Received: 20 June 2022 | Revised: 23 August 2022 | Accepted: 29 August 2022

DOI: 10.1002/bit.28227

ARTICLE

BIOTECHNOLOGY AND BIOENGINEERING WILEY

Biomanufacturing readiness levels [BRL]—A shared vocabulary for biopharmaceutical technology development and commercialization

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Funding information

This study was supported in part by the National Institute of Standards and Technology through 70NANB17H002, 70NANB21H085, and 70NANB21H086; U.S. Department of Commerce, Grant/Award Numbers: 70NANB17H002, 70NANB20H037

Abstract

The Manufacturing Readiness Levels (MRLs) developed by the Department of Defense are well-established tools for describing the maturity of new technologies resulting from government-sponsored Research and Development programs, from the concept phase to commercial deployment. While MRLs are generally applicable to a wide range of industries and technologies, there is significant value in offering an industry-specific view on how the basic principles may be applied to biomanufacturing. This paper describes Biomanufacturing Readiness Levels (BRLs) developed by the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), a public/private partnership that is part of the Manufacturing USA network. NIIMBL brings together private, federal, nonprofit, and academic stakeholders to accelerate the deployment of innovative technologies for biopharmaceutical production and to educate and train a world-leading biomanufacturing workforce. We anticipate that these BRLs will lay the groundwork for a shared vocabulary for assessment of technology maturity and readiness for commercial biomanufacturing that effectively meets the needs of this critical, specialized, and highly regulated industry.

KEYWORDS

biomanufacturing readiness level {BRL}, biopharmaceutical development and commercialization, manufacturing readiness level {MRL}, technology adoption, technology readiness level {TRL}

Abbreviations: 2nd Gen., second-generation process (for an approved drug); AAV, Adeno-associated virus; BRLs, Biomanufacturing Readiness Levels; CC, change control; CDER, the Center for Drug Evaluation and Research; cGMP, current good manufacturing process; Cp, process capability; CQAs, critical quality attributes; DNA, deoxyribose nucleic acid; DoD, Department of Defense; EMA, European Medicine Agency; ETP, Emerging Technology Program; FDA, US Food and Drug Administration; FTE, full time equivalent; HAZOP, hazardous operations; ICH, International Council for Harmonization; IND, investigational new drug application; KPP, key process parameter; mfg, manufacturing; MOU, Memorandum of Understanding; MRLs, Manufacturing Readiness Levels; NIIMBL, National Institute for Innovation in Manufacturing Biopharmaceuticals; NIST, National Institute of Standards and Technology; OPQ, Office of Pharmaceutical Quality; Phase 2B/Phase 3, pivotal make of a clinical drug candidate; PMDA, Pharmaceuticals and Medical Devices Agency; POC, proof-of-concept; QbD, quality by design; QMS, quality management system; QRM, quality risk management; RNA, ribose nucleic acid; R&D, research and development; SOP, standard operating procedure; Tech., technology; TRLs, Technology Readiness Levels; VMP, validation master plan.

1 | EXECUTIVE SUMMARY

Technology adoption in biopharmaceutical manufacturing depends upon product-specific, patient-centered, risk management approaches and the ability of the technology to enhance manufacturability, assure product quality, efficacy, potency, and strengthen supply chain robustness. Because innovation and technology development (unit operations, process technology, analytical approaches, data sciences, etc.) frequently occurs outside of the constraints of the clinical manufacturing paradigm (drug candidates), developers of new technologies sometimes lack a clear insight into the clinical and commercial manufacturing requirements for the technology throughout the entire lifecycle of the product. Biopharmaceutical manufacturers are often reluctant to adopt new technologies, due to the barriers that need to be overcome to meet the stringent quality, process development timelines, and robustness requirements for manufacturing biologics in a current Good Manufacturing Processes (cGMPs) environment (Mantle & Lee, 2020). Process validation and drug substance or drug product release criteria demand full control and documentation of raw materials, consumable supplies, process parameters, and product quality attributes to manage the residual uncertainties associated with complex biopharmaceutical systems. New technologies are evaluated at various points during preclinical and clinical process development stages, but the lack of a shared strategy, vision, and understanding between technology developers and biopharmaceutical manufacturers often becomes a major hurdle to technology adoption. Taking the opposite viewpoint and looking at things from the perspective of the manufacturing groups, they are often pushed to be more productive and innovative, but they have few tools with which new technologies can be assessed in terms of readiness or risk.

This document describes a set of Biomanufacturing Readiness Levels (BRLs) and best practices for classifying the status of a new manufacturing technology through the lifecycle of its development for which the intended end use is the production of a licensed biologic medicine. These BRLs serve as a shared vocabulary for prioritizing goals and assessing risks in the development and commercialization of biopharmaceutical process technologies.

Specifically, the BRL definitions provide a structure for performing assessments of new technologies or processes for purposes including:

- Identifying risks and performing gap analysis for specific technologies to improve development and adoption plans.
- Showing progress over time.
- Management of a portfolio of technology projects.
- Providing a toolkit for sharing a common vocabulary and quality risk management (QRM) plans.

The focus and depth of the current BRL definitions have been developed over several years of experience at National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) in identifying and testing new biomanufacturing technologies in collaboration with academic, federal, industrial, and nonprofit members.

2 | INTRODUCTION

Biopharmaceutical manufacturing includes a wide range of products such as therapeutic proteins, monoclonal antibodies (mAb), antibody fragments and bispecifics, nucleic acids (DNA, RNA, or antisense oligonucleotides), vaccines, and viral vectors for gene and cell therapy (Alford, 2006). Recent scientific advances have enhanced our capabilities to prevent, treat and often cure chronic and deadly diseases, but this often comes at the price of increased manufacturing complexity and business risk.

Biopharmaceutical manufacturers are constantly trying to improve the cost and reliability of their products and processes, with new technology advances constantly emerging to address these concerns. New technologies are evaluated both as part of, and separate from, bespoke product and process development. However, there are significant hurdles to the adoption of new technologies, often stemming from a lack of a coherent strategy and vision between technology developers and the numerous stakeholders who play key roles in biomanufacturing, such as commercial manufacturing leadership, the process development groups, regulatory scientists, quality assurance personnel, facility designers, and others. To add to this complexity, the development of new technologies needs to be aligned with regulatory and clinical requirements, depending upon the clinical phase of development for the biopharmaceutical product. For example, more stringent criteria are required for a technology that would be implemented in the commercial phase versus earlier in the clinical development for the product, but a clear business justification for the technology may exist at the later stage of development compared with the earlier stage.

The US Food and Drug Administration (FDA) defines advanced manufacturing technology (FDA Advance Manufacturing Technology) as technologies that improve drug quality, addresses shortages of medicines, and speeds time-to-market. The FDA has led a significant effort over the past several years to characterize and update guidance for advanced manufacturing technologies that can provide regulatory evidence of quality, safety, and efficacy during the manufacturing of biopharmaceutical products. The Center for Drug Evaluation and Research Office of Pharmaceutical Quality created a collaborative Emerging Technology Program (ETP) in 2014, where industry representatives meet with the ETP team to identify and resolve technical and regulatory issues related to the deployment of novel technologies into manufacturing processes before filing a regulatory submission. Recently, FDA formalized plans to collaborate with the National Institute of Standards and Technology through a Memorandum of Understanding (MOU) to advance the domestic manufacturing of drugs, biological products, and medical devices through the adoption of 21st-century manufacturing technologies (MOU, 2021).

New technologies are currently assessed by both the technology innovator and end user, applying the Technology Readiness Level (TRL) and Manufacturing Readiness Level (MRL) framework documents. The TRL concept was developed by NASA for evaluating the maturity levels of new technologies (Mankins, 2004). The Department of Defense spearheaded the development of MRL classifications (Manufacturing Readiness Level Desk Book, 2011) to define the ability to scale a given technology to commercial manufacturing. The MRLs incorporated elements, such as manufacturing costs, supply chain robustness, and pressures from competing markets, which evolve as technology production matures during scaleup from lab-scale through production-relevant and production-representative environments. TRLs and MRLs are milestone-based assessment toolkits and are centered around technology meeting product specifications. They are immensely useful in providing a roadmap for the development of technology to meet the end-product specifications and cover broad applications across fields from agriculture to aerospace, from biofuels and chemicals through building of defense systems and others. The high-level concepts are useful and applicable for technology evaluation in the context of biomanufacturing and there is an opportunity to refine these thoughts in the context of biomanufacturing. Similarly, the BRLs provide a hybrid approach for assessing technology maturation for manufacturing of biopharmaceuticals used during clinical trials and commercial manufacturing of products in a highly regulatory environment (i.e., cGMP), ensuring technology used is deemed robust from both quality and regulatory aspects for phase-appropriate manufacturing of biopharmaceuticals.

This paper describes BRLs developed by the NIIMBL from its experience in evaluating, launching, and executing numerous projects dealing with a wide range of different technologies that are relevant to biomanufacturing, in collaboration among academic, industry, and federal stakeholders. NIIMBL, like other Manufacturing USA institutes, plays a vital role in derisking technology innovations by "bridging the gap" between early research and product development (e.g., supported by federal grants innovation programs) and private sector investments (e.g., when technology has been sufficiently derisked to be implemented commercially) for technology adoption. The BRL concept described here provides a framework and an assessment toolkit for evaluating technology adoption and its hurdles, by creating a shared vocabulary from innovation to technology adoption in a commercial setting.

3 | BIOMANUFACTURING READINESS LEVELS

To avoid new technologies stalling in the "valley of death" or the "gap," the elements for success need to be put in place early in the Research and Development (R&D) process. This makes it easier to overcome the technology adoption requirements later during the pilot-scale demonstration and commercialization phases. This may slow the short-term progress of technology advancements, but in the absence of this strategy and vision, technology development can quickly go down routes that are "dead-ends" in the longer term of technology adoption. It is critical to develop the "big-picture" elements required for technology adoption to help derisk and accelerate the commercialization effort (with technology innovator, developer, and end user in mind).

The proposed BRL framework considers the technology adoption process as comprising three different phases: (1) Concept Development (BRLs 1–3); (2) Concept Demonstration (BRLs 4–7); and (3) Concept Realization (BRLs 8 and 9), as shown in Figure 1. This framework is applicable to both the technology developer as well as the end user and provides a platform for collaboration between these two groups to address technology needs and development criteria. As the technology progresses through the various phases of development, it is essential to overcome the barriers at various levels (BRLs 1–9) to be considered to advance technology from one level to another. BRL levels are assessed using three Readiness Criteria: (1) Technical Readiness, (2) Quality Readiness, and (3) Operation Readiness, also shown in Figure 1. Each subsequent BRL

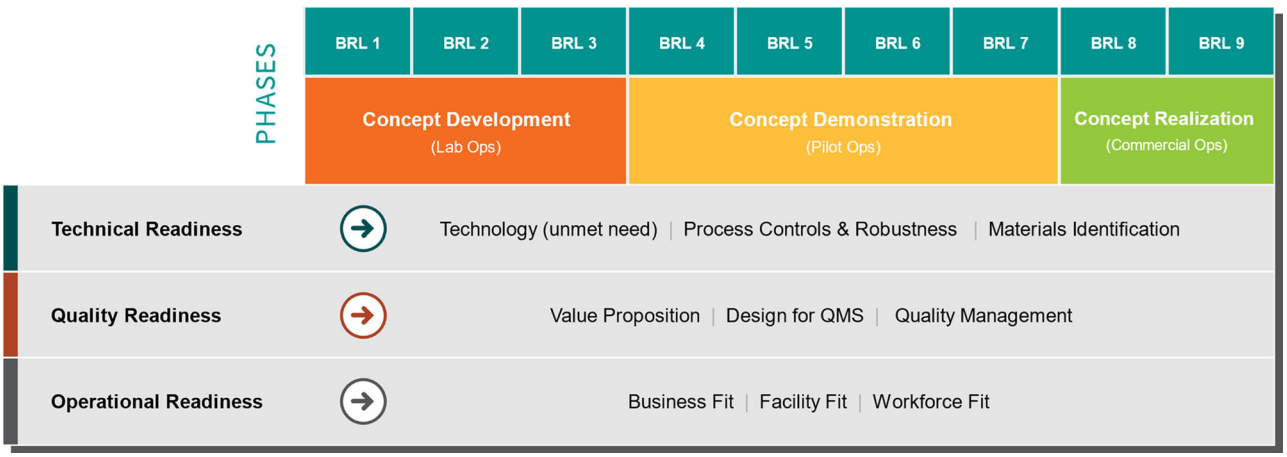

FIGURE 1 BRL assessment and progression matrix. BRL, Biomanufacturing Readiness Level; QMS, quality management system.

level addresses the attributes required across these three criteria, which are analogous to a drug development paradigm, where the regulatory requirements increase with each development phase for both the technology and biopharmaceutical product. BRL framework is derived from many of the same principles from TRLs and MRLs that could be translated to biopharmaceuticals, with the addition of quality, regulatory and operational criteria which are specific to biomanufacturing.

The BRL levels associated with each of these phases can be described in more detail:

Phase 1: Concept Development (BRL Levels 1–3): In this first phase, a technology is identified to solve a biomanufacturing problem, with the goal of achieving a relevant proof-of-concept (POC) typically demonstrated in a laboratory operation (Lab Ops).

Phase 2: Concept Demonstration (BRL Levels 4–7): During this key second phase of development, the technology advances through various stages to ensure it can be implemented into clinical manufacturing settings and is ready for a quality management system (QMS). This phase is associated with pilot-scale demonstrations, or Pilot Operations (Pilot Ops) and is akin to a production-relevant environment.

Phase 3: Concept Realization (BRL Levels 8–9): This final phase involves the implementation of technology in a commercial setting (BRL 8), and for routine deployment for other commercial approved biologics drug products (BRL 9). This phase is in the final commercial realm, or Commercial Operations (Commercial Ops), and is akin to a production-representative environment.

Decisions regarding the status or BRL level of a technology being evaluated are based on clear deliverables or achievements. Table 1 provides suggested *key criteria* and *technology achievements* for each BRL in each of the three different phases of technology development. Later in the document, the Supporting Information Appendix A provides a detailed set of criteria for each phase of development with respect to the readiness described below. Successful completion of a

TABLE 1 NIIMBL biomanufacturing readiness levels (BRLs) and exit criteria

Technology phase	BRL level	Key criterion	Summary exit criteria
Concept development	BRL 1	Concept ideation	Innovation conceived, based on solid, generally recognized scientific and technical principles; preliminary data or literature available
	BRL 2	Concept formulated	Documented description of the application/concept that addresses feasibility and benefit
	BRL 3	Proof-of-concept established for intended use	Peer-reviewed, documented results validating expectations of the concept. This could be a publication, disclosure, patents, or in-house technical review with key supporting data
Concept demonstration	BRL 4	Prototype built (Pilot Design 1)	Documented test performance with industry-relevant feedstocks demonstrating agreement with expectations. The preliminary plan developed for scaleup, integration, and robustness requirements
	BRL 5	Scaleup, integration, and limited robustness (Pilot Design 2)	Demonstrate results showing technology meets acceptance criteria determined in the areas of manufacturing scaleup, integration, and robustness studies. The determination that needed instruments, components, and supporting technology (e.g., software) can be reliably produced commercially
	BRL 6	Development with drug candidate (Pilot Operation 1)	Technology used for early GMP supplies for active drug/biological candidate or second-generation process for licensed compound
	BRL 7	GMP-Ready system built (Pilot Operation 2)	Demonstrate technology readiness to manufacture pivotal batches (e.g., Phase 2B/Phase 3/bridging studies, etc.) for approved IND
Concept realization	BRL 8	System validated and approved by FDA, EMA, PMDA, or other regulatory agencies (Commercial Operations)	Technology used in at least one licensed commercial product
	BRL 9	Broad implementation established through successful commercialization (Tech Deployment)	Technology demonstrated in routine commercial manufacturing of multiple approved products from multiple companies

Abbreviations: EMA, European Medicine Agency; FDA, US Food and Drug Administration; GMP, Good Manufacturing Process; IND, investigational new drug application; NIIMBL, National Institute for Innovation in Manufacturing Biopharmaceuticals; PMDA, Pharmaceuticals and Medical Devices Agency.

given technology achievement for a given BRL implies that the technology is ready to move into a new set of testing or development activities to achieve the next BRL target.

4 | READINESS CRITERIA (TECHNICAL, QUALITY, AND OPERATIONAL)

Because of the highly regulated nature of the biopharmaceutical industry, the assessment criteria for a technology to be successfully implemented in a biomanufacturing environment needs to address three different aspects: Technical, Quality, and Operational Readiness. Within each of these readiness considerations, we provide specific questions that could be asked as the evaluation is being performed, and these are arranged in different categories, generally corresponding to the issues listed in Figure 1, and described as:

4.1 | Technical readiness

Does the technology work the way it is supposed to?

To answer this question, there are many important questions that need to be taken into consideration and that need to be addressed, as a technology is being considered for manufacturing, which includes:

- *Technology for unmet need*: Does it address an unmet need for biomanufacturing? Can the technology or method be developed from feasibility to POC, and further into a demonstration at pilot scales in a cGMP environment?[1] Can the technology be commercialized? Can a detailed assessment required at each phase of development be documented as the technology progresses (Figure 1) from BRL 1 through BRL 9? A developer needs to collaborate across the supply network (quality, technical operations, pilot facilities, etc.) for biomanufacturing, for example, some of the technical components described in Table 1 under BRL 6 prompt the use of technology during clinical drug manufacturing, whereas BRL 8 prompts if the technology has been fully validated (or qualified) to be used for commercial biomanufacturing to be adopted.
- *Process controls and robustness*: This segment addresses the question of whether the technology is robust enough and does it ensure that the process is under control? Some aspects to address would need to consider a detailed assessment that identifies scaleup issues related to technology robustness and quality. There is a need to address process capability "Cp" indices (statistical measures of the inherent process variability of given characteristics, for example, product titer, glycan measurements, and other key process and critical quality attributes) that are within control. Also, the user needs to periodically evaluate process capability targets, ensuring that technology is controlled within the said parameters and robust before implementation in commercial settings.
- *Material identification*: Have all the aspects of materials required for the technology been considered? This prompts the user to provide details of materials used to develop the technology, material properties, identifying vendors, and supply chain issues if any, along with addressing Hazardous Operations and any special handling considerations that the adopters need to address before use. A risk mitigation plan needs to be developed to address any concerns observed during the material use for the technology.

4.2 | Quality readiness

Does the technology meet cGMP requirements, and is there a QMS plan (based on global regulatory guidance, such as International Council for Harmonization [ICH], US FDA, European Medicine Agency, Pharmaceuticals and Medical Devices Agency, etc.), that can be implemented before introducing the new technology into commercial settings?

To answer this question, there are key elements that need to be taken into consideration and that need to be addressed, as a technology is being considered for manufacturing, which includes

- *Value proposition*: Is there a clear value proposition for the technology that exists? Some aspects that need to be addressed are defining components that need to include the overall cost-to-benefit factor for technology adoption, developing and refining end-to-end cost models, estimating capital expenditures needed to implement the technology and its impact on the overall supply chain for the biomanufacturing of the molecule. The value proposition needs to be re-evaluated during the phases of technology development to ensure the assumptions made originally are still valid.
- *Design for QMS*: Has the technology taken into consideration various aspects of QMS during the development? The QMS focuses on key aspects such as the identification of key process parameters (KPPs), drafting a validation master plan (VMP), and execution of the VMP during the commercial stage adoption of the technology.
- *Quality management*: Does a quality management plan exist, or can it be developed before implementing the technology at commercial scale? To address this need one can consider the guidance provided by The ICH (International Council for Harmonisation Quality guidelines), which can be applied throughout the development lifecycle of the technology. Aspects of the ICH guidelines, such as generation and implementation of a quality management plan, change control (CC) procedures, supplier qualifications, and QRM, are some of the things to consider during the technology development process.

4.3 | Operational readiness

Is there a sound business case for the technology (addressing an unmet need) and are there current facilities capable of implementing the technology?

To answer this question, there are many important issues that need to be taken into consideration and that need to be addressed, as a technology is being considered for manufacturing, which includes:

- *Business fit*: Is there a business plan that establishes a clear advantage for new technology implementation? To answer this, the technology workflow needs to be considered with the end user in mind. Also, the technology developer needs to initiate a change management plan to define risk and mitigation strategies for new technology disruption. A stakeholder management plan would also be beneficial that details a make-versus-buy decision matrix, assessing component supply network strategy, derisking supply chain, building out a manufacturing plan for technology insertion across the supply network, and ensuring production systems are in place to accommodate technology implementation into the site.
- *Facility fit*: Can the new technology be fitted into an existing facility? This requires a study of any new specialized facility requirement or modifications to existing facilities before technology implementation. Aspects of facility fit would include the development of a prototype tooling set, an equipment maintenance plan, and a quality plan for tooling and testing. Also, a key component during facility fit is to evaluate manufacturing capacity and its impact during the implementation of new technology across the supply network to produce a biological drug product.
- *Workforce fit*: Is there a trained workforce available to support new technology implementation? Evaluation of this requirement involves identifying skillsets needed to implement and operate the new technology in the facility. It should also include any necessary training and recruitment of key workforce required at various stages throughout the development and implementation of the new technology across the supply network.

The discussion above summarizes a general strategy and guidelines that need to be followed in determining the appropriate BRL for new technology. In Supporting Information Appendix A, we provide, in tabular form, a representative list of considerations that may be involved in BRL assessment. Not all these considerations listed in Supporting Information Appendix A need to be applied to every technology, and there might be more, or different, issues that need to be examined in each case, for example, Supporting Information Appendix B provides detail for evaluating criteria listed in Supporting Information Appendix A for new method development for Adeno-associated virus vectors.

5 | BRL EXIT CRITERIA QUESTIONNAIRE

As the technology progresses through the various phases of development, it is essential to overcome the barriers at various levels (BRLs 1–9) considered for the advancement of the technology from one level to another. Each subsequent BRL level addresses the technology solution required across the readiness criteria, analogous to a drug development paradigm, which increases in regulatory and quality requirements for the technology. Some of the key questions that need to be addressed during the technology development for exit from each of the BRL categories are enumerated in a nonexhaustive summary below:

BRL 1—Concept ideation: Is there a sound scientific concept underpinning the new technology or a process? Some aspects may require users to identify materials, equipment, and/or supplies which are essential to establish *technical readiness* for the technology. A success criterion to exit this BRL would involve the documentation of the proposed concept and its potential benefit for biomanufacturing. Documentation can be in many forms, depending on the specific situation, but could involve peer-reviewed publications, or peer-reviewed invention disclosures, patent filings, or company internal reports.

BRL 2—Concept formulated: Is there a broad application to the biomanufacturing field identified? Key assessment components may require information about material availability, lead times, and estimated potential scaleup risks (*technical readiness*). The innovator also identifies the potential value proposition, approximate manufacturing cost for adding/implementing the new technology, and process flow (*quality readiness*). The success exit criteria would be a documentation of the application or concept that addresses both the feasibility and benefit of biomanufacturing.

BRL 3—POC for the intended use: Is there a POC established for the technology? *Technical readiness* components need to include laboratory studies that demonstrate the technology in an appropriate context with respect to biomanufacturing processes. The technology can be experimentally tested, modeled, and/or simulated, to complete the POC for the technology. Plans for technology lifecycle and manufacturing assessments would be established and documented. Potential manufacturing sources for the components of the technology should be identified and documented. Also, for *quality readiness*, manufacturing assessments should include the following components: benefits beyond those of the state-of-the-art existing technology; analysis of special handling requirements; hazards and operability; and potential supply chain and any potential regulatory issues. A high-level cost structure for the technology should also be developed comparing existing technology to the new technology. For addressing *operational readiness*, the technology developer needs to specify and document any special facility requirements for the adoption of technology, and any new workforce skills that are required to implement such technologies.

BRL 4—Prototype built: Is the prototype built complete? Key aspects that need to be addressed for *technical readiness* include that a prototype is built and operated to demonstrate the performance of

critical parameters using feedstocks and/or samples from a process. Test results demonstrating agreement with analytical predictions are also documented. KPPs for the process/technology should be identified, including any process constraints, and are documented. At this phase, the technology innovator should perform a gap analysis for risk associated during prototyping for scaleup, and mitigation plans for the same are documented. *Quality readiness* aspects such as a QMS as per ICH guidelines and a draft VMP are both initiated at this stage. Similarly, *operational readiness* aspects such as prototype tooling requirements are established, and specifications for the same are developed. Manufacturing facilities are identified for demonstration build. Workforce skills are identified, and training plans are established (standard operating procedures, training curricula, etc.). Stakeholder management plans for technology disruption detailed in an end-to-end cost model (e.g., materials, employee requirements, equipment, facility modification costs, etc.) are developed to gain buy-in for technology adoption.

BRL 5—Scaleup, integration, and limited robustness proven: Can the technology be scaled up and is it robust? To address *technical readiness* at this stage one needs to consider scaleup and robustness testing, while integrating the technology using real feedstocks or samples (e.g., for analytical instrumentation) at relevant manufacturing scale and environment. Technology performance needs to be demonstrated (to meet or exceed BRL 4 performance metrics) for at least two major areas that may include multiple sites or molecules. Technical risk assessment is initiated to include the potential impact on *X*, *Y*, *Z*, and gap analysis completed with a mitigation plan for future BRLs. Multiscale technology availability assessment may include demonstrating performance at various bioprocess scales to address potential scaleup challenges. A validated master plan is also established (VMP) as part of the *quality readiness*. As needed, a sole-supplier justification for technology components and other supply chain risks is evaluated. A sensitivity analysis is also generated comparing findings from lab- to production-relevant environments. Process capabilities are evaluated against the target and improvement plans are developed. As part of the *operational readiness*, a "make-versus-buy" decision matrix based on production considerations addressing demonstration is developed, scaled up, and other associated risk is identified. Manufacturing risk mitigation plans are defined for technology adoption into clinical make. Tooling

TABLE 2 Removable purification/quantification tag in a university incubator (concept development)

Technology phase	BRL level	Key criterion	Technology BRL achievement(s)
Concept development	BRL 1	Basic principle observed and published	Removable Purification Tag identified and published in a peer-reviewed public journal, based on work in a university incubator
	BRL 2	Concept formulated	Documented/predicted/modeled targets for improvements A, B, C, and so forth compared to the current method of protein A; improvements D, E, F, and so forth compared with lacZ; demonstrated using off-the-shelf proteins and nominal solution conditions
	BRL 3	Proof-of-concept established for intended use	Proof-of-concept demonstrated in the lab for a number of proteins/purification conditions in laboratory settings
Concept demonstration	BRL 4	Prototype built (Pilot Design 1)	Laboratory methodology and SOP are being developed to use this for biomanufacturing a drug candidate. *Technology currently is established BRL 3*, and is currently being developed to establish procedures and methods for accomplishing BRL 4 (as per Supporting Information Appendix A)
	BRL 5	Scaleup, integration, and limited robustness (Pilot Design 2)	Not applicable
	BRL 6	Development with drug candidate (Pilot Operation 1)	Not applicable
	BRL 7	GMP-Ready system built (Pilot Operation 2)	Not applicable
Concept realization	BRL 8	System validated and approved by FDA (Commercial Operations)	Not applicable
	BRL 9	Broad implementation established through successful commercialization (Tech Deployment)	Not applicable

Note: New affinity tags have been developed in a lab that improves original protein fusion compared with protein A and lacZ that are commonly used.
Abbreviations: BRL, Biomanufacturing Readiness Level; FDA, US Food and Drug Administration; GMP, Good Manufacturing Process; SOP, standard operating procedure.

specifications are established, and manufacturing sites are identified to reliably produce units for cGMP use. *This is a key stage gate before implementation of technology for cGMP use, demonstrating the technology meets the acceptance criteria as determined, and can reliably be manufactured for use in clinical drug manufacturing environment*.

BRL 6—Development with a drug candidate: The technology is being tested with a biological drug candidate in manufacturing environment: To demonstrate *technical readiness*, one needs to review that the manufacturing processes flow has been selected for the end-to-end manufacturing, even if engineering and/or design variables still need to be optimized. Sole-supplier requirements for the component build are minimized, and the supply chain risk assessment conducted includes special handling procedures if any, material availability issues are identified, and mitigation plans are established. A cost model is updated with design and material specifications in a production environment. Key components of *quality readiness* such as QRM plan and CC procedures are established for the implementation of the technology in a clinical-scale manufacturing process. Plans for manufacturing technology units across R&D network are established and equipment maintenance plans are developed for addressing *operational readiness*. The manufacturing workforce is trained to operate the technology in the R&D environment. Stakeholder plans are also updated with risks identified and mitigation plans developed.

BRL 7—cGMP-Ready system built: Has the technology met all GMP requirements to be used for a biological drug candidate or product as a step towards technology adoption? Key things to consider for *technical readiness* are if the technology has been demonstrated in the production-representative environment and if risk assessments are finalized. Technology can also be made available at multiscale and multisite for deployment across different manufacturing sites. *Quality readiness* components such as a VMP (including any qualification of instrumentations) and supplier qualifications plans are executed during this phase of development. Other considerations include a commercial cost model for a cGMP system being built, including capital expenditure and tech transfer cost required. *Operational readiness* criteria such as the supply chain for commercial scale manufacturing are established, including mitigation for sole-supplier components for the technology. Process capability data are collected during tech transfer to cross-validate refined targets and improvements compared with previous benchmark studies. Manufacturing plans for commercial units are finalized, and quality plans for tooling are established. Technology needs to demonstrate it meets acceptance criteria at this stage gate to exit

TABLE 3 New structural assay development for glycoform analysis from a contract lab (concept demonstration)

Technology phase	BRL level	Key criterion	Technology BRL achievement(s)
Concept development	BRL 1	Basic principle observed and published	New assay identified for glycoform analysis, provides a fast alternative to existing techniques by *X*-fold and published in article *X*
	BRL 2	Concept formulated	New assay was developed and optimized for a drug candidate
	BRL 3	Proof-of-concept established for intended use	Proof-of-concept demonstrated for the new assay
Concept demonstration	BRL 4	Prototype built (Pilot Design 1)	Assay method developed for new drug candidate for glycoform analysis
	BRL 5	Scaleup, integration, and limited robustness (Pilot Design 2)	New assay used for identification of glycoform during the development of new clinical trial materials. The method yielded satisfactory measurements compared with existing analytical techniques
	BRL 6	Development with drug candidate (Pilot Operation 1)	New assay currently used in the development of new drug candidates at a contract lab for clinical trials. Bridging studies between the release method and new assay are under way. *Assay development currently at BRL 5*, progressing to achieve BRL 6 as listed in Supporting Information Appendix A
	BRL 7	GMP-Ready system built (Pilot Operation 2)	Not applicable
Concept realization	BRL 8	System validated and approved by FDA (Commercial Operations)	Not applicable
	BRL 9	Broad implementation established through successful commercialization (Tech Deployment)	Not applicable

Note: A new structural assay has been developed using high-resolution mass spectrometry coupled with specialized HPLC techniques, to yield rapid glycoform analysis and compare it to the QC technique for an existing drug candidate.

Abbreviations: BRL, Biomanufacturing Readiness Level; FDA, US Food and Drug Administration; GMP, Good Manufacturing Process; HPLC, high-performance liquid chromatography; QA, quality assurance.

BRL 7, to be ready to be implemented in commercial settings for the biomanufacturing process in BRL 8.

BRL 8—System deployed in commercial setting: Are all requirements for licensure completed to be deployed into commercial settings? *Technical readiness* components to consider are if the technology is qualified (or the method is validated) to be used to make pivotal batches in a manufacturing environment. Other aspects include that the process is maintained under a validated state (International Council for Harmonisation Q7 Good Manufacturing Practice), and supplier specifications and risk mitigation are established for commercial manufacturing. Commercial costs are revised along with a capital investment plan to implement the technology in manufacturing. Technology robustness is evaluated, and improvement plans are established. *Quality readiness* processes such as supplier qualifications, quality plans, CC procedures, and QRM procedures are established. Quality and equipment maintenance plans are established for commercial units, and facility capacity plans are shared across the supply chain network. *Operational readiness* aspects such as stakeholder management plans are updated including manufacturing and supply chain management for the technology. The workforce is fully trained and qualified for routine commercial operations. Certain technologies (e.g., like-for-like) can be implemented during the process validation stage for a biological drug product, provided all the other elements required for tech adoption are already established, thus providing a high value add for the new technology at this stage.

BRL 9—Technology deployment for existing biopharmaceutical product: Are all the required components for the technology available to fully deploy the technology for an existing biopharmaceutical drug product? Key *technical readiness* components to establish are if the technology has been previously deployed for a commercial biopharmaceutical drug product and if all aspects described in BRL 8 previously are completed. Also, *quality readiness* aspects to consider are if the technology is continuously used in commercial settings across the network (across sites and/or products). Is there a continuous improvement plan established for the technology, to ensure manufacturing processes are stable and controlled to maintain a state of continuous validation? Continuous improvement for QRM is also established. All *operational readiness* criteria for manufacturing risk are mitigated at this stage, including supply chain management established for the product lifecycle. Equipment maintenance and performance matrices are established, along with capacity planning to meet future demands for the biopharmaceutical drug product. Workforce skillsets are maintained as needed for routine production.

TABLE 4 In-line probe/sensor development to control glucose at a low level (±0.1 g/L) to limit glycation which impacts bioactivity in a bioreactor (concept demonstration in GMP mfg)

Technology phase	BRL level	Key criterion	Technology BRL achievement(s)
Concept development	BRL 1	Basic principle observed and published	New in-line probe identified for glucose control, provides a fast alternative to existing techniques by *X*-fold and published in article *X*
	BRL 2	Concept formulated	New method was developed and optimized for a drug candidate under GLP conditions
	BRL 3	Proof-of-concept established for intended use	Proof-of-concept demonstrated for the new assay
Concept demonstration	BRL 4	Prototype built (Pilot Design 1)	Assay in-use for drug candidate
	BRL 5	Scaleup, integration, and limited robustness (Pilot Design 2)	Currently used for the development of new clinical trial materials
	BRL 6	Development with drug candidate (Pilot Operation 1)	New assay currently used in the development of new drug candidate for clinical trials. Bridging studies between the in-process method and the in-line probe are under way
	BRL 7	GMP-Ready system built (Pilot Operation 2)	Instrument qualification is underway to demonstrate the control during GMP make. Method currently at BRL 6, progressing to achieve BRL 7 as listed in Supporting Information Appendix A
Concept realization	BRL 8	System validated and approved by FDA (Commercial Operations)	Not applicable
	BRL 9	Broad implementation established through successful commercialization (Tech Deployment)	Not applicable

Abbreviations: BRL, Biomanufacturing Readiness Level; FDA, US Food and Drug Administration; GMP, Good Manufacturing Process.

6 | EXAMPLES

The evaluation process using the proposed BRL framework is demonstrated using three examples (Tables 2–4) to assess technology maturity, demonstrate quality readiness, and progress towards commercial adoption of such technology. The evaluation process involves using a matrix approach whereby the user identifies the BRL level for the technology (using Table 1), and subsequently identifies the gaps using the detailed questionnaire as described in Supporting Information Appendix A for the relevant BRL levels.

As shown in the case studies above, the proposed BRLs provide a structured assessment toolkit to enable technology developers to:

- define current maturity level,
- identify risks and perform gap analyses,
- provide a toolkit for sharing a common vocabulary and QRM plans,
- facilitate collaboration and transparency across technology innovators, developers, and implementors alike,
- refine the value proposition throughout the lifecycle of technology development, and
- provide a framework to derisk technology implementation over the course of development.

7 | CONCLUSION

Biomanufacturing faces unique challenges in the implementation and adoption of new technologies because of the highly regulated nature of the industry and the long lifecycles of its products, and it needs a tailored solution to overcome technology adoption hurdles during the various stages of technology development. The BRL framework presented here provides a common approach for technology innovators, developers, and adopters, for assessing the maturity level of technology in clinical trials and commercial scale manufacturing processes. Such a shared framework will facilitate collaboration across the network of technology inventors to adopters (e.g., academia, small-to-medium technology developers, large biopharmaceutical companies, and federal stakeholders) and help create novel technologies impacting high-value biopharmaceutical products, by overcoming technology adoption hurdles from inception to commercialization. This BRL framework is provided as a tool to solve the technology adoption challenges in biopharmaceutics, and further invite discussion and refinement of this toolkit to enhance technology adoption in the biopharmaceutical space. To submit feedback relating to this document, please email BRL@NIIMBL.org with your written comments or an attachment for consideration.

AUTHOR CONTRIBUTIONS

Sandeep B. Kedia: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing—original draft preparation, and writing—review and editing. **Jeffrey C. Baker**: Formal analysis, methodology, supervision, validation, and writing—review and editing. **Ruben G. Carbonell**: Conceptualization, Formal analysis, methodology, supervision, validation, and writing—review and editing. **Kelvin H. Lee**: Conceptualization, funding acquisition, resources, supervision, validation, and writing—review and editing. **Christopher J. Roberts**: Conceptualization, resources, supervision, validation, and writing—review and editing. **John Erickson**: Formal analysis, visualization, and writing—review and editing. **John E. Schiel**: Data curation, formal analysis, and writing—review and editing. **Kelley Rogers**: Methodology and writing—review and editing. **Gene Schaefer**: Methodology and writing—review and editing. **Stefanie Pluschkell**: Methodology and writing—review and editing.

ACKNOWLEDGMENTS

This study was supported in part by the National Institute of Standards and Technology through 70NANB17H002, 70NANB21H085, and 70NANB21H086.

ETHICAL STATEMENT

This article represents the views of the author (and of NIIMBL) and should not be construed to represent FDA's views or policies for technology adoption in biopharmaceutical manufacturing.

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ENDNOTE

[1] cGMP refers to relevant portions of 21CFR; however, for the purpose of the BRLs, some of the activities may take place in a "cGMP-like" (vs. cGMP) environment

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kedia, S. B., Baker, J. C., Carbonell, R. G., Lee, K. H., Roberts, C. J., Erickson, J., Schiel, J. E., Rogers, K., Schaefer, G., & Pluschkell, S. (2022). Biomanufacturing readiness levels [BRL]—A shared vocabulary for biopharmaceutical technology development and commercialization. *Biotechnology and Bioengineering*, 119, 3526–3536. https://doi.org/10.1002/bit.28227