacturing quality control and immunogenicity if applicable.
- Manufacturing: Scale-up and validate manufacturing process at a scale compatible with specific requirements. Begin stability studies of the product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production.

ISO 9000 Project phase: Industrialization

Actors: Research and Development, industrialisation (mainly), manufacturing, QC, purchasing dept, finance

Scenario: Internal validation, QC process and release procedures are finalised. Financial management of future product is developed

TRL 8 ACTUAL SYSTEM COMPLETED AND "MISSION QUALIFIED" THROUGH TEST AND DEMONSTRATION IN AN OPERATIONAL ENVIRONMENT: Technology has been proven to work in its final form and under expected conditions. In almost all cases, this TRL represents the end of true system development

Biomedical field: finalize manufacturing process. Complete pivotal animal efficacy studies or clinical trials (e.g., Phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit NDA.

- Manufacturing: Complete validation and manufacturing of consistency lots at a scale compatible with specific requirements. Complete stability studies in support of label expiry dating.

ISO 9000 Project phase: Validation of industrial prototype

Actors: Research and Development, Industrialization, Manufacturing, QC, Marketing (mainly), Sales, external testing sites, Regulatory Affairs

Scenario: External validation in reference centres according to a pre-defined protocol. Final draft of regulatory documentation for CE Mark or other regulatory approvals.

TRL 9 ACTUAL SYSTEM “MISSION PROVEN” THROUGH SUCCESSFUL MISSION OPERATIONS:

Actual application of the technology in its final form and under mission conditions, such as those encountered in operational test and evaluation.

Biomedical field: Commence post-licensure/post-approval and Phase 4 studies (post-marketing commitments), such as safety surveillance, studies to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate.

ISO 9000 Project phase: Product launch on the market and monitoring in the market

Actors: Research and Development, manufacturing, logistic, Marketing (mainly), Sales, QC, media

Scenario: End of product development process and start of distribution activities through sale force or distributors. Acquisition of further inputs from the market (sales force, operators, customers) useful for future product / process improvements is started.

NOTE:

- This document has been drafted on the basis of the first TRL scale developed in 1974 by NASA researcher Stan Sadin.
- Comments on biomedical field are based on the Guidelines issued by the School of Pharmacy of the University of Southern California.
- This document has been drafted by Adriano Savoini & Alessandro Tronchin (T&B Associati s.r.l) and first presented to Trans2Care meeting at Nova Gorica University (Vipava location) on December 20, 2013; updated version was discussed at the CBC Italy-Slovenia BioMed Conference on February 27, 2014. A further updated version was drafted on May 23, 2014 including description of specific scenarios and actors involved at the various stages.