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Insight on PMDA Regulatory Procedures, Key Stages, Timing, and CMC Requirements for Bio-Therapeutic Products in Japan

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ABSTRACT

The purpose of this manuscript is to provide a basic understanding of legal regulatory systems, marketing authorization application, the Pharmaceutical and Medical Device Agency (PMDA) review process, key stages and timing and CMC (Chemistry, Manufacturing and Controls) requirements in Japan, with a focus on biotherapeutic/biological drug products for human use. The PMDA has some stringent CMC data requirements, which make Japan unique. Japan's regulatory environment is significantly more complicated than any other country. The level of accuracy and details required by the Japanese regulatory authority is sometimes even greater than the US FDA (the United States Food and Drug Administration), the EMA (the European Medicine Agency) or any other pharmaceutical regulatory agency.

Global biopharma companies often complete their development for US/EU markets before considering Japan. It is clearly an important part of the drug development process and Japan needs to be considered in parallel with activities required for other major regulatory authorities (USFDA and EMA). In context, another significant consideration is that approval for a drug product in the US/EU is a well-understood and documented process, whereas Japanese approvals are often more complicated, unclear and time consuming. Here, the author has studied various unique features and the challenging regulatory framework for biopharmaceutical products, including regulatory procedures, registration, authority review, compliance, approval, and a key focus on CMC requirements. The proposal is to identify priority measures and controls that companies should have in place in order to build quality into procedures for compiling flawless regulatory submissions and to reduce review time by minimizing regulatory queries. This also provides a way for overseas manufacturers for development of bio prescription drugs for the Japanese market and provides a brief of precise requirements.

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Introduction

Japan represents the largest pharmaceutical market, after the United States and China, in the world. Recently, Japan has become very attractive for inward investment propositions for the dozens of biopharmaceutical products that are on the market, and the many more that will be approved in the coming years.

It is of paramount importance that the production of biopharmaceutical products is tightly controlled, as these are produced using a living system or organism, thus are different from conventional drug products in many ways. The manufacturing process of biopharmaceutical products is highly complex and is a determining factor in the development of a biological medicinal product, so that the product tested in clinical trials is consistently produced when batch sizes increase during commercial production. To gain approval, not only the end product must be approved by the regulatory agency but also the manufacturing process, critical quality attributes, manufacturing equipment, excipients, culture medium and the cell lines that go into the production. It takes several years of intense research to develop an effective, safe, quality biotherapeutic product, which goes through preclinical and clinical evaluations, followed by new drug application submission, reliability review and GMP compliance survey, etc.

In this manuscript, emphasis is put on three important topics regarding new drug approval in Japan. First, the basic understanding of Japan's regulatory bodies, marketing authorization application for new biotherapeutic drugs (hereafter J-NDA), GMP compliance, the PMDA review process, key stages, and timing, from application through approval. Second, Japan-specific CMC requirements, with a focus on biopharmaceutical drugs for human use. And third, key considerations for an effective CMC regulatory strategy.

(1) NAVIGATING REGULATORY FRAMEWORK AND MARKETING AUTHORIZATION PROCESS FOR NEW BIOPHARMACEUTICAL DRUG PRODUCT

Regulatory agency

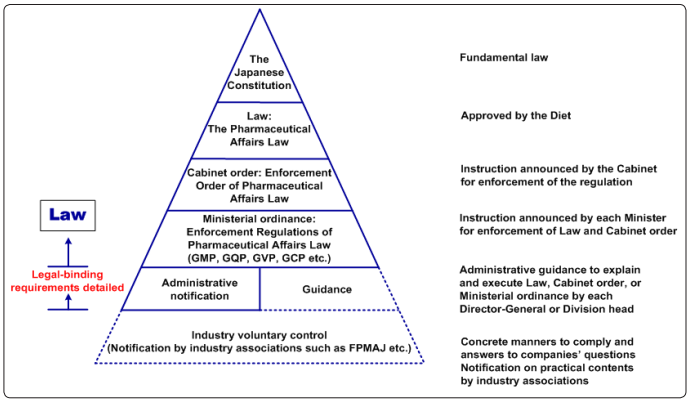
Koseirodosho, which is the Japanese Ministry of Health, Labor and Welfare (MHLW), is the regulatory agency for pharmaceutical regulatory affairs in Japan. Formal approvals and licenses are

required to market drugs in Japan, which are obtained from the MHLW. The Pharmaceutical and Food Safety Bureau (PFSB), which works under the MHLW, handles clinical studies, approval reviews and post-marketing safety measures The Pharmaceutical and Medical Devices Agency (PMDA), or SOGO KIKO in Japanese, was established through the integration of different pharmaceutical institutes. It provides consultation concerning clinical trials of new drugs and manages and oversees the new drug approval (J-NDA) process. The PMDA performs GCP compliance review (document review and GCP inspections), as well as GMP compliance inspections. The PMDA handles all activities from the preclinical stage to approvals, and post-marketing surveillance [1,2].

Overview of Pharmaceutical Legislation

The pharmaceutical affairs law (PAL, also called "Yakuji ho", in Japanese) is the primary law in Japan for the regulation of drugs and other medical products.

Figure 1 shows the hierarchy of the Japanese legal system. The constitution of Japan is the fundamental law of Japan, under which all the nation's laws are created. Japanese laws are legislated by the Diet (Parliament/Congress). Upon approval, a Cabinet order is issued, and a Ministerial Ordinance is made to support the enforcement of the law. The law and the Ministerial Ordinance are construed as legally binding requirements [3].



(**Source:** PDA,s Book - Pharmaceutical Legislation of the European Union, Japan and the United States of America – An Overview, ISBN-978-0-939459-85-8)

Figure 1: Law System of Japanese Pharmaceutical Regulation

Acquisition of Marketing Authorization License is a pre-requisite, which allows an applicant (organization) to continuously market the approved medicine as a business in Japan.

MHLW Ministerial **Ordinance No. 136** describes Good Quality Practices (GQP) that are applicable to all Market Authorization Holders (MAH). Drug manufacturers are required to be formally designated as an MAH for their products to be marketed in Japan. They should be familiar with the requirements of this ordinance in order to establish and properly maintain their status as an MAH. The GQPs specified in this Ordinance are requirements for anyone who applies for an MAH in Japan, i.e., marketers of products, distributors, and importers in Japan, but they are not requirements for manufacturers, either within Japan or overseas. The assessment of each MAH's compliance with GQP is conducted by the prefectural government in which the MAH has its registered place of business. Every manufacturer should be familiar with the ordinance and its specific requirements, which stipulate cooperation between the MAH and the manufacturer.

MHLW Ministerial **Ordinance No. 101, 2005**, for the Regulation for Buildings and Facilities for Pharmacies etc. (Buildings and Facilities Regulation). This ordinance applies to buildings and facilities of the manufacturing sites for medical products (general process, aseptic process, specified biological, etc.) as well as for quasi-drug and medical device manufacturing sites located in Japan.

MHLW Ministerial **Ordinance No. 179, 2004**, for the Standard for Manufacturing Control and Quality Control of Drugs and Quasi-drugs. This describes the GMP that is applicable to all manufacturing business-license holders and relates to standards for manufacturing control and quality control of drugs and quasi-drugs. Ordinance No. 179 also covers manufacturing control and quality control for APIs (Section 2; Articles 21 and 22), sterile drugs (Section 3; Articles 23, 24, and 25), and biological drugs (Section 4; Articles 26 to 30). "Biological drug" includes any product manufactured with raw materials or materials derived from humans or other organisms (excluding plants), that are designated by the Minister of MHLW upon learning the opinion of the Pharmaceutical Affairs and Food Sanitation Council as requiring special precautions in terms of public health and hygiene (Article 2).

The main licenses that are required for the manufacture, importation, and marketing of drug products in Japan are as follows [5]:

- Marketing business licence for MAH
- Manufacturing business licence
- Accreditation as foreign manufacturer (of drugs manufactured overseas)
- Marketing Authorization for each product (J-NDA approval)

An organization or person without a marketing and manufacturing-business license from the Minister of MHLW is not allowed to place drugs on the Japanese market. It is expected of a licensed MAH to enhance, strengthen, and make accountable post-marketing safety arrangements. Commercial importation is allowed if a licensed MAH submits an import declaration to a regional bureau of the MHLW prior to customs clearance.

New drug products must be produced at a manufacturing plant that has a Manufacturing License (also called Seizou-gyou Kyoka, in Japanese), which is a permit to manufacture medicinal products. The period of validity of the license (Kyoka) is 5 years (Article 13, of PMD Act). An ML must be obtained for product quality control, even for facilities where drug products are packaged, labelled, or stored. The license is valid for five years and renewal is necessary when manufacturing is intended to be continuously carried out after the period of validity (Article 13, Paragraph 3, Article 10, and Article 30, of PMD Act.).

If a manufacturing plant that is located outside of Japan intends to manufacture drugs in a foreign country and export them to Japan, it is required to be accredited by the MHLW as an "Accredited Foreign Manufacturer" (also called Gaikoku seizō gyōsha nintei, in Japanese), specified in Article 13-3 of PAL, rather than the manufacturing license which is required for domestic manufacturing plant.

For accreditation of a manufacturing plant, on-site inspection, or in most cases, a document (desktop) investigation is conducted by PMDA.

Note: Before applying for accreditation, a Japanese MAH must apply and obtain a "Business Number" for the accreditation.

Regulatory framework for biotherapeutic drugs (from a quality perspective)

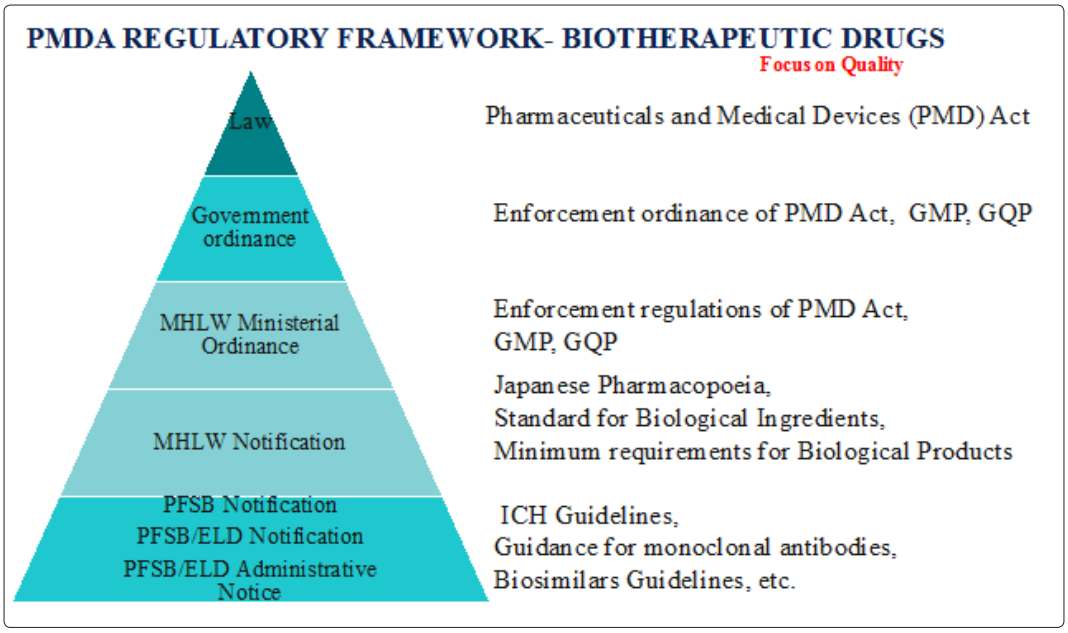
Pharmaceutical administration in Japan consists of various laws and regulations, of which the Pharmaceutical Affairs Law (PAL) is fundamental. It consists of 11 chapters and 91 articles. The PMDA's Office of Biologicals provides consultations concerning clinical trials of new drugs and handles biotechnology medicines, including biosimilars. The MHLW designates a product as biological after the Ministry consults with its Pharmaceutical Affairs and Food Sanitation Council (Note: Regenerative medicines are not considered in this manuscript).

Pharmaceutical and Biotherapeutic Drugs are regulated by Japanese pharmaceutical affairs laws (PAL) and several MHLW Ministerial Ordinances.

Japan is a part of the ICH countries; hence, it follows ICH Guidelines, but Japan does have some additional unique requirements. The PMDA has comparatively more stringent requirements for biological products than the USFDA and the EMA. Furthermore, it is recommended to follow the guidelines and standards below.

- Pharmaceuticals and Medical Devices Act (PMD Act)
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products (MRBPJ)
- Japanese Pharmacopoeia (JP) (General / Formulation specific test)
- ICH guideline Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products". Q5C also specifies the need to examine the stability of reconstituted lyophilized products as well as drug substances, drug products and intermediates. Hence, applied.
- ICH guideline Q1A (R2) and ICH Q6B: some principles that are applicable and guidance to ensure we deliver regulatory-driven stability data suitable for your biologic and regulatory submission documentation.
- ICH Q5A (R1) Quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
- ICH Q5B Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
- ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- ICH Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
- ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

Figure.1. Shows the PMDA Regulatory Framework for Biotherapeutic Products (Focus on Quality)[6,19,21].



Source: PMDA - Malaysia-Japan Symposium on Pharmaceutical Regulatory System

Figure 2: PMDA Regulatory Framework for Biotherapeutic Products (Focus on Quality)

PMDA Consultation Services

PMDA has established a consultation system to improve and reinforce the quality of clinical studies and new drug application. Major consultation categories are those for procedure, bioequivalence studies, safety, quality, consultations before start of Phase I/II/III studies, pre-NDA consultation, orphan designation consultation, consultations when planning clinical studies for reevaluation and reexamination, etc. The procedure of scientific advice meeting action items, timing and process is as given in Table 1 and Figure 3 [7].

Table 1: Action items and timing of Consultation /interview advice meeting

Timing	Action	By
Approximately 2 months (1st working day of the month)	Submission of a request for a consultation meeting	Applicant
	Notification of acceptance of consultation meeting date (within 5 days of the request)	PMDA
	Submission of a formal application with the copy of the receipt of fee transfer	
Approximately 5 weeks (Monday of that week)	Submission of briefing documents (both paper document and electronic media)	Applicant
	Q&A dialogue in writing, and request for submission of additional documents, if these are required	PMDA/Applicant
Approximately 4 days	Provision of PMDA's view of consultation in writing	PMDA
Day of meeting	Face-to-face consultation meeting	PMDA/Applicant
Approximately 1 month (post meeting)	Preparation of draft minutes/Confirmation of draft minutes	PMDA/Applicant
	Finalization of official minutes	PMDA

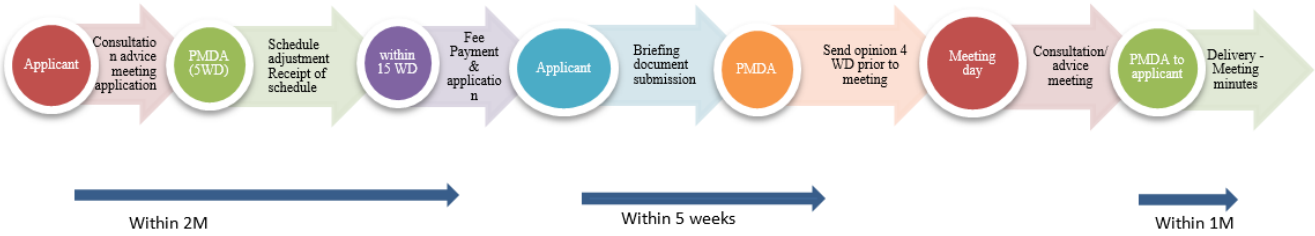


Figure 3: Procedure of Consultation (Scientific Advice Meeting)

New drug application (J-NDA) for biotherapeutic drug product

The basic procedure for the Approval Examination System as outlined in Figure.4 can be summarized as follows: Any applicant who plans to begin clinical trials (called rinsho-shiken in Japanese) must submit a clinical trial notification (CTN) to the PMDA for each trial. The applicant provides relevant documents: a statement regarding the reason that the sponsoring of the proposed clinical trial is scientifically justified, a protocol of the proposed clinical trial, an explanation document used for informed consent and a consent form, and an investigator's brochure. The PMDA conducts a scientific review and makes inquiries to the applicant within 30 days if the CTN is a first-time submission. In this period, the PMDA and the applicant must resolve all inquiries before the applicant begins clinical trials.

After successful clinical trials, the applicant can submit a new drug application (J-NDA, also called shin iyakuhin no seizo hanbai shonin shinsei, in Japanese) to the PMDA, where all the data is reviewed by a multidisciplinary PMDA reviewer. The approval review process consists of the following steps: the J-NDA evaluation process, Compliance Review (including GCP inspection) and GMP. The J-NDA procedure for approval begins by submitting an application dossier to the PMDA, which is an electronic submission (e-CTD).

The applicant can meet with the PMDA prior to submitting the application for approval in order to discuss the review schedule and to cross-check the necessary actions before and after each event, confirmation of matters relating to reliability inspections, GMP inspections, electronic submission of data and any other important matters. The Application dossier in eCTD format and the usability of a gateway system are both mandatory for all new drug applications to PMDA.

When the PMDA accepts an application for new pharmaceuticals, it formally checks the application documents for compliance of format, attachments, signatures, etc. with the specified requirements. After a formal compliance check and validation of a submitted application dossier, the applicant will be notified of validation via the portal site. After the filing of a dossier it is not recommended, in principle, to provide additional data, except for cases when the PMDA has already given approval in prior consultation with the reviewers for the submission of additional data that is required by the PMDA reviewer. For example, results of ongoing stability studies in support of a shelf-life claim, results of the review of NDA /BLA from another jurisdiction, etc.

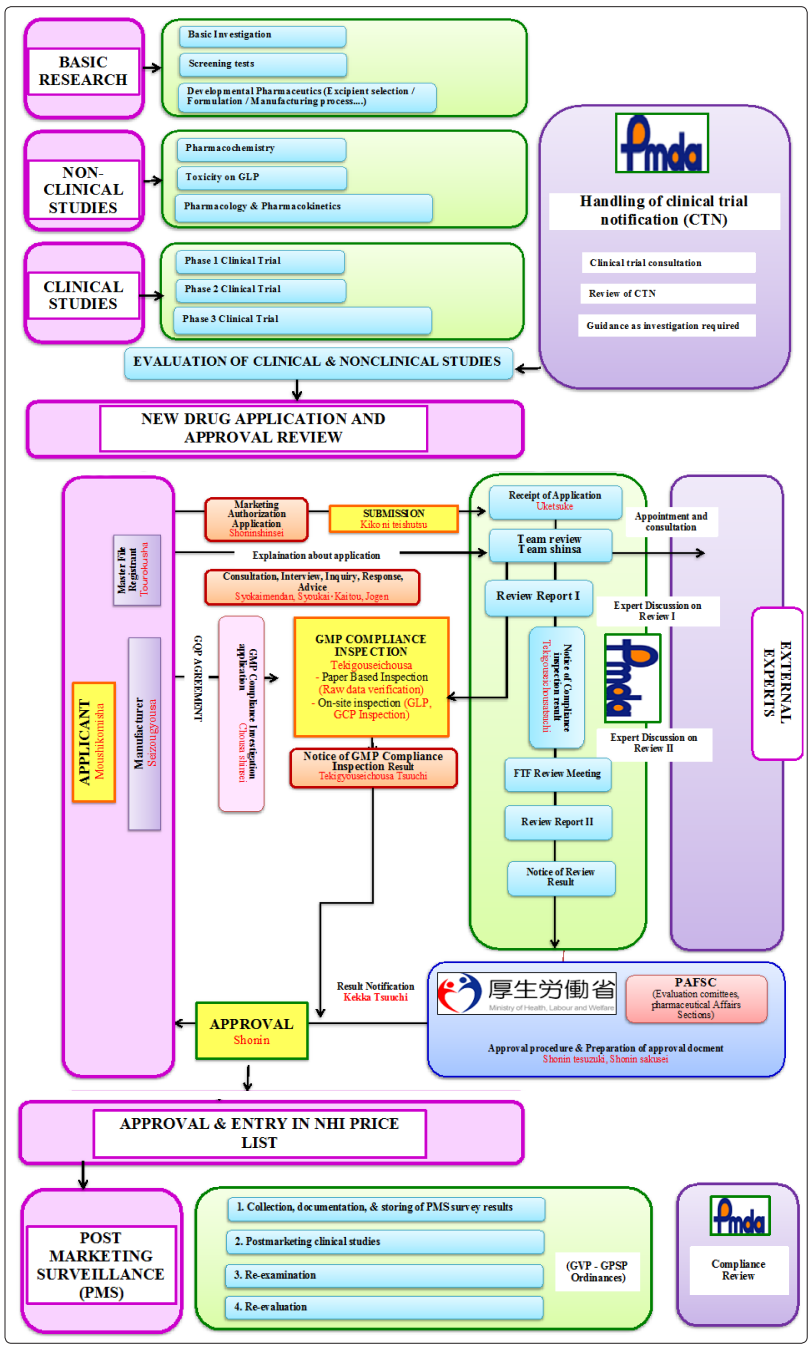
After that, the PMDA sends preliminary inquiries to the applicant, followed by the first interview meeting to be held (shokai mendan,) with a PMDA reviewer and a non-PMDA expert. This is followed by an ongoing reliability assessment (shinrai-sei chosa), including inquiry-response (shokai kaitou) sessions that include the applicant and PMDA reviewers.

The reliability assessment review and the GMP inspection report (koto hokokusho sakusei-ryaku shuri) are then completed. After the review by the PMDA is completed, the application is then discussed with a PMDA reviewer and a non-PMDA expert and reported at a second committee (bukai shingi) by the Committee and Department on Drugs of the PAFSC, on the basis of the most

recent and advanced scientific knowledge. The final decision concerning approval is made by the MHLW. The MHLW issues approval or rejection on the NDAs and once a drug wins approval from the MHLW, it enters the National Health Insurance (NHI) list for pricing negotiations. Frequency of approval is 4 times per year. The PMDA does not provide an official letter to inform the applicant of approval/rejection of the application. The probability can be communicated in the interview meeting and/or questions in writing that are sent to the applicant during the due course of the review process of J-NDA [8-10,12].

Points to be noted for post authorization of manufacturing and marketing of new drug:

- The MAH must undergo a written or on-site conformity survey (periodic survey) every five years after having obtained approval, to determine whether the manufacturing control or quality control methods at the manufacturing site of the pharmaceutical product pertaining to the item of approval conform to the standards specified by the MHLW (GMP ordinance).
- The Marketing Authorization License holder must adhere to the GQP (Good Quality Practice) and GVP (Good Vigilance Practice) when marketing the approved drug product.
- Any changes to the approved items should be reported as described in Article 14, Para. 9 of PMD. Act.
- Marketing Approval of a product can be cancelled if marketing of the product has been discontinued for three years with no due reason.



(**Source:** Pharmaceutical Administration and Regulations in Japan, Japan Pharmaceutical Manufacturers Association, March, 2014. (http://www.jpma.or.jp/english/parj/whole.html)

Figure 4: Flow of New Drugs from Development to Marketing [11]

J-NDA - review timing and milestones

Although each new drug will, theoretically face all these elements on its way to approval, the approval process is, in many ways, different for each new drug. The PMDA J-NDA application requirements may be influenced by many factors, including PMDA familiarity with the biotherapeutic drug for which application is being made, or similar biological entity, proposed indication, formulation type and the availability of competing therapies in Japan. Similarly, these factors may have significant influence on PMDA review of the product J-NDA, affecting the time that the regulatory agency must invest in the evaluation of the safety, efficacy, quality of drug for its proposed indications and the priority of the application itself.

All new drugs are subject to approval by J-NDA before they can be legally marketed in Japan. The standard drug-review process takes approximately 12 months, while priority review takes 9 months, and review of sakigake products only takes 6 months. Figure 5 (A, B, C) depicts the (A) Standard review, (B) Priority review (Orphan designation product) and (C) Sakigake product (forerunner designation) review timeline for New Drug Application (J-NDA).

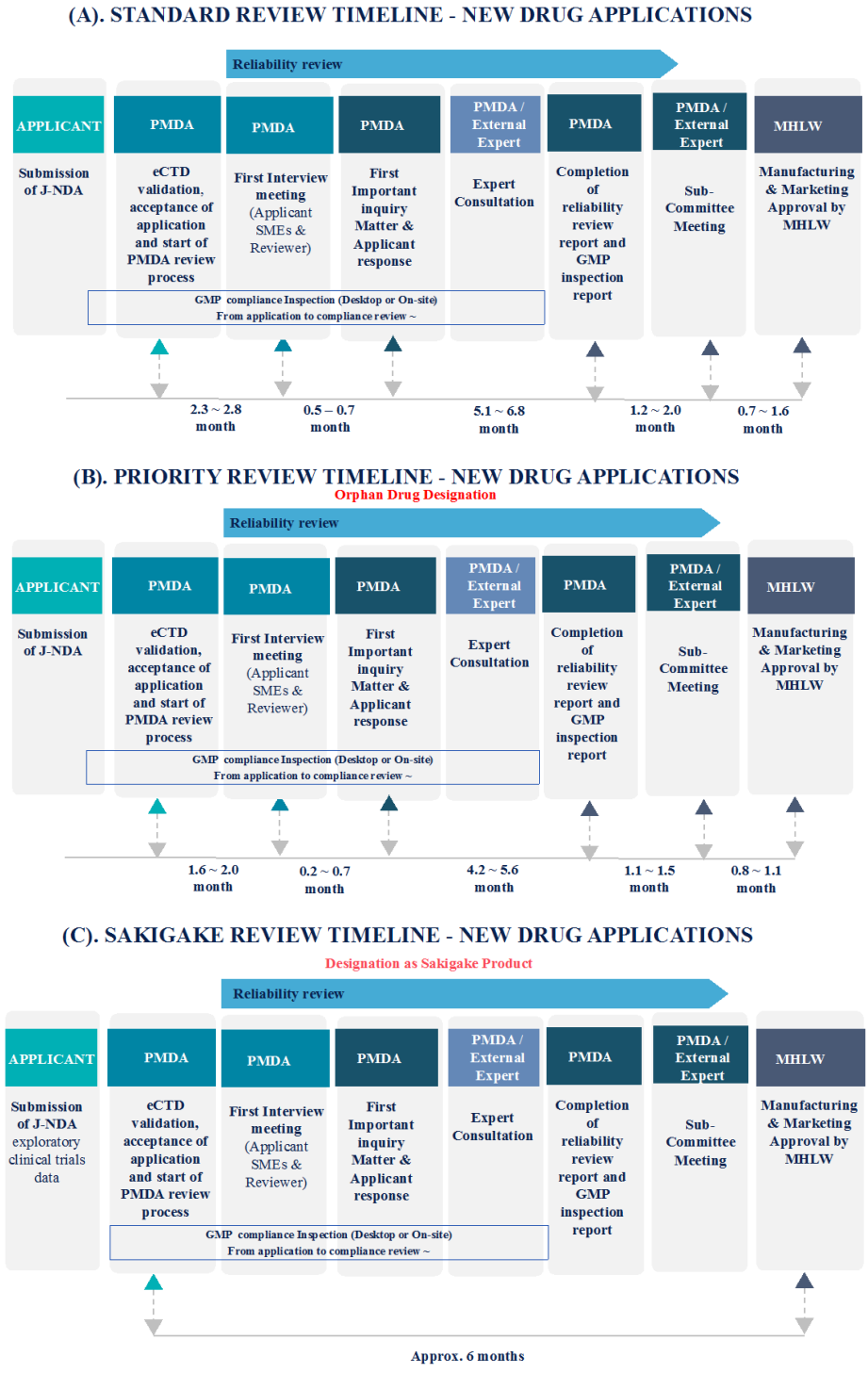


Figure 5: (A), (B), (C). Standard review, Priority review (Orphan drug designation) and Sakigake (forerunner designation products) review timeline – JNDA

Overview of accelerated review system

In general, CMC is on a critical path in the era of accelerated review and conditional early approval system for drug products. Various Japanese procedures are described in Table 2, including Expedited Review, Priority Review, Sakigake, Conditional Early Approval, Conditional and Time Limited Authorization [13,19].

Table 2: Summary of Accelerated review system in Japan

Summary of Accelerated review system (PMDA)		
Type	Area	Designation requirements
Expedited review	Any product categories	Designation is not needed Needed to expedite the review
Priority Review		Designation is needed 1. Orphan drugs 2. Apparent improvement of medical care and for severe diseases
Sakigake (Forerunner Designation)		Designation is needed 1. Innovative medical products 2. For serious diseases 3. Development and NDA in Japan (Being world's first or simultaneous with other countries) 4. Prominent effectiveness expected on non-clinical and early phase clinical studies
Conditional Early Approval	Drugs	Designation is not needed Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials
Conditional and time limited Authorization	Regenerative Medicines	Designation is not needed

(2) JAPAN-SPECIFIC CMC DATA AND OTHER REGULATORY ASPECTS

CMC data package of biotherapeutic drugs

Overall, biotherapeutic drug development are relatively difficult compared with chemically synthesized drugs. Raw materials are complex biologicals, and manufacturing processes don't involve chemical reactions, but cellular expressions. Process conditions are gentle separation steps. Upstream production is very complex, whereas downstream production is delicate. When comparing conventional chemical drug substances, resulting drug substances manufactured through biotechnology methods or through the use of bio raw materials are not pure. Even after undergoing filtration/purification processes, there is still much heterogeneity. Final fill/finished products also require a significant amount of meticulous processing, as even a small mistake could denature the material. Thus, finished products can be highly heterogenous in nature. Formulation development is also quite detailed, as its ability to mimic a biological state is unlike chemically synthesized drugs in target dosage form. Analytical testing is a multifarious process, as it requires characterization of large heterogenous molecules, development of chemical/physical analytical methods, as well as biomolecular/bioactivity determinations. The stability profile is synergistic and non-linear kinetics, wherein, in due course of storage, there is not only loss of assay that results in loss of efficacy of drug, but also degradants increase. Degradants of biotherapeutic drugs might cause a surge in immunogenicity. Leaching from container closure-systems not only causes toxicity, like chemically synthesized drugs, but it also produces immunogenicity. The most important quality aspects are specifications of biotherapeutic drugs that have numerous parameters.

The following are important analytical data to be gathered to compile quality module:

1. Excipients selection, and stable formulation development
2. Specification and product profile, which includes physiochemical properties, compositional, structural, and functional analysis
3. Degradation evaluation (forced degradation to assess product and process)
4. Analytical method qualification and validation, which includes linearity, precision, accuracy, specificity, robustness, and stability indicating capability.
5. Batch release test data to prove manufacturing consistency, critical quality attributes, and quality of product
6. Reference material characterization
7. Stability test results including accelerated and real time storage conditions
8. Assessment of contaminations possibility by process, drug substance, container closure e.g., Extractables / Leachable
9. Adventitious Agents Safety Evaluation

From a regulatory perspective, biological medicinal products are distinguished from conventional medicinal products. Per definition, biological as a medicinal product for which the active substance is a biological substance. According to PAL, biological products are classified into "bio-derived products" and "specified bio-derived products", which use raw materials derived from humans or other organisms, and which require special precautions in terms of public health and safety measures. "Specified bio-derived products" are defined as products with a high theoretical or actual risk of infection, e.g., blood products. "Bio-derived products" are products, such as antibodies, produced in human cells or animal cells, including manufacturing steps such as viral inactivation and removal steps that confirm the absence of viral pathogens.

When applying for a J-NDA for a biological drug product the applicant must submit data for product designation review to define the classification of the biological product as listed above. For each component used in the manufacturing process that is derived from human or animal origin, a special form must be completed. This form lists the category of the human- or animal-derived material (e.g., human blood-derived component, ruminant-derived component, animal-derived component), the purpose of use (e.g., active pharmaceutical ingredient, host cell, cell culture component, excipient), a description of screening/controlling humans/animals that are the origin of the raw material (e.g., manufacturing process of the raw material, including viral safety measurements, certificate of the origin from the supplier).

Special CMC requirements and regulatory aspects which must be taken into consideration when dealing with J-NDA for Biotherapeutic Drug products

Application Form And Cmc Package

CMC package includes (1) Application Form "CTD Module 1.2" (2) CTD Module 2.3 Quality Overall Summary and (3) CTD Module 3 Quality

❖ **Application Form "CTD Module 1.2"** is also called Iyakuhin seizō hanbai shōnin shinsei-sho (医薬品製造販売承認申請書) in Japanese. Application form shall be in Japanese language. Contents described in the Application Form "Module 1.2" are legitimate matters subject to approval. In Japan, regulatory commitments are the contents of Application Form viz., Japanese accepted name (JAN)/non-proprietary name, brand name, Composition, Manufacturing process, including control of materials, specifications and analytical procedures, dosage and administration, indications, storage condition and shelf-life, manufacturing sites information. The application form can define a classification of post-authorization procedure during a review period unlike US/EU. Matters to be described in the manufacturing method column of the Application Form are all manufacturing process steps (Flow chart as well as narrative description of manufacturing process), from raw material(s), charge-in amount, yield, solvents, starting material, intermediate materials, process parameters (eg., target value/set value), to packaging, in process control and acceptance criteria. Regulatory commitments are clearly separated by Application Form because CTD M2.3 and M3 are references for a review.

❖ **CTD Module 2.3 Quality Overall Summary:** Called Gaiyo (概要), in Japanese. Module 2.3 shall be in Japanese language. Module 2.3 can be a good communication document and can facilitate PMDA assessment, as it is the primary review document in Japan. Members of an MHLW's council and external specialists can smoothly grasp the contents of the application from the Quality Overall Summary.

❖ **CTD Module 3 Quality:** It is acceptable to submit in English or in Japanese, per ICH requirements.

Explicit CMC Data Requirements for Biopharmaceutical Products [20]

- **Source of Raw Materials:** This shall provide a description of the control of
- source of raw material, especially considering that the raw material is of animal origin. If the raw materials are of animal origin and are used as the source and production, such raw materials must be provided in detail. For any measurements performed by the vendor, e.g., viral inactivation steps and

viral testing methods need to be described. A transmissible spongiform encephalopathy risk assessment needs to be presented, especially for bovine-derived raw materials. If bovine derived raw materials are still sourced from the United States, it must be elucidated as to why no other source is available and if there is any possibility to switch to a different source.

- **Cell bank information:** Should include characterization data to confirm the cell line identity, purity, and genetic stability. This component demonstrates that the cell line maintains the recombinant-gene that expresses the target protein after the number of passages are established according to the quality procedures. Viral testing of MCB and WCB must be explained. The ability of specific manufacturing steps to remove or inactivate viruses must be described. A viral risk assessment must be provided. Assuring viral safety of biotechnological products is a complex process, but description of cell culture and viral safety studies system in-depth assessment must be performed. Cell substrates and source materials, cell banks (storage, testing and other requirements) must be described.
- **Drug substance and Drug product characterization:** Shall include analytical methodologies and bioassays to assess the physicochemical and functional properties of the product (composition, shape, size, mass and charge, affinities, and mechanism of action). The characterization determines such properties that might impact its functionality and helps to establish its critical quality attributes (CQAs) that should be considered in the quality specifications
- **Manufacturing Process for Drug substance and Drug product:** Shall include process mapping steps including the critical process parameters (CPPs) for each critical process step. The acceptance criteria of the process validation protocol should be based on the quality target product profiles (QTPPs) intervals of the Critical Quality Attributes (CQAs) to demonstrate the consistency of manufacturing with at least three batches. Determination of CQA and justification. Details on sterility assurance/aseptic processing should be well presented. Upstream processing shall include preparation of media, fermentation, harvesting/recovery, critical process parameters. Downstream processing includes purification strategies, process impurities, clearance studies.
- **Manufacturing Method and conditions:** Description of the manufacturing method column in the application form (Module 1.2) is unique. Module 1 consists of several region-specific information besides application form (AF). The contents of AF are considered as legally binding details. The manufacturing process column shall include details of raw materials, reagents, critical processes, major equipment, critical process parameters, in-process control test and acceptance criteria, key intermediates (storage conditions, hold time/duration, in-process control tests. All processes from raw material(s) to the packaging process.

✓ A flow diagram of manufacturing process including:
– Raw materials
– Charge-in amount
– Yield
– Solvent
– Intermediate materials
– Process parameter (e.g., Target Value/Set Value)

✓ A narrative description of manufacturing process
– Acceptance criteria of starting material(s) and intermediate materials
– In process control, Design Space and Real time release testing (RTRT *) etc.
– Validity of intermediate material, Drug substance and drug product
✓ **Bracketing for in-process controls under manufacturing method shall be described**.

Enter target/set values of process parameters and standard charge-in amounts in the following parenthesis in accordance with their control strategy in the manufacturing process.

《》 : Partial change matter (PCA)
『』 : Minor change matter (MCN)

Enter items other than target/set values in "__" commas
"__" : Minor change matter (MCN)
No parenthesis: Partial change matter (PCA)

PCA & MCN BRACKETING STARTEGY IN APPLICATION FORM				
Critical process parameters	CPP without brackets	PCA matter	Manufacturing deviation not allowed	PCA
	《Target /Set value or midpoint of NOR/PAR or NOR》	PCA matter	Manufacturing deviation allowed*	PCA
Non critical process parameters	Non-CPP without an acceptable range *	MCN Matter	Manufacturing deviation not allowed	MCN
	『Target /Set value or midpoint of NOR/PAR or NOR』	MCN Matter	Manufacturing deviation allowed*	MCN
*: Acceptable range/Normal Operating Range (NOR)/ Proven Acceptable Range (PAR) for bracket value must have been established and well documented at the manufacturing site e.g., batch records, manufacturing standard operating procedure and control strategy etc.				

Any post approval changes to the bracketed conditions in the manufacturing method column of AF requires appropriate regulatory actions [18].

• **Specifications and Analytical procedure:** In principle, the following shall be considered when setting specifications and test procedures: Japanese pharmacopeia (JP) and Minimum requirements for biological products in Japan (MRBPJ) general rules, general formulation rules, general test procedures, reference standards, reagents and test solutions are applied besides ICH Q6B Specifications: Test Procedures and Acceptance criteria for Biotechnological/Biological Products. This section ensures batch-to-batch consistency of quality attributes for identity, content, purity, potency, and heterogeneity. For this purpose, the use of methodologies suitable for the evaluation of such CQAs should be supported by a validation exercise. The specifications should also be addressed to demonstrate long-term stability during the

shelf-life of the drug product following the same rationale of the batch consistency CQAs.

• As cited above, test methods considered acceptable only when follow MRBPJ/JP in general, however, test methods considered acceptable with slight deviations from MRBPJ/JP when justified (in acc. to MRBPJ General rules 34/35). Any specifications or test methods that are not according to MRBPJ/JP are not considered applicable for prothrombin complex concentrates (PCCs) or plasma products. Specifications must incorporate JP-specific test items (for each type of formulation viz., for parenteral: appearance, pH, foreign insoluble matter test for injection, color and clarity test, particulate matter test for injections, extractable volume of parenteral preparation, etc.

• Identification test of DNA sequencing, protein expression e.g., a peptide mapping test as an identity test of primary structure of protein in drug substance is required. The PMDA advises to show correlation between bioassay as potency test for mAbs and other physiochemical assays, characterization, and manufacturing experience. It must include the impurity test for both process-related impurity e.g., residual DNA, host cell protein, media ingredients, chemical reagents, or any other process-related materials and product-related impurity e.g., aggregates, etc.

• Tests including sterility tests (JP), tests for the presence of mycoplasma (JP), Virus tests (ICH Q5A), Endotoxin tests (JP) must be included as control strategy of Adventitious agent safety evaluation.

• Test method in Application form and M2.3 shall be written in Japanese pharmacopeia monograph style, especially the testing conditions, e.g., HPLC analysis must define data integration time range, and system suitability includes system suitability solution preparation, followed by required detectability (interference), system performance (RT, RRT, theoretical plates, tailing factor), system repeatability (Resolution, RSD) and shall have example well labelled chromatogram/spectra. Basic chemical data, identification, purity and test method should follow guidelines for the establishment of the specification and test methods for new drugs, notified by the MHLW in 1994. Please note that if similar biological products are listed in MRBPJ, follow the given specification of the product.

• **Batch Analysis:** Shall include batch analysis data from three commercial-scale size batches per each presentation or/per each container closure type. Data from pilot-plant scale batches or Non-GMP production batches are not recognized by the PMDA. Conduct 3 additional lot studies with each type of container closure system (two or more stoppers, vial types). Poolability or combination results from different lots are not acceptable. The PMDA expects products to be tested for all the test items per JP specifications at the same time There are cases where companies test some items separately on retention samples to compensate a lack of test items per specification of product for Japan. Such an approach might not be acceptable to the PMDA. The PMDA may require new batch analysis data of 3 batches per strength/pack in accordance with agreed specifications for Japan. Utility of successful cases might not work well with the PMDA. Hence, prior quality consultation is advisable.

• **Stability study data of drug substance and drug product:** Shall include batch analysis and stability data on at least 3 batches of manufacturing scale of production per strength/packs types. The quality of the batches of drug substance entered into the stability program must be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made for manufacturing scale. Full testing required per set specification at the time of release, intermediate test points, and at the end of shelf life. There is a common specification for release and shelf life of product. Validated stability-indicating test methods need to be used for testing of stability samples. Testing must be done at all critical terminal test points in the considered stability design. Shelf Life/Re-test Period is based on actual duration of long-term study. However, it is strongly suggested that studies also be conducted on the drug substance and drug product under accelerated and stress conditions also. Extrapolation of data is not acceptable for shelf-life justification. Long term stability studies shall be at constant temperature condition per ICH Q guideline, Mixed-temperature condition data will not be accepted for claiming shelf life of a product. Poolability or combination resulting from different lots or/ and of different storage conditions are not acceptable. There is no post approval stability data commitment, as such. It is required to submit full shelf-life stability in the new drug application. However, submission of ongoing long-term stability data shall be possible during the reliability- review process of J-NDA, but that condition requires pre-consultation and agreement of the PMDA reviewer. Also, data must be submitted at least 6 months prior to J-NDA approval timing, during the reliability review. Hence, it is advisable to consult PMDA regarding stability program to ensure regulatory compliance.

• Reduced-sample design stability study (Matrixing and bracketing) per ICH Q1D is acceptable if selected reduced-stability design and design factors can be scientifically justified (Seek *PMDA opinion on acceptability of applied reduce sample design*). Stability data to support patient-handling practices, handling by physicians without refrigerators, shipping-excursion data have strong impact upon sales in Japan market. However, a temperature-shift study would not serve a purpose for both. I.e., shelf-life claim and robustness under excursion due to shipping. Data on shipping stability, i.e., cyclic temperature stress testing (Freeze and Thaw study) must be included. Also, stability after reconstitution of a freeze-dried product and an in-use stability study for multi-dose containers are required. Stability data of MCB/WCB, starting material, intermediates along with a hold-time study is a must. Stability data trend analysis is also required to justify shelf life of a product. Note that room temperature per Japanese pharmacopeia is 1~30 degree C. It is strongly recommended to increase the retention sample quantity. Additional retention samples for one or two complete tests are required, besides the planned retention sample, per stability test protocol. [The PMDA sometimes asks for test data for an additional JP- specific test items/compensate test data for failure of JP-specific test items from global stability program]. Legacy product data are sometimes missing some non-stability indicating test items per ICH recommendations. However, the PMDA would rather accept the omission of only those test items if omission is justified based on (1) purpose of the testing that indicates that the test is independent of time course and also (2) it is not effected due to variation among the lots, (3) if alternate option for test is available in the specification/stability protocol

• **Excipients:** Standards for excipients are Japanese pharmacopoeia (JP), Japanese Pharmaceutical Codex, Japanese Pharmaceutical Excipients (JPE) and Standard for Biological Ingredients. JP is considered a legally binding requirements in Japan. Raw materials of biological products need to conform with Biological Material Standards and description of source of raw material requirements. Products using materials of which the origin is cells or tissues of human and other living beings (except plants) and that require special attention in terms of public health and hygiene require

submission of details on source, origin, and BSE Certification for Human or animal origin raw materials. Regulatory system for use of excipients in drug products is very complex. Excipient is considered novel excipient, if drug product contains an excipient with no precedence of use as pharmaceutical excipient in Japan. Novel (first time use in human, no prior use in Japan) and requires DMF submission along with data of toxicology studies for new excipients (same amount of CMC information as drug substance). The PMDA provides consultancy and information on "precedence of use of excipients." In addition, precedence of use can be made by referring to the Japanese Pharmaceutical Excipients Dictionary (JPED, published by MHLW) which provide information on use, route of administration and patient exposure. For excipients section, must provide suppliers certificate of analysis (COAs) per JP, JPE etc., for all excipients and test per compendial monograph. There requires CMC, Drug master file (DMF), supporting analytical data for non-compendial excipients.

• **Reference and working standards:** Shall include characterization and control of reference and working standards
• **Adventitious Agents Safety Evaluation:** this must be described the sterility tests (JP), tests for the presence of mycoplasma (JP), Virus tests (ICH Q5A), Replication competent virus, Endotoxin tests (JP)

Important Note for GMP Compliance and Prior Approval Inspection (Pai)

New drug application of biological product being developed by many foreign manufacturers whose Chemistry, Manufacturing & Control (CMC) and Quality Assurance (QA) teams have varying degrees of familiarity with the PMDA CMC regulatory and GMP compliance requirements for biological products. Local representatives of CMC regulatory and QA clearly understand the critical importance of dependencies of J-NDA application (CTD Module 1.2, Module 2.3) and GMP inspection documentation of subjected manufacturing sites. However, lack of coordination and infrequent communication among local and overseas CMC and QA teams results in a disaster for some companies. This happens when either a discrepancy is found in the CMC review or in the GMP compliance inspection due to non-synchronization of content information given in application form and GMP documents for inspection. Each of these complexities can result in approval delay.

Along with the general regulations for GMP, the specifics of biological products require additional measures to maintain their quality. Those additional requirements are mostly related to the utilization of recombinant DNA and genetic and cell engineering, cell, and tissues of animal and human origin, handling of material in terms of prevention of contamination by infectious pathogens, including those causing sexually transmitted diseases, cancer and neurodegenerative disorders.

The CMC review and GMP compliance review process can take longer if there are any discrepancies between the J-NDA dossier and test- and manufacturing records implemented in the facilities subject to GMP compliance inspection. Hence, manufacturing-site quality assurance and regulatory affairs shall work together and appropriately assess the actual manufacturing process, quality controls, etc. and prepare J-NDA and GMP compliance inspection application. Also, applicants shall respond promptly to the PMDA for any CMC review or GMP compliance observation matters.

(3). KEY CONSIDERATIONS FOR AN EFFECTIVE CMC REGULATORY STRATEGY

Competent cross-cultural regulatory cum project management teams channeled with strategic regulatory lead that understands culture, language, and leverage expertise. It is very important that the strategic regulatory lead shall have a good understanding of Pharmaceuticals and Medical Devices Agency (PMDA) regulations and expectations. He or she should, from time to time instruct overseas counterpart on Japan specific regulatory requirements. Provide clarity on prerequisites, organize gap analysis of global CMC package, risk assessment, and deliver risk mitigation pathways. The Japan regulatory submission dossier is unique. Attributable to PMDA special requirements and format, Japanese Submissions are typically the largest and most thorough and complex of any. It's difficult for foreign parent-company regulatory personnel to write a Submission dossier for Japan. To overcome hurdles for Japan Submission dossiers, often foreign companies either approach a contract research organization (CRO), which are the Marketing Authorization Holder (MAH), for the creation of regulatory documentation and to handle all matters of Japanese submission. Otherwise, they establish their own local office. MAH collects the global CMC package, prepares the entire Japan dossier, and submits it. Many companies have products on the market based upon older submissions that were entirely authored by their Japanese offices.

Considering delays from a global manufacturer in exploring the Japanese market, it is required to build **(1) Strategic**, **(2) Tactical and (3) Operational plan** for CMC data generation based on criticality in data requirements, stages of product development (a new development product or established product) and lessons learned from previous projects.

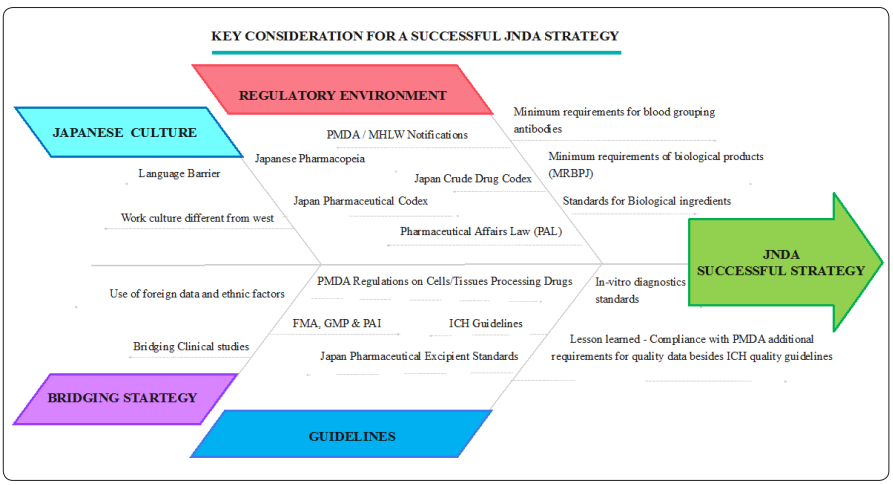


Figure 6: Key Factors in formulating successful strategy for J-NDA

Following are the key points to be considered while formulating regulatory strategy for submission in Japan [19,20].

- **Regulatory Intelligence Laws, ordinance, standards, guidelines, practicality**
- **Consideration of other substantial matters** besides knowledge of regulatory landscape, including intellectual property rights, price listing and reimbursement, supply, health care infrastructure, and the health authority's interest in encouraging development of products.
- **Plan comprehensive long-term strategy for product life cycle:** Integrate with development of typical practices for Japan regulatory submissions or a project charter.
- **Conducting intelligence-gathering activities:** Have "lessons learned" sessions before beginning a new project for Japan, and leverage expertise, educate your overseas regulatory counterparts, maintain trust, and involve Japanese associates in global R&D in the early development phase.
- **Access to right knowledge and expertise:** Because effective strategic planning and access to knowledgeable regulatory experts in Japan, is difficult.
- **Inter-country team building and appointment of skilled and knowledgeable English-speaking regulatory lead:** For leading projects and to manage scientific communication to maintain effective submission in Japan.
- **Early, frequent, and transparent communication between inter-country team**
- **Obtaining and managing documentation:** Global CMC package evaluation, gap analysis to identify challenges and risks and an appropriate risk mitigation plan that helps avoid serious J-NDA approval complications later.
- **Standard gap analysis ad risk assessment:** Required in early development phase.
- **Strategic planning of health authority meeting:** In order to discuss glitches of data and advice on solution strategies.
- **Workflow Process:** Planning, preparing, and maintaining regulatory submissions, schedules, and correspondence. all within budget. Strategy to prepare quality and comprehensive CMC dossier with limited complications.
- **Strategy for preliminary consultation:** Face-to-face CMC review meeting with PMDA (as necessary) and other internal meetings with in-line function to identify potential regulatory solutions for possible roadblocks. Provide enough details with scientific rationale in meeting briefing packages to spur a meaningful dialogue.
- **Concurrent GMP inspection and J-NDA dossier preparation:** Guide manufacturing site on document needs for GMP inspection, help quality assurance personnel in review of raw data and SOPs from regulatory submission perspectives. Application form of J-NDA content shall correspond to executed batch-manufacturing records, testing records, standard operating procedures. etc.
- **Obtain necessary certifications:** Before submission of marketing authorization application or J-NDA viz., application for accreditation of foreign manufacturer for all manufacturing and testing sites involved
- **Drug Master File or Master file (MF):** Points to consider for adequate contact with the person registering the MF, verification of MF registration conditions, and submission of information of registered MF corresponding to CTD Module 2.3, without delay, after filing a marketing authorization application for the product.
- **Source and complexity of the raw material with variability lot-to-lot:** raw materials or excipients used in the manufacture of a biologic drug product ranges from mammalian cell lines that produce a biologic and media and media components to gels and filters that are used in the purification process. What makes the process even more overwhelming is the fact that the manufacturing of biologic happens at different sites globally. Each of the suppliers and the number of raw materials require contingencies for back up. And then, there is also the possibility of quality difference from one lot to another. The use of different suppliers, the discontinuation and disruption of the supply chain, the substitution of low-quality raw materials to the raw materials list present new challenges. Hence, way out is to understand the raw material attributes of their raw materials, which of those affect the variability and control the variability. Test each excipient that is used in the production of the biologic drug all major pharmacopoeias including JP and monitor products of each phase during production and release testing for a variety of attributes. Fix the gaps. Such a testing, monitoring, and release testing will inform the production team to take steps to resolve any identified issues.
- **Company affiliate connection with PMDA reviewers:** In Japan, some things corresponding to data requirements in the regulatory guidelines and PMDA notifications are left undefined. Hence, knowledge and interpretation of regulatory requirements, data need and data presentations in the dossier and in response to PMDA inquiries often rely on experience and regular communication with PMDA reviewers. Pre-submission consultation meetings and post-submission review meetings are available in Japan to understand PMDA expectations. Close acquaintance with PMDA personnel for pre- and post-submission makes it possible to move forward more swiftly.
- **Understanding of PMDA expectation on format and content of application form and responses to inquiries;** Many companies that do business in Japan wish to utilize global format and content of dossier or response to health authority inquiries in Japan. However, it is advisable to rely on their Japanese affiliates to handle the creation of regulatory documentation due to the complexities of Japanese regulations, PMDA expectations on content writing or data presentation, the Japanese language, and cultural considerations.
- **Prepare style guide and Japan-specific templates: These are** for writing specifications, test procedures, justification of specification, and manufacturing methods, with detailed explanation on marking post-change approval (PCA) and minor change notification (MCN) regulatory approval matters. If you build those templates up front and use them for the English version, it will save time later. Direct interaction between translators and clients is not common, but it can have big benefits.
- **Translation for submission**. It is very important to ensure that the content of Module 1.2 application forms and Module 2.3 qualities overall summary in English with translated Japanese version, and later there are no questions about what is submitted. It can be a nightmare to respond to PMDA inquiry or issues when you do not know exactly what was submitted. In the end, it is the parent company that is responsible for the content upon which its products are market-approved. Regulatory lead shall do consistency check between English and Japanese version of submission dossier and application. Translators are not often technical personnel, but occasionally, inexperienced translators are used, which leads to failure to find errors, inaccuracies, or misstatements, which can of course alter the entire meaning.

Conclusion

- The PMDA has some stringent CMC data requirements, which make Japan a unique and highly regulated market compared with other countries around the world. Japan's regulatory environment is significantly more complicated compared with other countries. The level of accuracy and details required by the Japanese regulatory authority is sometimes even greater than US FDA/any other regulatory agency. Nevertheless, it is not always possible to harmonize the complete dossier, due to regional requirements, not only for Module 1. In Japan, Module 2 contains more information than Module 2 documents of the EU and the US, thus it is advisable to update the whole Module 2 section with the respective information.
- Global Bio pharma companies often complete their development for US/EU markets before considering Japan. It is clearly an important part of the drug development process and there is a need for consideration of Japan in parallel with activities targeted for other major regulatory authorities (US and EU). Submission of clear and comprehensive country-specific regulatory submission is essential to achieve successful approval of new biopharmaceutical drug products in Japan. Besides understanding the Japan-specific regulatory requirements and PMDA expectations, understanding of the Japanese culture is important, as it is quite different from the West. Additionally, incorporating Japan-specific requirements in the early development stages will eventually help manufacturers overcome hitches in data requirements for Japan submission. The US, EU and Japan all follow ICH guidelines, but differences exist among them. Japanese submissions are the most comprehensive and complex of the three. In this dynamic environment, where regulations are constantly changing, challenges still remain, thus it is very important to have a regulatory plan in place before you actually start executing your regulatory steps in order to facilitate your entry into the Japanese market.

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