

Global Approval Process for new Pharmaceutical Products and Timelines for Market Applications



WITH DALTON

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Company Vision

"To make the impossible possible, Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

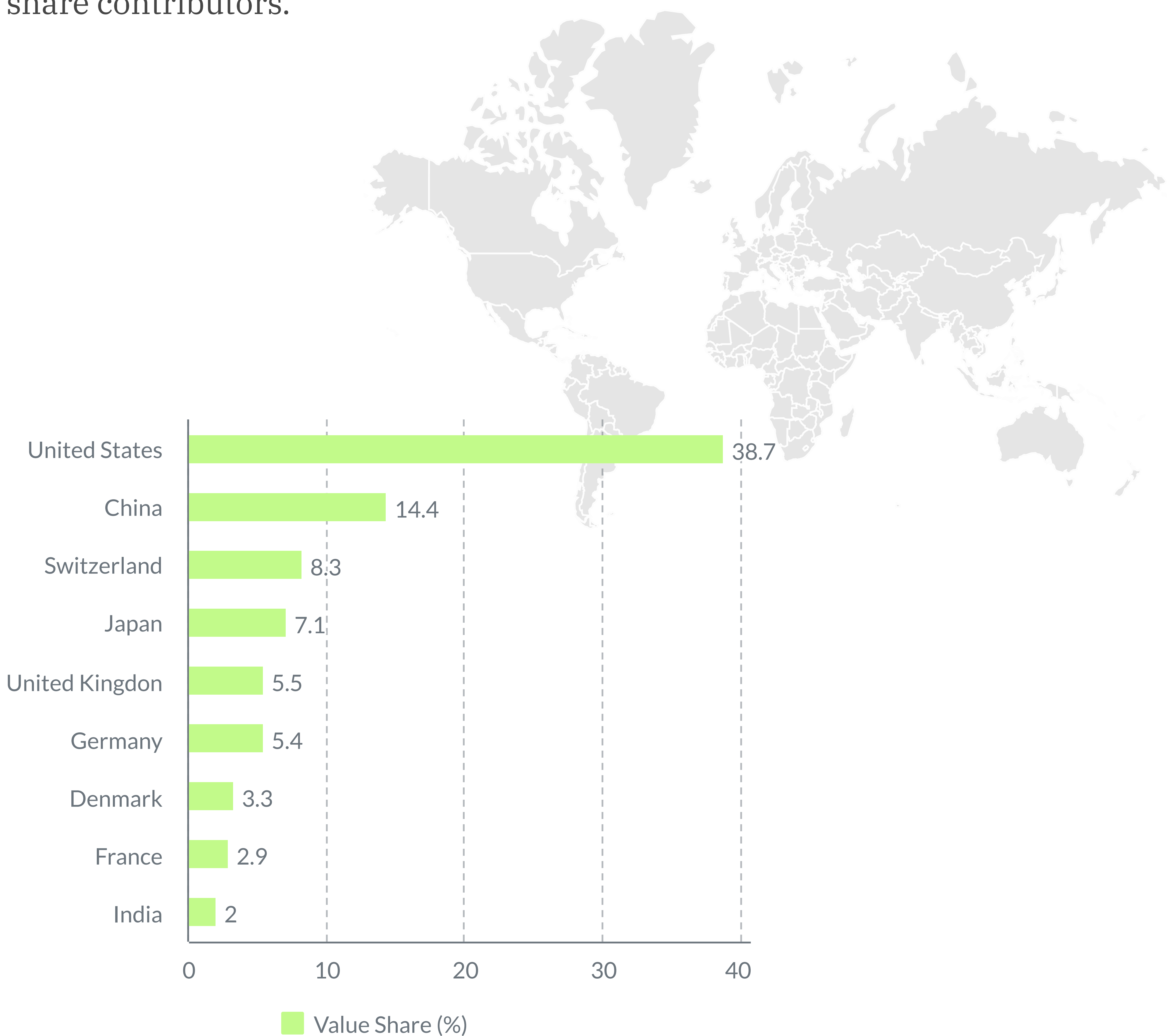
This technical report is intended to provide information to quality and regulatory correspondents on the regulatory marketing applications approval process and timelines in Canada, the US, Europe, Japan, and China. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

✔ FDA inspected, HC approved, & MRA with EMA

Global Market Share

Global pharmaceutical market share in 2020

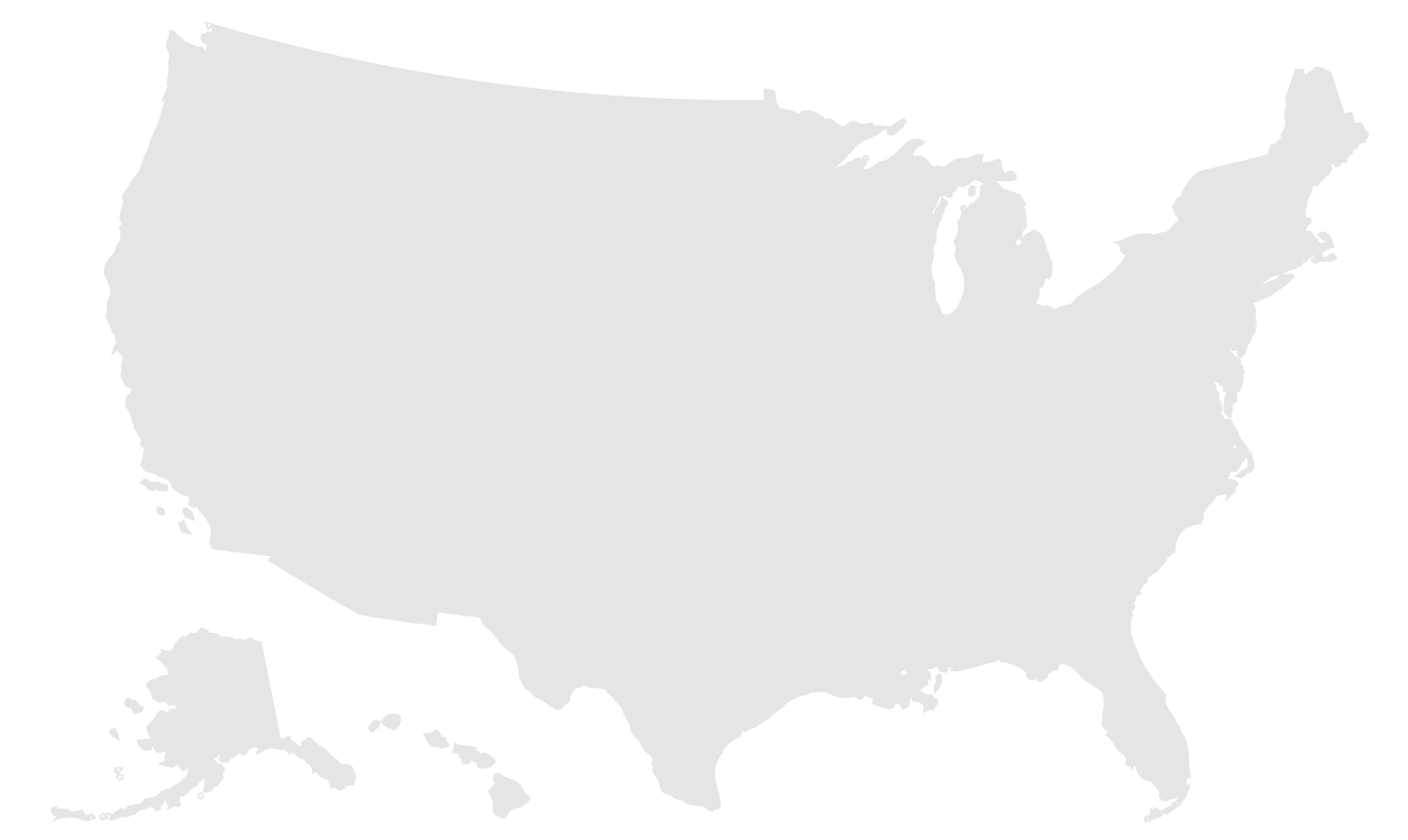
According to [Statista](#), the United States held a 39 percent market share of the entire global pharmaceutical value in 2020, while China had a 14.4% share. The graph below illustrates the other top pharmaceutical market share contributors.



World pharmaceutical sales by region forecast 2024

North America's total pharmaceutical sales are expected to reach \$633 billion in 2024, making it the largest regional submarket in terms of global pharmaceutical sales. China, which is set to hit second place is expected to spend a maximum of 195 billion dollars in that year.

The regulatory marketing applications approval process and timelines for the countries with the top market shares will be discussed in this technical paper.



Submission *Process*

The Federal Food, Drug, and Cosmetic Act (FD&C) and Public Health Service Act (PHS Act) prohibit the introduction of a prescription drug or biological product into interstate commerce unless the drug manufacturer has submitted an application to the FDA and obtained agency approval.

- FD&C governs prescription drugs and biologics. PHS governs biologics only. NOTE: non-prescription drugs do not require applications. For non-prescription drugs, standard and monographs attestations suffice.

Marketing applications for over the counter and prescription drugs, including biological therapeutics and generic drugs are sent to the Center for Drug Evaluation and Research (CDER) while marketing applications for biological products for human use are sent to Center for Biologics Evaluation and Research (CBER).

Approval Process & *Timeline* (5)

Prescription Drug User Fee Act (PDUFA), Biosimilar User Fee Act (BsUFA), and Generic Drug User Fee Act (GDUFA) are legal frameworks that define the timelines and fees of an application. The PDUFA approval process and timeline is described below.

Day 0: Upon receipt of the application, FDA has 60 days to determine whether the application is sufficiently complete to allow for a substantive review.

Day 60: If FDA determines the application is complete, it will be filed on Day 60. If FDA determines the application is not complete (see 21 CFR 314.101[d]), FDA may issue a Refuse to File (RTF) Letter by Day 60, providing the reasons for the decision. The applicant then has 30 days to request a meeting with the FDA if desired.

Day 74: The FDA will inform the applicant if there are filing review issues by issuing a letter within 14 days of the determination. This is called the Day 74 letter. The Day 74 Letter states the date the application was received (which is also the date the review clock begins), the planned review timeline, when FDA will provide a decision on the application, and expected feedback dates on proposed labeling and post marketing commitments.

- **Standard Review:** ~ 10 months; Applied to a drug that offers at most, only minor improvement over existing marketed therapies.
- **Priority Review:** ~ 6 months; Applied to drugs that offer major advances in treatment or provide a treatment where none existed.

EUROPE



Submission *Process*

The Europe Union (EU) has two regulatory authorities, the European Medicines Agency (EMA) and the National Competent Authorities (i.e., Italian authority, France authority).

- The EMA **only** evaluates marketing applications submitted through the centralized procedure.
- The national competent authorities evaluate marketing applications submitted through the other procedures.

There are 4 different options or procedures to submit a marketing application (1):

National Procedure

- Used to request marketing authorization in one EU member state.
- Each EU member state has its own national authorization procedure.
- Since January 1998, independent national procedures have been strictly limited to the initial phase of mutual recognition and to medicinal products not to be authorized in more than one member state. For instance, most **generic medicines** and medicines available **without a prescription** are assessed and authorized at national level.

Decentralized Procedure

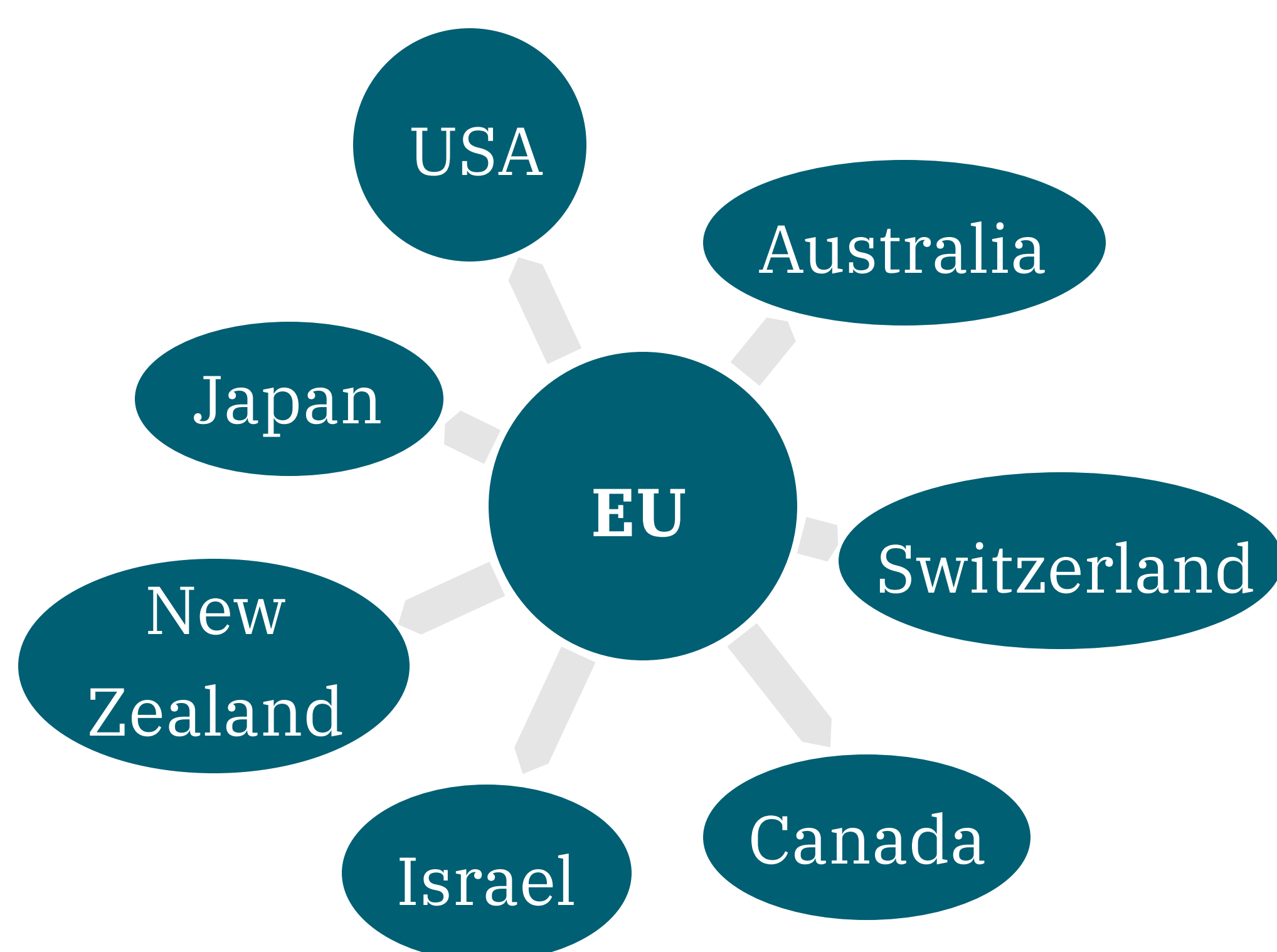
- Used to request marketing authorization in several EU member states for products that don't qualify for centralized procedure and do not have a national approval.
- In force since November 2005.

The 27 National Competent Authorities/ EU member states (2)

Austria	Italy
Belgium	Latvia
Bulgaria	Lithuania
Croatia	Luxembourg
Republic of Cyprus	Malta
Czech Republic	Netherlands
Denmark	Poland
Estonia	Portugal
Finland	Romania
France	Slovakia
Germany	Slovenia
Greece	Spain
Hungary	Sweden
Ireland	

Mutual Recognition Procedure

- Used to request marketing authorization in several EU member states. This is only granted if a national approval in another EU member state already exists, since they serve as the mutual recognition reference country.
- A **Mutual Recognition Agreement (MRA) country** is a country that officially recognizes reports, certificates, authorizations and conformity marks, such as GMP inspections, conducted in *countries* outside of their respective jurisdictions.
- To choose a MRA country of reference you must consider the following:



- What products and APIs are covered?
- Are excluded products definite or temporary?
- Is there pre-approval or surveillance inspection or both?
- Is there territorial applicability?
- Is exchange of information required?

Above is a non-exhaustive diagram that demonstrates the Territorial applicability via EU.

Centralized Procedure

- Used to request marketing authorization in all EU member states.
- **Compulsory** for medicinal products manufactured using biotechnological processes (i.e., recombinant or growth hormone), orphan medicinal products, human products containing a **new active substance** not authorized in the community prior to May 20, 2004, and those intended for the treatment of AIDS, cancer, neurodegenerative disorders, or diabetes.
- **Optional** for drugs constituting a significant therapeutic, scientific, or technical innovation or for which a community authorization is in the interest of patients or animal health. This option may also be used for generic medicinal products where the reference product is authorized by the community.
- Introduced in 1995.

What is a New Active Substance?

- A chemical, biological, or radiopharmaceutical substance not previously authorized as a medicinal product in the EU,
- An isomer, a mixture of isomers, a complex or a derivative or salt of a chemical substance previously authorized as a medicinal product in the EU, but differing in safety and efficacy properties from previously authorized chemical substance,
- A biological substance previously authorized as a medicinal product in the EU, but differing in molecular structure, nature of the source material or manufacturing process, or
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously authorized as a medicinal product in the EU, or for which the coupling mechanism to link the molecule and radionuclide has not been previously authorized in the EU.

Approval Process & *Timeline*

CENTRALIZED PROCEDURE

18 to 7 months before submission of marketing authorization application.

Submit an eligibility request to determine if the medicinal product can be evaluated under the centralized procedure.

The Committee for Medicinal Products for Human Use (CHMP), and the Pharmacovigilance Risk Assessment Committee (PRAC) appoints (co-) rapporteurs to conduct the scientific assessment. For advanced therapy medicinal products, (co-)rapporteurs are also appointed from members of the Committee for Advanced Therapies (CAT) who will lead the assessment.

2-3 months before submission of marketing authorization application

Re-confirm communicated submission date.

Validation of the application by the CHMP, with input from the PRAC on aspects of the risk-management plan and the CAT for advanced-therapy medicines. This takes up to 210 active days.

Within 67 days of receipt of CHMP opinion.

European Commission decision.

7 months before submission of marketing authorization application.

Submit a notification for intention to apply.

6 to 7 months before submission of marketing authorization application

Conduct a pre-submission meeting (recommended).

Submit the application. Applicants should use the electronic common technical document (eCTD) format and submit the application through the eSubmission gateway or web client.

CHMP scientific opinion issued on whether the medicine may be authorized or not. EMA sends this opinion to the European Commission, which issues the marketing authorization.

For the full centralized procedure approval process and timeline click [here](#).

Approval Process & *Timeline*

MUTUAL RECOGNITION (3)

Day 0 – 48

Referentials Management Service (RMS) evaluates and circulates a report on the applicant's response document to Concerned Member State (CMSs).

Day 90

CMS notify RMS and applicant of final position (and in case of negative position also the CMDh secretariat of the EMA).

If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMDh by the RMS within 7 days after day 90.

7 days after close of procedure

Applicant sends high quality national translations of Summary of Product Characteristics (SmPC), Product Label (PL) and labelling to CMSs.

Day 55 – 59

The applicant and RMS are in close contact to clarify if the procedure can be closed at day 60 or if the applicant should submit a further response at day 60.

Day 150

Final position adopted by the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh)

30 days after close of procedure

Granting of national marketing authorizations in the CMSs subject to submission of acceptable translations.



For the full mutual recognition approval process and timeline click [here](#).

Approval Process & *Timeline*

DECENTRALIZED PROCEDURE (4)

Until Day 100

CMSs send their comments to the RMS, CMSs, and applicant.

Until Day 105

Consultation between RMS, CMSs, and applicant.

Day 120

RMS sends the Draft Assessment Report (DAR), draft SmPC, draft labelling, and draft PL to CMSs and the applicant.

Day 150 – 180

If consensus is not reached by day 150, until day 180, RMS is to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report, and forward it to the CMSs and the applicant.

Day 210

If consensus is reached:

- Positive position from RMS: closure of the procedure including End of Procedure letter, final Day 210 overview AR, SmPC, labelling, PL, active substance /finished product specifications and proceed to national 30 days step for granting the MA.
- Negative position from the RMS: closure of the procedure negatively, End of Procedure letter and final Day 210 overview AR is circulated.

If consensus is not reached:

Referral to the CMDh.

7 days after close of procedure

Applicant sends high quality national translations of SmPC, labelling, and PL to CMSs and RMS.



30 days after close of the procedure

Granting of national marketing authorization in RMS and CMSs if outcome is positive and there is no referral to the CMDh.

30 days after close of CMD referral procedure

Granting of national marketing authorization in RMS and CMSs if positive conclusion by the CMDh and no referral to the CHMP.

For the full centralized procedure approval process and timeline click [here](#).

Canada



Submission *Process*

The drug application is submitted to and reviewed by the appropriate directorate in the Health Products and Food Branch (HPFB) of Health Canada, and on occasion, outside experts, to assess the safety, efficacy, and quality of a drug.

Health Canada's HPFB branch has 10 directorates (7):

1. Biologic and Radiopharmaceutical Drugs Directorate
2. Food Directorate
3. Marketed Health Products Directorate
4. Medical Devices Directorate
5. Natural and Non-prescription Health Products Directorate
6. Office of Nutrition Policy and Promotion
7. Policy, Planning and International Affairs Directorate
8. Resource Management and Operations Directorate
9. Therapeutic Products Directorate
10. Veterinary Drugs Directorate

Approval Process & *Timeline* (6), (8)

The length of time for review depends on the purpose of submission (clinical/chemistry & manufacturing, clinical only, comparative studies/chemistry and manufacturing, chemistry and manufacturing only, published data, switch from prescription to over-the counter, labelling only, or administrative), the application type (NDS, ANDS, SANDS, or DIN-A), and the medicine type (biologic or pharmaceutical).

HPFB has set internationally competitive performance targets for its conduct of reviews. To view service delivery standards click [here](#). Note that the length of time for review also depends on the size and quality of the submission and is influenced by HPFB's workload and human resources.

Filing of information and material

A control number will be assigned to the original information/ material filed.

1

Screening

Health Canada's target for screening review of NDSs, SNDSs, SNDS-Cs, ANDSs, SANDSs, and DINAs is 45 calendar days. If clarification is required, a clarifax will be issued and the sponsor has 15 calendar days from the original request date to respond.

If during screening it is determined that the original information and material is unacceptable, the sponsor will be issued a **Screening Deficiency Notice** identifying the deficiencies. The sponsor is to submit the required information within 45 calendar days from date of request. This will initiate a new screening period. If the sponsor fails to provide requested information, a rejection letter will be issued, and the original submission will be returned at the sponsor's expense. Re-submission will be processed as new material/new control number.

DINAs may be rejected during screening (w/o Screening Deficiency Notice):

- if the drug is considered a new drug (a NDS is required)
- if a proposed ingredient is a prohibited substance
- if a monograph attestation is found not to reflect the submission content.

2

3

Submission Evaluation

If deficiencies make the submission non-compliant with the FDA and Regulations, the sponsor will receive a Notice of Deficiency (NOD). The sponsor is required to provide a complete response to a NOD within 90 calendar days. If a sponsor fails to respond to a NOD within 90 calendar days a Notice of Non-Compliance (NON) will be issued.

Japan



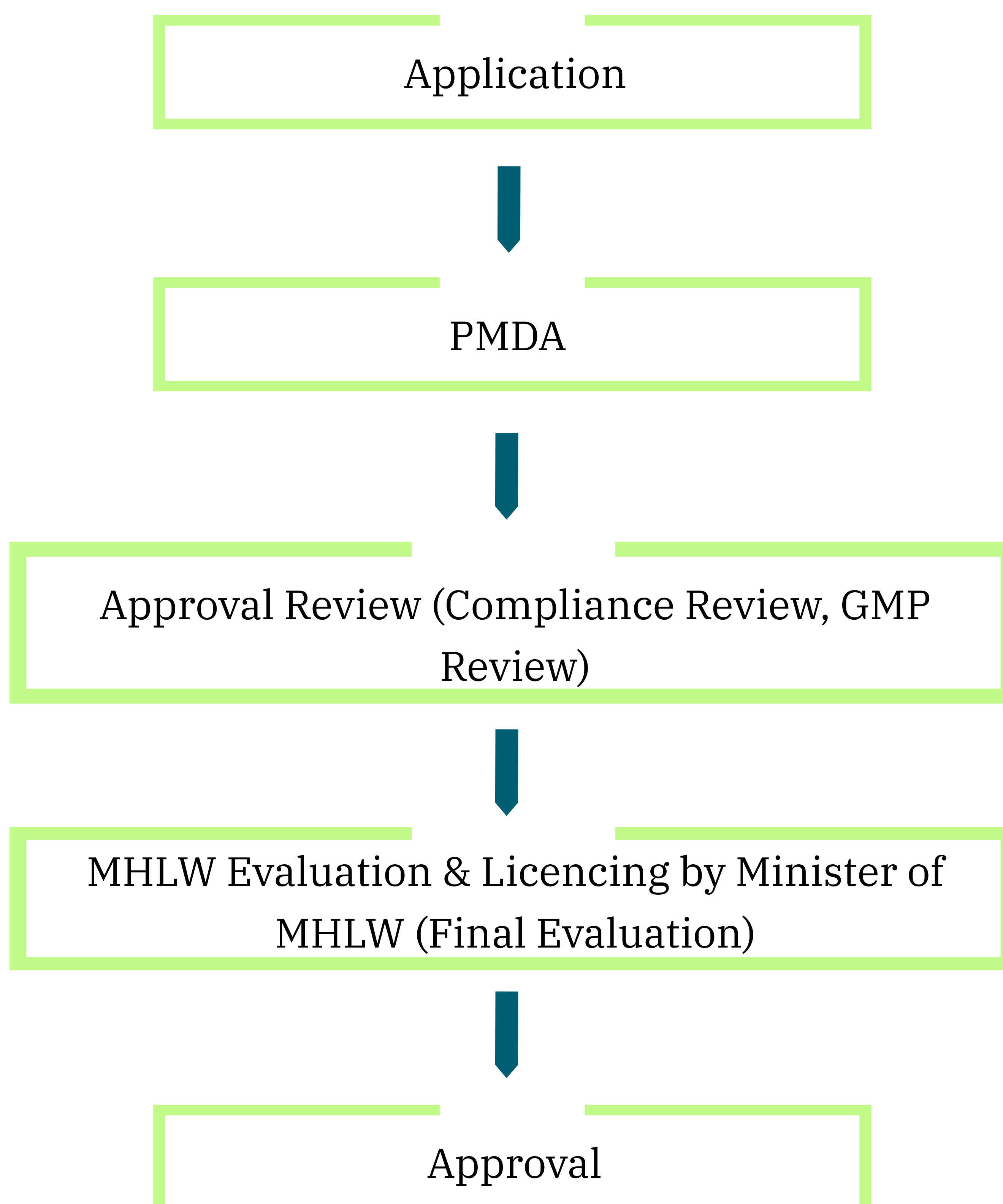
Submission *Process* (9)

There are the two crucial regulatory bodies that review and approve drugs in Japan:

- Pharmaceuticals and Medical Devices Agency (PMDA), and
- Ministry of Health, Labour, and Welfare (MHLW)

Submissions must be made to these regulatory bodies.

Approval Process & *Timeline* (9)



The standard time for review and approval of an NDA is approximately 12 months. The time for review and approval of an NDA is reduced to 9 months for priority reviews.

China



Submission Process ⁽¹¹⁾

The National Medical Products Administration (NMPA) is the primary regulatory agency in charge of drug registration management, formulation of drug registration standards, and review and approval of drug registrations. Drug marketing authorization applications, additional applications, and drug re-registration applications for abroad manufactured medications are all reviewed by the NMPA's Drug Evaluation Center (CDE).

The criteria for developing and registering a medicinal product in China depend on the medicinal product:

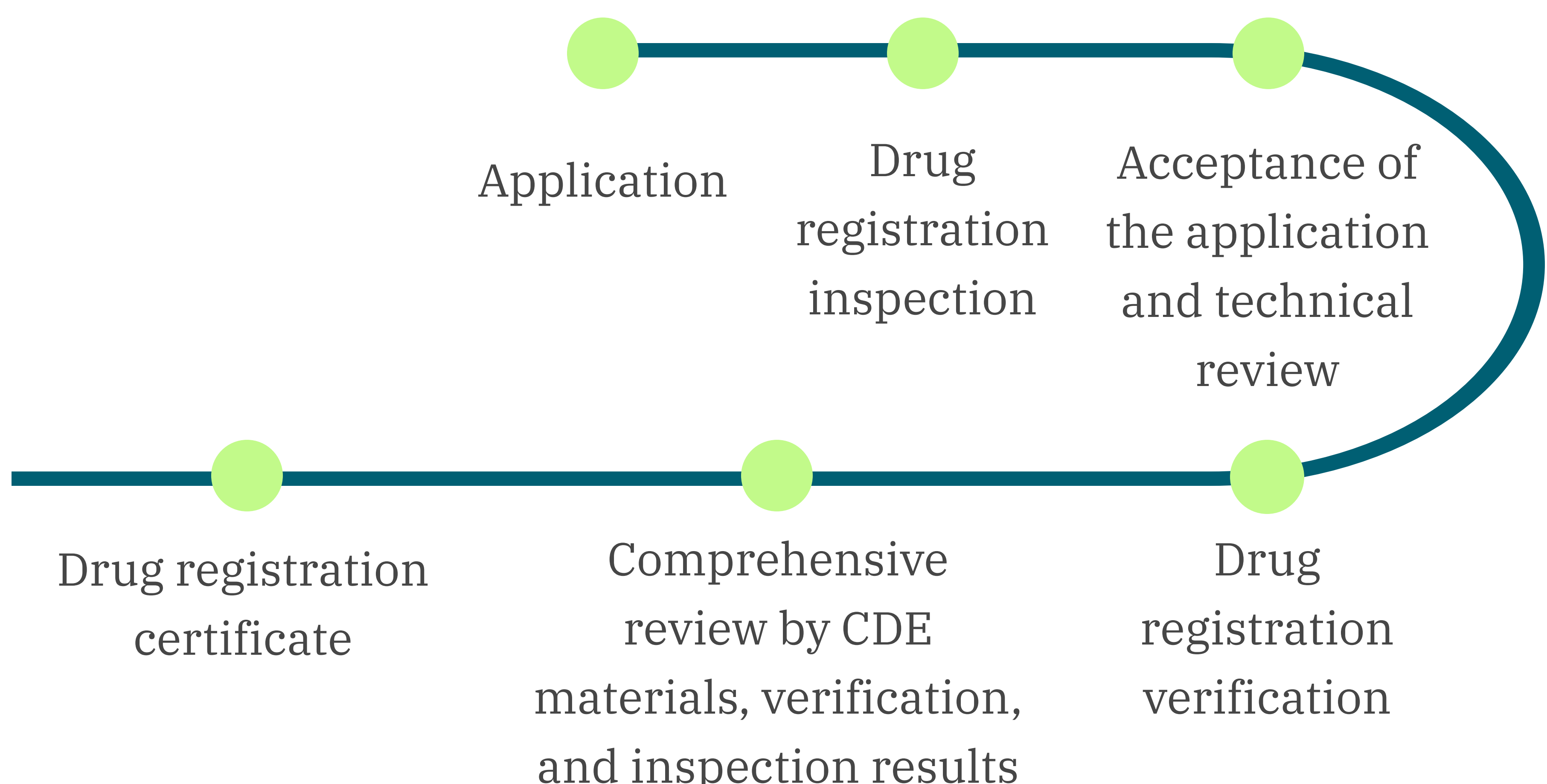
1. Chemical medicine
2. Biological products
3. Traditional Chinese medicine

Approval Process & Timeline ⁽¹⁰⁾

Many policies and initiatives have been devised and authorised by China's government in recent years to support innovative and worldwide drug research and improve review timelines and processes for new medication and clinical trial approvals. The Drug Registration Regulation (DRR), which was recently updated and went into force in July 2020, is one of the most frequently mentioned.

Highlights of China's new drug registration provisions and chances

- Clear review and approval timelines for various types of drug registration applications.
- Prioritized evaluation during the marketing approval process, allowing for faster drug registration to meet unmet medical needs in China.



Dalton's Services

At Dalton, we offer both contract drug development and manufacturing services ranging from early-stage research and development through to developing material for both clinical trials and commercial production. As a CDMO, we enhance our customers production efforts through expertise from highly qualified chemists and researchers to accelerate the end-to-end process, while ensuring regulatory standards are met throughout. Given that Dalton is Health Canada approved and an FDA inspected facility, quality control is essential to meeting these strict regulatory standards for pharmaceutical manufacturing.



Dalton Pharma Services is a leading cGMP contract service provider of integrated drug discovery, development and manufacturing services to the pharmaceutical and biotechnology industries.

We deliver fully integrated solutions with emphasis on speed, flexibility, and quality.

We are experts in

- [Custom Synthesis](#)
- [cGMP API Manufacturing](#)
- [Formulation Development](#)
- [API Process Development](#)
- [Sterile Filling Services](#)
- Accelerated Stability



For more information on services we provide, visit our [website](#).

References



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