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Proposing a Local "Technology Readiness Assessment" Model for Biopharmaceutical Industries of Iran

Masoud Faramarzi[1], Javad Noori[2*], Abbas Kebriaeezadeh[1,3], Meysam Seyedifar[3]

1. Department of Pharmacoeconomics and Pharmaceutical Administration, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
2. Research Institute for Science, Technology and Industry Policy, Sharif University of Technology, Tehran, Iran.
3. Pharmaceutical Management and Economics Research Center, The Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background: Reliable assessment of innovative technology readiness is crucial for industrial decision-making. Technology Readiness Assessment (TRA) is an established tool used to qualify technology development and help make investment decisions and deploy systems or technology elements to an end-user in a timely fashion. "Manufacturing readiness levels" (MRLs) and "ATLAS technology method" (technology components evaluation) metrics are commonly employed in TRA to assess the impact of technologies for future R&D programs and development of manufacturing and risk of a given technology, system, and or subsystem.

Methods: In this study, *E.coli-based* recombinants were chosen as the objective. Two questionnaires were designed on their manufacturing process and sent to 13 biopharmaceutical experts in Iran.

Results: The findings show that Iranian biopharmaceutical experts validated the proposed MRLs model inspired by the US Department of Defense's published questionnaire. To run the "ATLAS technology method", the relative importance of technology components (software, hardware, and human resources) involved in each stage of manufacturing and each stage's relative importance was determined by experts in the percentage scale.

Conclusion: Policymakers and managers must have enough knowledge of how to evaluate manufacturers' abilities, and in this way, TRA is a usable and exquisite tool. In this article, two TRA methods that appear compatible with Iran's environment of the biopharmaceutical sector are proposed.

Keywords: Readiness assessment, Biopharmaceutical of Iran, Manufacturing readiness levels, Technology components, *E.coli-based* recombinants

*** Corresponding Author:**
Javad Noori, PhD.
Address: *Research Institute for Science, Technology and Industry Policy, Sharif University of Technology, Tehran, Iran.*
E-mail: *j.noori@sharif.edu*

Introduction

Accurate and timely assessments are very important for the cost-effective management of advanced technologies and proposing tools such as Technology Readiness Assessment (TRA) to meet management challenges. TRA is a tool that helps make the right decisions concerning the inclusion or exclusion of new technologies and novel concepts. It provides metrics for technology and manufacturer's maturity (current status, optimal status, and capacity building roadmap), identifies the risks associated with technologies and investment requirements and potential problems early in a development process when solutions are less expensive and easier to execute. This article has been prepared to propose two TRA methods [1, 2, 3]. TRA is vital to the process of developing technologies to the point where they can be operationally produced and deployed. It supports that process by:

- Providing guidelines to evaluate and track technology and manufacturer maturity levels and program milestones.

- Informing decisions associated with allocating resources and funds for given technology development.

- Providing a systematic method for ensuring a project's success by tracking the completion of various steps as a project develops.

- Identifying gaps in testing, demonstration, and knowledge of a technology's current readiness level and the information and steps necessary to reach the required technology readiness level [2].

The benefits of technology readiness assessment (TRA) are as below:

- Designing, applying, and implementing legal, scientific, standardized, and documentary methods to identify capable builders and select a strategic partner.

- Creating a platform for production capacity, design-engineering, testing, and other vital links in the production value chain.

- Contributing to the formation and acceleration of knowledge-based companies and the development of technology and knowledge-based economies.

- Gaining the necessary competence to export and create a reputable domestic and international brand.

- Measuring the level of progress and the effectiveness of strategic plans.

- Comparing the firm's situation with the competitors in a particular technology [4, 5].

Different models have been proposed to assess technology, in most of which there are almost the same standard definitions and basic concepts. Some of these methods are as follows:

- **Real-time Technology Assessment (TA):** The proposed real-time TA comprises four linked components (development of analogical case studies, mapping the resources and capabilities of the relevant innovation enterprise, eliciting and monitoring changing knowledge and attitudes among stakeholders, and engaging in analytical and participatory assessments of potential societal impacts) that can result in an inherently reflexive R&D enterprise [6].

- **Turgul and Nuttavut Model:** In this model, technology assessment is implemented according to three different perspectives, which are "technological" (financial return, risks or uncertainty of technology, manufacturing difficulties or ease of technology adoption, and acquisition channel), "organizational" (employment stability, employee capability, the compatibility with the current manufacturing process, and low cost and low risk of investment) and "marketing" perspectives (customer skepticism about a new innovative product, customer satisfaction, and legal regulations) [7].

- **Owens Model:** In this model, technology is examined and evaluated in three stages. In the first step, the technical features of the technology are emphasized. The relevant device's usefulness and efficiency, information system, and technology strategy are examined in the second stage. In the third stage of technology evaluation, the health and the economics of technology outputs are evaluated [8].

- **Technology readiness levels:** TRLs are a set of management metrics that enable the assessment of the maturity of a particular technology and the consistent comparison of maturity between different types of technology, application, and operational environment in nine levels: basic principles observed and reported, technology concept and or application formulated, analytical and experimental critical function and or

characteristic proof-of-concept, component and or breadboard validation in the laboratory environment, component and or breadboard validation in a suitable environment, system/subsystem model or prototype demonstration in a relevant environment, system prototype demonstration in a space environment, the actual system completed and "flight qualified" through test and demonstration, and the actual system "flight-proven" through successful mission operations [6].

- Quick and dirty modeling: It is called quick, as it can provide fast results, and is called dirty because it may not consider all the details due to its short-term implementation. In this model, technology assessment is performed in six stages: identification of competencies and applications of technology, analysis of internal relations of competencies and applications of technology, analysis of external relations of competencies and applications of technology using quantitative and qualitative conditions, stabilization technology position (measuring the levels of the superiority of technology over the latest technology), processing data and information in the first three stages, summarizing the results and evaluating the technology in question [9].

- Manufacturing readiness levels: MRLs criteria create a quantitative measurement scale and vocabulary for assessing and discussing manufacturing maturity and risk. Using the MRLs criteria is a structured evaluation of a technology, component, and manufacturing process. The United States Department of Defense (DoD) [4] has probably been most active in defining a manufacturing readiness standard. The DoD approach consists essentially of a series of manufacturing readiness levels designed to provide visibility for some relevant 'threads' (technology and industrial base capabilities, design, cost and funding, materials, process capability and control, quality management, manufacturing personnel, facilities, and manufacturing management). Although the MRLs are numbered (there are ten MRLs), the numbers themselves are unimportant. The numbers represent a non-linear ordinal scale that identifies what maturity should be as a function of where a program is in the acquisition life cycle. Using numbers is simply a convenient naming convention [10].

- ATLAS technology method: ATLAS technology is a quantitative and purely scientific method that focuses on various technical aspects. It is based on the premise that the four components of technology always impact any production. Technology is divided into four general components (software, hardware, manpower, and organization ware). Technology assessment is done by surveying manufacturers' readiness of the four technology components in each manufacturing stage [8].

Producing biological medicines has a relatively long background in Iran. As a consequence of the 1918-1919 influenza pandemic in Iran, some institutes for microbiology and immunology research were established. These institutes (such as Pasteur Institute) tried to produce vaccines and other biologic medicines like insulin. After developing biotechnology in the world and consequently, in Iran, some of the researchers of these institutes, in cooperation with some academicians working in biotechnology, tried to establish a few spinoff firms to produce genetic testing and analysis kits in the late 1990s. After a few years and in cooperation with German, Indian, and Cuban BPFs, leading Iranian firms started investing in biosimilars production in the early 2000s [11]. Today, in addition to institutes and firms producing biologic medical products, 18 private BPFs produce biosimilars approved by the Ministry of Health [11]. Iranian firms have recently started to export their products to countries such as Russia, Turkey, Iraq, Syria, Pakistan, Armenia, Azerbaijan, Malaysia, and Kazakhstan [11] (Table 4 and 5).

Materials and Methods

In this study, two methods are proposed to evaluate the TRA for Iran's biopharmaceutical. At the first step, *E.coli-based* recombinants were chosen as the objective, and then two questionnaires were designed on their manufacturing process.

First method

To simplify and liken DoD's questionnaire to biopharmaceutical of Iran and at the suggestion of the study's supervisors, the number of asked questions decreased from 403 (which was proposed in DoD's questionnaire) to 49 in this study. Although the DoD's published questionnaire is used as a pattern to design MRLs method's questionnaire, in this study, related questions to 9 threads of MRLs have been asked in three levels rather than ten, which was considered in DoD's questionnaire (to design a simplified version for more general use) (Table 3).

Definition of various levels are

MRL 1 (MRLs 1 to 4 in DoD's questionnaire): Basic studies and technical knowledge of manufacturing, MRL 2 (MRLs 5 to 7 in DoD's questionnaire): Pilot line capability demonstrated and prepared conditions to

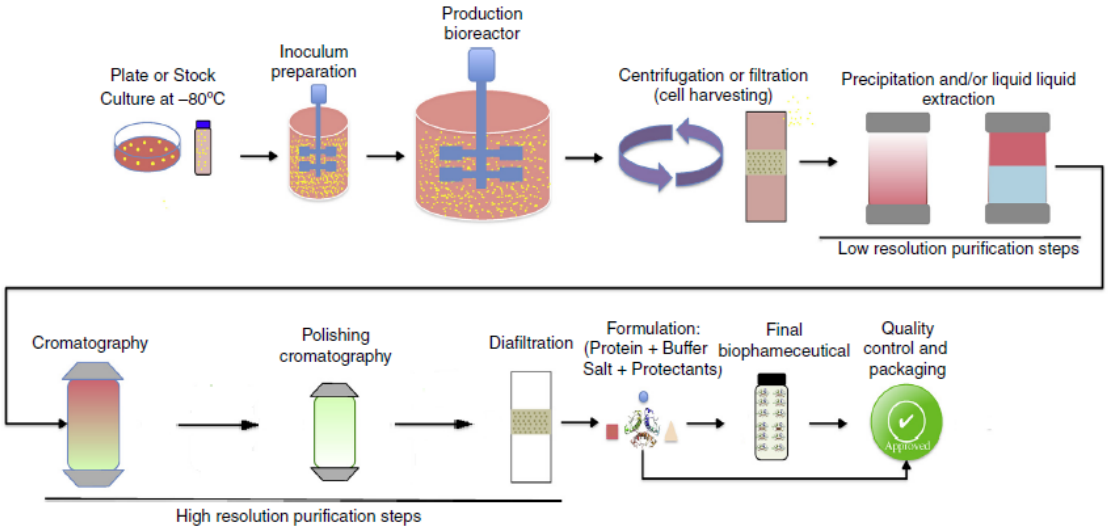

Figure 1. *E.coli-Based* recombinants manufacturing technology flowchart

begin low- and full-rate initial production, MRL 3 (MRLs 8 to 10 in DoD's questionnaire): Low- and full-rate production is demonstrated.

The MRL computing in this method will be done by scoring each question from 0 to 3. If a question is considered unrelated by the manufacturer, the responder will select the N option. Before computing MRLs, first, the irrelevant questions should be omitted, then the number of omitted questions will be deducted from the number of initial questions of each level. The average score, computed by dividing the sum of related questions' scores by the number of related questions, will be each level's quantity. The product of each level's quantity by its relative importance percentage will be added to similar quantities of two other levels. The average of these three quantities will be the final MRLs of the manufacturer. Thus the relative importance of each level has to be determined. The designed questionnaire containing 49 questions (related to 9 threads of MRLs) was validated using the CVR method by 13 Iranian biopharmaceutical experts. They also determined the relative importance of each level. Experts scored a percentage for each level one by one. An average of 13 quantities related to each level was considered a relative importance percentage of each level.

Second method

In the second method of study, the relative importance of three threads or technology components (software or technical knowledge, hardware, manpower) involved in each stage of manufacturing and the relative importance of each stage in determining the final value chain of the product was evaluated by experts and expressed as a percentage (three technology components has been assessed rather than four in this method).

The manufacturer declares the readiness of threads in each manufacturing stage on the scale of percentage. The product of the declared percentage for each thread by the relative importance percentage of thread in the related stage will be added to similar quantities of two other threads in the same stage. Then the result is divided by three. The product of multiplying the recently obtained quantity by relative importance percentage of the stage will be the stage's quantitative readiness. Finally, by summing the computed quantitative readiness of each stage and dividing the product of it into the number of stages involved through the manufacturing process, the final readiness will be obtained.

Manufacturing of *E. coli*-based recombinants involves nine stages in the following order (Figure 1): "sequencing", "recombinant and working cell production" (stock culture and inoculum preparation), "fermentation", "harvest", "extraction", "high-resolution purification", "formulation", "final production", and "quality control" [12, 13]. The main technologies used to produce *E.coli-based* recombinants are as follows: "capillary electrophoresis machines" (related to sequencing) [1, 14], "spectrophotometers" (related to recombinant and working cell production) [15], "fermenters" (related to fermentation) [13], "centrifuge machines" or "diafiltration" (related to harvest) [13, 16], "opposed-jets contacting devices" (related to extraction) [17], "chromatography columns" (related to high resolution purification) [13], "freeze dryers" (related to formulation) [18], "filling

Table 1. Relative importance percentage of *E.coli-Based* recombinants manufacturing stages

No.	Manufacturing Process	Relative Importance of Stages (%)
1	Sequencing	7.4
2	Recombinant and Working Cell Production	7.8
3	Fermentation	6.4
4	Harvest	9
5	Extraction	12.4
6	High Resolution Purification	15.5
7	Formulation	14.8
8	Final Production	14.9
9	Quality Control	11.8
		100

machines" or "pump fillers" (related to final production) [19], and "biosensors" (related to quality control) [20].

To determine the relative importance of each stage, first, a questionnaire was designed based on the "Analytical Hierarchy Process" (AHP) method, then 13 experts of biopharmaceutical in Iran compared stages in pairs. Also, the relative importance of the three threads involved in each stage of manufacturing was determined by experts. Experts allocate a percentage for each thread one by one. An average of 13 quantities related to each stage's threads was considered the relative importance of three threads in each stage.

Results

Following the deliberation of the first method's questionnaire by experts, 38 questions were validated following the CVR method, and three questions were added to the questionnaire by experts (Appendix). The

Table 2. Relative Importance Percentage of Manufacturing Stages

		%				Total
		Manufacturing Process	Relative Importance of Technical Knowledge	Relative Importance of Hardware	Relative Importance of Labor Skills	
7.4%	1	Sequencing	56.4	25	18.6	100
7.8%	2	Recombinant and working cell production	47.27	35.45	17.28	100
6.4%	3	Fermentation	29.1	57.27	13.63	100
9%	4	Harvest	28.63	52.27	19.1	100
12.4%	5	Extraction	27.72	53.18	19.1	100
15.5%	6	High resolution purification	37.26	48.2	14.54	100
14.8%	7	Formulation	55	28.64	16.36	100
14.9%	8	Final production	19.54	69.1	11.36	100
11.8%	9	Quality control	30.9	47.74	21.36	100

Table 3. Manufacturing Readiness Levels Definition

MRLs	Definitions
MRL 1	Basic manufacturing implications identified
MRL 2	Manufacturing concepts identified
MRL 3	Manufacturing proof of concept developed
MRL 4	Capability to produce the technology in a laboratory environment
MRL 5	Capability to produce prototype components in a production relevant environment
MRL 6	Capability to produce a prototype system or subsystem in a production relevant environment
MRL 7	Capability to produce systems, subsystems, or components in a production representative environment
MRL 8	Pilot line capability demonstrated; ready to begin low-rate initial production (LRIP)
MRL 9	Low rate production demonstrated; Capability in place to begin full-rate production (FRP)
MRL 10	Full-rate production demonstrated and lean production practices in place

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relative importance percentage of each level based on experts' opinions was obtained, too.

The relative importance value of the primary studies and technical knowledge was found as 46.04%. The pilot line capability demonstrated and prepared conditions to begin low-, and full-rate initial production proved to be 22.91%, and at last, the low and full-rate production was attained 31.05%.

Thirty-six binary comparisons based on the AHP in the second questionnaire, done by experts, were computed with "Expert Choice" software. The results are shown in Table 1.

The relative importance percentage of three threads in each step of manufacturing is as follows (Table 2):

The product of multiplying the relative importance percentage of each thread or technology component individually by the relative importance percentage of each step was added to the similar computed quantities of other stages. By dividing each of the recently obtained quantities for each technology component to a hundred, the relative importance percentage of three technology components in the manufacturing process of *E.coli*-based recombinant proteins was computed.

The relative importance percentage of three technology components in the manufacturing process of *E.coli*-based recombinant proteins is as follows:

The relative importance percentage of "technical knowledge" in the manufacturing process of *E.coli*-based recombinant proteins is 36.21%.

The relative importance percentage of "hardware" in the manufacturing process of *E.coli*-based recombinant proteins is 47.22%.

The relative importance percentage of "labor skills" in the manufacturing process of *E.coli*-based recombinant proteins is 16.57%.

Discussion

Following the established methodology, for the assembly of a set of Subject Matter Experts (SMEs) who rated each item on a 3-point scale: essential, helpful but not essential, and finally not necessary. The Content Validity Ratio (CVR) is a linear transformation of the ratio of the number of SMEs judging an item to be essential to the total number of SMEs in the panel. In particular, $CVR = \frac{n_e - \frac{N}{2}}{\frac{N}{2}}$, where the number of SMEs indicating that the item is essential, and N is the total number of SMEs in the panel. When all SMEs rate the item as being essential, the value of CVR will be 1. When the number rating the item as essential is more than half but less than all, the value of CVR will be between 0 and 1, and when less than half of the SMEs rate the item as essential, the value of CVR will be negative [21].

Table 4. Biosimilars produced by Iranian BPFs

No.	Products	Companies
1	IFN α 2b	PooyeshDarou
2	Peg-IFN α 2b	PooyeshDarou
3	IFN β 1a	CinnaGen, Actoverco
4	IFN β 1b	ZistDarouDanesh
5	IFN γ	Exir
6	Insulin	PooyeshDarou , Exir, Daroupakhsh, Ronak, Vitan
7	Antihemophilic factor VII	AryoGen
8	Antihemophilic factor VIII	SamanDarou
9	Filgrastim	CinnaGen, PooyeshDarou, AriaTinaGen, Ronak, Zahravi, Armanpharmed
10	Pegfilgrastim	CinnaGen
11	EPO	CinnaGen, PooyeshDarou, NoTarkib
12	Somatropin	PooyeshDarou, Sobhan, Homapharmed
13	Gonadotropin	PooyeshDarou, Daroupakhsh, Homapharmed, Roozamad
14	Reteplase	Osveh, Zahravi
15	Rituximab	CinnaGen, AryoGen, Sobhan
16	Etanercept	AryoGen
17	Trastuzumab	AryoGen
18	Follitropin	CinnaGen, Osveh
19	Teriparatide	CinnaGen
20	Bevacizumab	AryoGen
21	Streptokinase	Homapharmed, DarmanAra

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The AHP is described as a methodology to rank alternative courses of action based on the decision-maker's judgment concerning the importance of the criteria and the extent to which they are met by each alternative [22].

By MRLs method, readiness assessment of companies producing *E.coli-based* recombinant proteins is done in more detail. It is based on 41 questions in three levels corresponding to 9 threads and integrated without entering the nine stages of production. During the "ATLAS technology method", however, readiness assessment is performed with a closer look at the technology and its three components. When the establishment readiness of each of three components in each stage is determined and combined, the establishment readiness is expressed. Finally, by combining nine production stages, the establishment's national ability to produce recombinant proteins can be achieved.

In this study, to localize MRLs in the Iranian pharmaceutical industry—despite basing key threads under the DoD definition—changes have been made in the number of questions designed and the levels considered. This action was proposed by the supervisors of the study and was done because—due to the non-pharmacological origin of this method—many of the questions in the initial questionnaire seemed unrelated to the specific principles and processes governing the

Table 5. Leading Iranian biotech exports

No.	Name of Product	Producer
1	CinnoVex®	CinnaGen
2	ReciGen®	CinnaGen
3	Cinnal-f®	CinnaGen
4	CinnoPar®	CinnaGen
5	PDpoetin	PooyeshDarou
6	ZIFERON®	ZistDarouDanesh
7	Interferon gamma 1b	Exir
8	AryoSeven®	AryoGen

Iranian pharmaceutical industry and the critical steps in the production of pharmaceutical products are not considered in the questions raised. Despite efforts to maximize the simulation of these questions with the environment of the Iranian pharmaceutical industry, the partial familiarity of the industry experts with the literature and principles of MRLs introduced by DoD was effective in reducing the number of questions and changing the number of levels of this method. Related to the MRLs method and based on the opinion of the experts, it can be said that to produce pharmaceutical products, knowledge of the mechanisms of drug action, the necessary tests and studies during and after production, necessary knowledge of existing facilities and limitations, and the process of policy-making on how to navigate the production and post-production path (all of which are in the first category of MRLs) are more important than the product production process itself and how it is implemented.

Based on the results of the ATLAS technology method, the hardware used in the production process of *E.coli-based* recombinant proteins is relatively more important than other components of technology. Therefore, the desired hardware has a significant role in promoting the process satisfactorily. Performing calculations related to the relative percentage importance of each manufacturing stage of *E.coli*-based recombinant proteins based on the AHP indicate important issues. According to the specific conditions of the Iranian biopharmaceutical industry and based on the experts' opinion, the initial manufacturing stages of *E.coli*-based recombinant proteins that are associated with the steps leading to the production and analysis of recombinant proteins, the production of second-generation cells, the fermentation and extraction of proteins, and in a general expression of those stages called the upstream process, is of less importance than the stages of purification, formulation, final product production and quality control or the downstream process in general.

Although the necessary measures have been taken to introduce two models of TRA to the Iranian biopharmaceutical industry in this study, these measures have not been implemented in practice. The most important reason for this problem, which can be mentioned as the most prominent limitation of this study, is the confidentiality system of manufacturer companies and their non-cooperation with the trustees of this study to provide essential information and conduct relevant evaluations. The authors hope and expect that by solving this key challenge, the limitations and obstacles to implementing a technology readiness assessment based on this study result will be minimized.

Conclusion

TRA is a systematic, metric-based process and accompanying report that assesses the maturity of specific technologies used in systems. TRA, an assessment of how far technology development has proceeded, provides a snapshot in time of the maturity of technologies and their readiness for insertion into the project design and execution schedule. TRA is a valuable management tool for reducing technical risk and minimizing the potential for technology-driven cost increases and schedule delays [2, 4]. In this study, two TRA models based on existing DoD's MRLs and "ATLAS technology method" principles have been proposed. MRLs in ten levels were performed to provide visibility for "technology and in-

dustrial base capabilities", "design", "cost and funding", "materials", "process capability and control", "quality management", "manufacturing personnel", "facilities." Finally, "manufacturing management" threads and surveying manufacturers' readiness of "software", "hardware", "organization ware", and "manpower" was done within the ATLAS technology method.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethics committee of Tehran University of Medical Sciences.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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Appendix: MRLs Questionnaire

	Questions	Declared As Is					Final Declared Score
		N	0	1	2	3	
1	Has the necessary knowledge and awareness of the typical characteristics and capabilities of the product been obtained?						
2	Have limitations and problems related to critical technologies or production processes been identified?						
3	Is there a necessary knowledge of the selection criteria between different types of construction methods?						
4	Are all the necessary facilities for the production process and quality control determined?						
5	Are there any plans to provide the necessary facilities?						
6	Has the cost model been designed (to determine methods for evaluating and estimating costs)?						
7	Has access to the required materials been assessed?						
8	Have problems with access to and supply of materials been identified?						
9	Are the details of the product production process specified?						
10	Are quality control test designs during and after production developed?						
11	Are there any study plans for surveying the efficacy and safety of the product?						
12	Has a study plan for surveying the pharmacodynamics and pharmacokinetics of the product been developed?						
13	Are critical people selected to run the production process?						
14	Have the problems and stages of entering the product in the country's drug list been considered?						
15	Have any measures been taken to use product-related insurance coverage?						
16	Are there any policies on how to market and sell the product?						
	MRL 1						
17	Has the existing industrial capability and facilities met the needs of prototype production?						
18	Have the predefined constraints and problems been reduced in the initial production phase so that there is no significant risk left in the small-scale production phase and full capacity?						
19	Have the costs been analyzed using the actual results of prototype production?						
20	Are the specifications of all materials used in the initial production stage controlled?						
21	Have the necessary measures been taken to investigate the absence of significant changes in the initial properties of the material?						
22	Has access to materials been minimized?						
23	Have quality control test designs been completed and implemented during prototype production?						
24	Have the quality control test designs been completed and implemented after the production of the prototype?						
25	Are all the key features of the quality control test in the acceptable range at the prototype production stage?						
26	Has the safety and efficacy survey of the pilot sample been completed and implemented in the form of clinical trials?						
27	Has the efficacy and safety of the product been proven?						
28	Have any studies on the pharmacodynamics and pharmacokinetics of the product been performed?						
29	Did the pharmacodynamics and pharmacokinetic characteristics of the product match the brand-name drug?						

	Questions	Declared As Is					Final Declared Score
		N	0	1	2	3	
30	Has the capability of the production process after the production of the prototype been reviewed and approved?						
31	Has the manufacturing plan for small-scale, full-capacity production been updated?						
32	Are there any plans to provide the necessary facilities for small-scale production and full capacity?						
	MRL 2						
33	Has the industrial capability and available facilities met the needs of small-scale production and full capacity?						
34	Is there the ability to make corrections, updates, abrupt changes, and other potential build requirements?						
35	Did the program have a sufficient budget for the production phase at full capacity?						
36	Are the specifications of all materials used in the production stage on a small scale and at full capacity controlled?						
37	Have quality control test designs been completed and implemented during the production of the final product?						
38	Are the quality control test designs completed and implemented after the final product is produced?						
39	Are all the critical characteristics evaluated during the quality control in the production stage at a small scale and full capacity, within the appropriate range?						
40	Are all remaining constraints in the small-scale production phase identified and approved programs designed to reduce them?						
41	Have programs related to providing the required facilities and removing construction restrictions been followed and implemented during production at full capacity?						
	MRL 3						