APPENDIX
Regulatory Landscape for Raw Materials: CMC Considerations

Drug Shortages

Impact of Drug Shortages and Health Authority Requirements

The Federal Food, Drug, and Cosmetic Act defines drug shortage to mean "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug." Many health authorities, including the US FDA and European Medicines Agency (EMA), have drug shortage databases [1, 2].

The clinical and financial effects of shortages are both substantial and are among the greatest challenges that healthcare providers and patients face. Shortages can occur for many reasons—including manufacturing problems, quality issues, delays, discontinuations, natural disasters, or public health emergencies—and have been a persistent problem despite public and private sector efforts to prevent and mitigate them. Drug shortages can affect patient treatment options and require doctors to make difficult decisions that can compromise care, which can profoundly affect healthcare and worsen patient health outcomes by leading to either no treatment or to delays in treatment due to rationing of supplies or the use of more readily available alternative treatments that may be not as effective or as well tolerated. Drug shortages can also lead to increased costs for healthcare providers. They are expensive for healthcare systems to manage, incurring additional costs for replacement of medicines and absorbing significant staff time. In an example cited by the International Pharmaceutical Federation, shortages cost US hospitals US $416 million (i.e., US $200 million to purchase more expensive alternatives and US $216 million in labor costs) [3].

In July 2018, FDA Commissioner Scott Gottlieb, MD, established the Agency Drug Shortages Task Force to identify the root causes of drug shortages and advance potential long-term solutions. The FDA developed a comprehensive three-pronged approach that focuses on preventing shortages, early identification of anticipated shortages, and responding by remedying the underlying problems when shortages arise to the extent possible within the current authorities. Later in 2019, the FDA published "Drug Shortages: Root Causes and Potential Solutions" [4]. This report examined the underlying factors responsible for drug shortages, and it was identified that one of the root causes of drug shortages was that logistical and regulatory challenges make it difficult for the market to recover after disruption.

Similarly, a European Union (EU) task force was set up by EU regulators to address problems with the supply of medicines and to develop and coordinate actions to facilitate the prevention, identification, management, and communication of shortages. The task force laid the foundations for an improved and harmonized EU approach to address the problems of medicine availability issues to improve continuity of supply across Europe. In 2019 the task force published two articles—(1) "Guidance for Marketing Authorization Holders on Reporting of Shortages in the EU," which provides guidance for the pharmaceutical industry on addressing shortages, facilitating detection, and early notification to

authorities, and (2) “Good Practice Guidance for Communication to the Public on Medicines Availability Issues,” which helps the EU national competent authorities and the EMA lay out principles and examples of good practices for communicating shortages to the public, including patients and healthcare professionals, and ensuring continuity of care [5, 6].

The number of drug shortages has fluctuated over the years: 2020 and 2021 were particularly challenging years for drug shortages. The COVID-19 pandemic greatly affected the raw material supply chain and led to an increase in demand for many drug products.

Response to Drug Shortages During the Pandemic

Early in the COVID-19 pandemic, countries across the world went into lockdown, shutting down or reducing transport within and between them. Many workers stayed at home, disrupting labor at material manufacturers and their suppliers, leading to raw material shortages. This affected the manufacturing, supply, and distribution of medicines, leading to constraints in the global medicine supply chain. In parallel, demand also increased for some medicines used in patients with COVID-19. These included some anesthetics, antibiotics, and muscle relaxants, as well as some medicines used off-label, further contributing to raw material demand and drug shortages. Additionally, there was an impact on other therapeutic areas as both COVID-19 and non-COVID-19 therapies can utilize similar raw materials.

Because the current situation has created unprecedented strain on the entire biopharmaceutical supply chain (raw materials suppliers, manufacturers, wholesalers, and distributors), potential regulatory strategies to address the challenges of delayed global approvals are urgently needed to preempt shortages.

As part of the COVID-19 response, the FDA continues to take steps to monitor the supply chain and has asked manufacturers to evaluate their entire supply chain, including active pharmaceutical ingredients, finished dosage forms, and components. Manufactures should notify the FDA regarding any drug shortage due to the COVID-19 outbreak. The EMA and its partners in the European medicines regulatory network and European Commission have put measures in place to help prevent and mitigate possible disruptions to the supply of medicines in the EU during the COVID-19 pandemic, including taking quick and coordinated regulatory action during the pandemic across all EU member states.

Reasons for Drug Shortages

- Quality manufacturing issues: 37%
- Raw materials: 27%
- Quality: delays/capacity: 27%
- Increased demand: 5%
- Loss of manufacturing site: 2%
- Discontinuation: 2% [4, 7]

Excipient Functional Attributes: Case Study

According to the EMA's "Guideline on Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product," when the formulation includes excipients that are described in the European Pharmacopoeia or in the pharmacopoeia of an EU member state: "It may be necessary to add tests and acceptance criteria to the pharmacopeial specification, depending on the intended use of the excipient (functionality-related characteristics)" [8]. Therefore, in addition to ensuring that excipients meet the requirements of the compendial monograph, an applicant should evaluate physical and functional related characteristics. The challenge is that different excipient suppliers may have different specification ranges for many of these functional characteristics, such as particle size, specific surface area and bulk, and tapped density. It is therefore important to consider the role of each excipient in the drug product formulation and understand if there are any critical functional attributes. Only relevant characteristics should be included in the specification to avoid limiting sourcing options.

Microcrystalline cellulose is a commercially available multicompendial excipient that meets the requirements of the United States National Formulary (NF), European Pharmacopeia, and Japanese Pharmacopoeia. Different manufacturers of this excipient produce material with variable properties due to the different types of pulp used as raw materials and the manufacturing process parameters. These variable properties include physicochemical properties of the product, including moisture content, particle size, particle morphology, crystallinity, bulk density, and degree of polymerization. As a result, microcrystalline cellulose is available in different grades, including Avicel PH 101, Avicel PH-102, Avicel PH-200, and Avicel PH-302. (PH stands for the pharmaceutical grade.)

During a recent submission for a synthetic small molecule product, the EU requested the inclusion of additional functional parameters to the excipient specifications for all multicompendial excipients. Alternatively, the type/grade of the excipient should be defined. One of these excipients was microcrystalline cellulose; however, instead of specifying Avicel PH-102, we opted to provide specifications for particle size.

Similarly, in the case of Opadry II Yellow, it was requested that additional specification tests be disclosed. Opadry II Yellow is a blend of components that meet compendial requirements. It is a nonfunctional film coating agent that is used to provide consistent tablet appearance and also aids in the differentiation of other products in tablet format. The material was released based on appearance and identity testing upon receipt. Based on the role of Opadry II Yellow in the drug product formulation and in response to the EU, the specification was updated to include ash, visual color difference, and wet dispersion:

1. The appearance test confirms that the material complies with the material description of color and consistency.
2. The color difference test compares the material to a reference and confirms consistent color to ensure consistency across batches.
3. The identity of the material by infrared spectroscopy compares the material to a reference.
4. The ash test ensures that the correct amount of inorganic material is present.
5. The wet dispersion test evaluates the excipient as a hydrated mixture to ensure the lot performs as expected at the time of manufacture.

Overall, the EU requirement to add functional attributes in addition to the compendial monograph tests can greatly reduce flexibility in the future in terms of the supply chain. Any single-sourced excipients are particularly at a high risk. Postapproval changes to functional attributes will be required to change or add an additional source of excipient. This is particularly challenging in accelerated programs because the addition of functional attribute specifications requires additional process characterization. Therefore, strategies for performing process development work to support functional attributes need to be developed early in development.

Change Categorization and Reporting Requirements for Raw Materials

The submission categories of postapproval changes for the FDA, EMA, Health Canada, Therapeutic Goods Administration (TGA), Pharmaceutical and Medical Devices Agency (PMDA), National Medical Products Administration (NMPA) and World Health Organization (WHO) are described in detail next, with examples of raw material changes. The submission categories assume all conditions are met and required documentation is available for submission. Note: Changes for synthetics and biologics are denoted as (S) and (B), respectively.

USA (FDA)

According to the FDA regulations, there are three types of changes depending on the potential risk of an adverse effect that the change may have on the identity, strength, quality, purity, or potency of the product as they relate to the safety or effectiveness of the product. These changes are major, moderate, or minor and are described as follows:

Major change: Change that has significant potential to have an adverse effect. These types of changes require notification to the FDA in a supplement (Prior Approval Supplement) and should be approved by the FDA before any product manufactured using the change is distributed.

Moderate change: Change that has moderate potential to have an adverse effect. There are two types of moderate changes:

1. Supplement–Changes Being Effected in 30 Days (CBE30): Require the applicant to report at least 30 days before the drug is distributed with the implemented change. For each change, the supplement has to inform about the effects of the change, and the drug cannot be distributed until the FDA approves it.
2. Supplement–Changes Being Effected (CBE): Permit the distribution of the drug when the FDA receives the supplement. However, if after review the FDA disproves a CBE30 supplement or CBE supplement, the FDA may order the manufacturer to cease distribution.

Minor change: Change that has a very low potential to have an adverse effect. These types of changes must be notified in the Annual Report.

Prior Approval	**<u>Raw Material Change</u>** • For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or change in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved drug product (S) • A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system (S) • Change to container closure composition (B) • Change in the composition of excipients (B) **<u>Raw Material Specification Change</u>** • Testing for viruses or adventitious agents: relaxing an acceptance criterion, deleting a test, or changing an analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency (S)
CBE 30	**<u>Raw Material Change</u>** • Changes in the size or shape of a container for a sterile drug substance (S) **<u>Raw Material Specification Change</u>** • Relaxing acceptance criteria or deleting a test for a raw material (S) • A change in an analytical procedure used for testing raw materials that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency (S) • Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements (S)
Annual Report	**<u>Raw Material Change</u>** • A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (S) • A change in the size and/or shape of a container for a nonsterile solid dosage form (S) • Change in the container closure system for the storage of a nonsterile drug substance when the proposed container closure system has no increased risk of leachable substances and the new container offers equivalent or greater protection properties from air and moisture (B) (S) **<u>Raw Material Supplier Change</u>** • A change in excipient supplier, where the technical grade and specification remain the same (S) **<u>Raw Material Specification Change</u>**

	• Any change in a specification made to comply with an official compendium if it does not relax an acceptance criterion or delete a test (S) • Addition of tests and acceptance criteria to specification for approved excipients (B) (S) • Tightening of acceptance criteria (S) • A change in an analytical procedure used for testing raw materials that provides the same or increased assurance of the identity, strength, quality, purity, or potency (S)

[9–11]

Europe (EMA)

The EMA guidelines cover the following categories of variations in the EU, defined in Article 2 of the Variations Regulation [13–15]:

1. Minor Variations of Type IA: Have only a minimal impact, or no impact at all, on the quality, safety, or efficacy of the medicinal product concerned. Type 1A minor variations do not require any prior approval but must be notified by the holder within 12 months following implementation ("Do and Tell" procedure). However, certain minor variations of type IA, called type IA_{IN}, require immediate notification after implementation to ensure the continuous supervision of the medicinal product.
2. Minor Variations of Type IB: Means a variation that is neither a minor variation of type IA nor a major variation of type II nor an extension. Type 1B minor variations must be notified before implementation. The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ("Tell, Wait and Do" procedure).
3. Major Variations of Type II: A variation that is not an extension and that may have a significant impact on the quality, safety, or efficacy of the medicinal product concerned. Type II major variations require approval of the relevant competent authority before implementation.
4. Unforeseen Changes Type IBz: This category for unforeseen changes is used when the change does not fall within any of the described variations. Unforeseen changes typically default to type IB, but the agency may decide that type II is more appropriate if there is a significant impact on quality, safety, or efficacy [12].
5. Editorial Changes: Include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions. They should generally not be submitted as a separate variation but included in a variation concerning that part of the dossier. They should be clearly identified as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation.

Both biologics and synthetics are included in the same guidance. For a biologic product, often the category of the variation is raised compared with a small molecule product (e.g., type IB to type II).

Major Type II	**<u>Raw Material Change</u>** • Change in synthesis or recovery of a non-pharmacopeial excipient when specifications are affected or there is a change in physicochemical properties of the excipient that may affect the quality of the finished product **<u>Raw Material Supplier Change</u>** • Change to manufacturer of a reagent that uses a substantially different synthetic route or manufacturing conditions that may have the potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physicochemical properties impacting on bioavailability • Change in source or introduction of an excipient or reagent with transmissible spongiform encephalopathy (TSE) risk **<u>Raw Material Specification Change</u>** • Deletion of a specification parameter of excipient or reagent that may have a significant effect on the overall quality of the active substance and/or the finished product • Change to specification of excipient or reagent outside of approved limits
Minor Type 1B	**<u>Raw Material Supplier Change</u>** • Change in the source of excipient or reagent from TSE risk material to vegetable or synthetic (used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product) **<u>Raw Material Specification Change</u>** • Addition or replacement (excluding biological or immunological substance) of a specification parameter for excipient or reagent with its corresponding test method as a result of a safety or quality issue Other changes to a test procedure (including replacement or addition) for an excipient not mentioned in type 1A
Minor Type 1A	**<u>Raw Material Change</u>** • Change in the name and/or address of a supplier of a reagent used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier • Change in the name and/or address of a manufacturer of a novel excipient (where specified in the technical dossier) • Deletion of supplier of a starting material, reagent, or excipient (when mentioned in the dossier) • Minor change in synthesis or recovery of a non-pharmacopeial excipient **<u>Raw Material Supplier Change</u>**

	• Change to manufacturer of a reagent used in the manufacturing process of the active substance to the same pharmaceutical group as the currently approved ($1A_{IN}$) • Change in source of excipient or reagent from TSE risk material to vegetable or synthetic (not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product) **<u>Raw Material Specification Change</u>** • Tightening of specification limits for excipient or reagent (with only minor or no changes to test procedure) • Addition of a new specification parameter to the specification of excipient or reagent with its corresponding test method • Deletion of a nonsignificant specification parameter for an excipient or reagent (e.g., deletion of an obsolete parameter) • Minor changes to an approved test procedure for a reagent or excipient • Deletion of a test procedure for a reagent if an alternative test procedure is already authorized for a reagent or an excipient • Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance

[13–15]

Australia (TGA)

The TGA takes a risk-based approach to regulating medicines, including assessing variations. The higher the risk associated with the variation, the greater the level of assessment required to make a decision. The types of quality variations that can be made to prescription medicines that are currently on the Australian Register of Therapeutic Goods (ARTG) have been classified into several categories:

Corrections, notifications, and quality information changes

- Category 1 – Major variations: A quality change to a medicine constitutes a category 1 application if it requires support by nonclinical, clinical, or bioequivalence data in addition to quality data.
- Category 3 – Requests changes to quality information requiring prior approval: Variations that require evaluation of quality-related data only, including quality-related labeling changes. Data submitted to support category 3 variations are evaluated by the TGA and require prior approval. An example of a change subject to a category 3 application is extension to shelf life.
- Self-assessable requests: Lower risk variations for which the sponsor can provide an assessment of their own data for the TGA to verify, subject to meeting specific conditions. If the specific conditions cannot be met, the change can be submitted for evaluation as a category 3 application.
- Notifications: Very low risk variations with specific conditions. TGA approval for these variations is made automatically upon lodgment and payment of the application. The applicant must provide legal assurances that all conditions are met and submit specified supporting data. If the specific conditions cannot be met, the change can be submitted for evaluation as a category 3 application.
- Corrections to an ARTG entry: A minor change to correct or complete information that was accidently incorrectly recorded or omitted in the ARTG entry.
- Changes to quality information not requiring prior approval
- Changes that do not require prior approval can be implemented either without informing or before informing the TGA of the change, depending on the type of change.

Category 3	**<u>Raw Material Change</u>** • Container/closure system: changes to container components and/or dimensions (B) (S) • Changes to container type (B) (S) **<u>Raw Material Source</u>** • Change to source or method of manufacture of raw materials and excipients of human and animal origin (B) • Changes to the source or method of manufacture of excipients of animal origin (S) **<u>Excipient Specifications</u>** • Any proposed changes to the specifications of the excipients or raw materials (S)
Self-Assessable Requests	**<u>Raw Material Source</u>** • Excipient's manufacturer (from category IC ruminant tissues): changes in source (from animal to nonanimal) and/or manufacturing process or site. The product must only be intended for oral, topical, vaginal, rectal, or inhalation routes, with no potential for cross-contamination with higher risk (category A or B) tissues. No changes to the specification of the excipients, except changes as allowed in excipient section (B) • Change to manufacturer or supplier of excipients or raw materials (not to materials of animal or human origin) (B) **<u>Excipient Specifications</u>** • Change to method of analysis of nonbiological excipients in a biological medicine (change to non-pharmacopeial method). Change should improve precision, accuracy, or specificity without reducing any of these parameters. Exception is improved specificity or accuracy may be associated with reduced precision, but only if precision remains within the specified limits (B) • Addition of new test and limit for an excipient (B) • Minor changes to physicochemical test methods but not to specification of excipients (B) • Change to quality control testing equipment (B) • Change to method of determining residual solvents (including water). Change should improve precision, accuracy, or specificity without reducing any of these parameters. Exception is that improved specificity or accuracy may be associated with reduced precision, but only if precision remains within the specified limits (B) • Change in dimensions or manufacturer of active pharmaceutical ingredient (API) storage container (B)
Notifications	**<u>Raw Material Change</u>**

	• Changes to container or closure system used to store a nonsterile API. The material of container/closure must be either unchanged or changed to a more protective material and thickness either unchanged or increased (S) • Changes to the size and shape of the container or closure system used for drug products that are nonsterile dosage forms. Must not result in a change to the container type and not increase headspace (S) • Changes to outer packaging or components of container that are not in direct contact with the drug product, components are not sterile (S) **<u>Raw Material Source</u>** • Changes to the source, manufacturing process, or site of manufacture of excipients derived from category IC ruminant tissues, including from animal to plant or nonanimal source. The product must only be intended for oral, topical, vaginal, rectal, or inhalation routes, with no potential for cross-contamination with higher risk (category A or B) tissues. No changes to the specifications of the excipients are permitted, except for the changes allowed within the changes to excipients section (S) **<u>Raw Material Specifications</u>** • Change of test method of excipient to pharmacopeial method (should not be viral safety testing method; stringency should not decrease; if different specifications between methods, the more stringent should apply) (B) • Narrowing of limits/more stringent of an excipient (same analytical procedure and within range of currently approved limits) (B) (S) • Amendments of excipient specification resulting from pharmacopeial or legislative instrument changes (not changing from one pharmacopeia to another) (B) • Changes to a method used for assaying an excipient. Proposed method improves at least one of precision, accuracy, or specificity without a reduction in the other parameters or must improve accuracy or specificity with reduced precision provided precision remains within the specified limits (S) • Changes in the specification of an excipient to a pharmacopeial test method (i.e., a monograph in the BP, USP-NF, or EP) where previously no default standard applied. Change or addition must only be to test methods for physicochemical parameters (S) • Changes to the specifications for an excipient as a result of pharmacopeial requirements (S) • Addition of a new test and associated limits to the approved specifications for an excipient (S) • Changes to the specifications for the container or closure system of the final drug product (no change to container dimensions or components), to include new tests, make specified limits more stringent, delete a test procedure or make minor changes to test methods (S)
Corrections	• Correct an ARTG entry (B) (S)

No Prior Approval	**<u>Raw Material Source</u>** • Change to local handling agent/distributer contact details of an excipient (no reporting requirement) (B) (S) • Changes to the manufacturing process and site of manufacture of excipients of the same specifications (excluding excipients of animal or human origin) (S) • Changes to the supplier or manufacturer of nonsterile containers or container components of the same material and specifications (S) **<u>Raw Material Specification</u>** • Changes to the test method and/or acceptance criteria for raw materials. No reduction in quality (reporting required) (B)

[16–18]

Health Canada

Health Canada has four levels of submission categories to provide guidance for quality-related changes. The levels are based on the potential of the change to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product, as these factors may relate to the safety or effectiveness of the drug product. The following descriptions of Canada's change categories are adapted from Health Canada's draft post-Notice of Compliance (NOC) guidance, dated 22 July 2021.

- Level I–Supplements (major quality changes): Changes to an approved drug that are "significantly different" and have the potential to impact the safety, efficacy, and/or effective use of the drug. Level I changes should be filed, along with the recommended supporting data, with Health Canada as a supplement to a New Drug Submission, a Supplement to an Extraordinary Use New Drug Submission, a Supplement to an Abbreviated New Drug Submission, or a Supplement to an Abbreviated Extraordinary Use New Drug Submission. Typically, supplements are supported by extensive documentation and/or require extensive assessment and may not be implemented until a sponsor is issued a NOC.
- Level II–Notifiable Changes (moderate quality changes) (for biologic and radiopharmaceutical quality changes): Changes that have moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product but do not require the issuance of an NOC. The changes included in this submission category should be filed, along with the recommended supporting data, with Health Canada as a Notifiable Change. All level II Notifiable Changes should not be implemented by the sponsor until a No Objection Letter has been issued.
- Level III–Immediate Notification (minor quality changes): Changes that have minimal to moderate potential to adversely affect the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product; however, the changes are such that Health Canada should be notified within 15 days of the date when a batch manufactured using those changes is first released to the Canadian market.

- The Level III–Immediate Notification category also includes major and moderate changes that have been downgraded to minor quality changes as a result of the execution of an approved postapproval change management protocol or for changes to established conditions (ECs) when submission categories have been negotiated to be classified as Immediate Notifications. In all cases, a moderate change can only be classified as an Immediate Notification when conditions are met and specific supporting information is available to confirm that the change is not significant. The general conditions and supporting information for a specific change are listed in the companion guidance documents. When the Immediate Notification category rather than a higher typical submission category is used for changes to ECs, the Immediate Notification category will be listed as the appropriate notification category in the product life cycle management document.
- Level III–Annual Notifications (minor quality change): Changes to a new drug that have minimal potential to impact the safety, efficacy, quality, and/or effective use of the drug. The changes included in this submission category may be implemented by the sponsor without prior review by Health Canada. The implementation date is the date when the product is manufactured using the new equipment or as per new methods. An Annual Notification change should be submitted within 12 months of the date of implementation of the change. This Annual Notification is considered by the minister to fulfill the requirements of the Annual Drug Notification as outlined in the Food and Drugs Regulations. For biologics, radiopharmaceuticals, and pharmaceutical drugs for human use, Health Canada recommends that level III Safety & Efficacy changes be filed at the time the change is implemented. The implementation date is the date when the change is made to the labels.
- Level IV Changes Not Reported (quality changes with no impact): Changes that are not Level I–Supplements, Level II–Notifiable Changes, or Level III changes.

These changes are not expected to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product, as these factors may relate to the safety or effectiveness of the drug product. Changes included in this submission category may be implemented without prior review by Health Canada. The changes should be retained as part of the drug product's record by either the sponsor or the manufacturer and comply with GMP requirements of Division 2 of the Food and Drug Regulations.

Supplement	**<u>Raw Material Change</u>** • Change to a less protective primary container closure system (or one used for storage and shipping) or one that may interact with the drug substance (S) **<u>Raw Material Supplier Changes</u>** • Change in source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk (B) (S) • Change in the source of an excipient from one TSE risk (i.e., animal) source to a different TSE risk (i.e., animal) source (S)

	• Change in manufacture of a biological excipient (B) • Change in supplier for a human plasma-derived excipient (e.g., human serum albumin) (B) **Raw Material Specification Change** • Change in the specifications or approved grade of a critical excipient (e.g., polymer, release controlling agent). Does not involve a qualitative or quantitative change in the excipient and does not affect the drug product performance or the specifications (S)
Notifiable Change	**Raw Material Change** • Change in the primary container closure system(s) for the storage and shipment of the drug substance (B) **Raw Material Supplier Changes** • Change in the auxiliary materials/reagents of biological origin (e.g., fetal calf serum, insulin), involving change in supplier or source (B) • Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source that does not concern a human plasma-derived excipient (B) • Change in manufacture of a biological excipient that does not concern a human plasma-derived excipient (B) • Change in supplier for a human plasma-derived excipient (e.g., human serum albumin) that is Health Canada approved and no CMC changes made by supplier since last approval (B) • Change in supplier of an excipient of nonbiological origin or of biological origin (excluding human plasma-derived excipient) (B) • Change in the supplier for a primary container closure (B) **Raw Material Specification Changes** • Change in the standard/monograph (i.e., specifications) claimed for the excipient (B)
Immediate Notification	**Raw Material Specification Changes** • Changes in critical controls for the raw materials (e.g., solvents, reagents, catalysts, processing aids) (S)
Annual Notification	**Raw Material Change** • Change in the primary container closure system(s) for the storage and shipment of the drug substance that is at least equivalent to approved container and does not concern a sterile drug substance or reduce stability (B) (S) **Raw Material Supplier Changes**

	• Change in compendial auxiliary materials/reagents of biological origin (excluding human plasma-derived materials), involving change in supplier or source (B) • Change in the supplier for a primary container closure, but no change in the type of container closure, materials of construction, specification (outside of approved range), or in the sterilization process (B) • Change in the source of an excipient from a TSE risk (e.g., animal) to a different TSE risk (e.g., animal source) that is supported by a valid TSE Certificate of Suitability (CEP) and is of the same or lower TSE risk, does not require assessment of viral safety, and does not concern human plasma-derived excipient (B) • Change in the source of an excipient from a vegetable source, synthetic source, or non-TSE risk (i.e., animal) source to a TSE risk (i.e., animal) source; or a TSE risk (e.g., animal) to a different TSE risk (e.g., animal source) does not involve qualitative or quantitative change in excipient. The change of source is supported by a valid TSE CEP issued by the European Directorate for the Quality of Medicines, or excipient is obtained from a previously approved source (S) • Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source (S) • Change in manufacture of a biological excipient. Any change in the specifications of the excipient or drug product is within approved ranges, and change does not concern a human plasma-derived excipient (B) • Change in supplier of an excipient of nonbiological origin or of biological origin (excluding human plasma-derived excipient) provided no change in the specifications of the excipient or drug product outside of the approved ranges and the excipient does not influence the structure/conformation of the active ingredient (B) • Replacement of the membrane (filter) used during the Ultrafiltration and Diafiltration (UF/DF) • UF/DF step considered “like for like” (e.g., change in supplier of same filter) (B) **<u>Raw Material Specification Changes</u>** • Change in specification for raw materials but not impacting a test for a critical attribute or impurity profile of drug substance outside of approved limits. Has no significant impact the quality of drug substance or drug product (B) • Change in specification of solvents, reagents, or catalysts to either the same or higher quality and not impacting impurity profile of drug substance or its specification outside of approved limits (B) • Minor changes to specifications for noncritical materials that are discrete chemical entities (e.g., raw materials, solvents, reagents, catalysts). No changes to drug substance specifications or impurity profile; does not affect sterilization procedures of a sterile drug substance (S) • Change in raw material testing site with no impact to the specifications outside of the approved ranges (B) • Change in the standard/monograph (i.e., specifications) claimed for the excipient. No change to functional properties outside approved ranges. No deletion of tests or relaxation of acceptance criteria except to comply with monograph (B)

	• Deletion of a specification test used to release the excipient, demonstrated to be redundant or is no longer a pharmacopeial requirement (B) • Addition of a specification test used to release the excipient. Any class 3 residual solvent is within the ICH limits (B) • Replacement of an analytical procedure used to release the excipient that is at least equivalent to approved procedure and is within the range of approved acceptance criteria or reflects a new pharmacopeial monograph (B) • Minor changes in the specifications used to release the excipient to an approved analytical procedure or reflect a pharmacopeial update (B) • Relaxation of an acceptance criterion used to release the excipient provided class 3 residual solvents is within ICH limits (a deleted test is demonstrated to be redundant/no longer pharmacopeial requirement and does not affect functional properties of excipient or drug product performance) (B) • Tightening of an acceptance criterion used to release an excipient provided class 3 residual solvents is within ICH limits and change is within the range of approved acceptance criteria or has been made to reflect new pharmacopeial monograph specifications for the excipient (B) • Change in excipient testing site. No change in specifications outside approved ranges (B)
Not Reported	**<u>Raw Material Specification Changes</u>** • Addition of a new GMP storage warehouse for raw materials, master and working cell banks, and drug substance (B) • Change in specifications for a compendial raw material to comply with an updated pharmacopeial standard/monograph (B)

[19]

Japan (PMDA)

Based on the PMDA guidance, there are two classifications of change:

- Partial change application: Prior approval required
- Minor change notification: Do and tell; notification of minor changes required

Biological drugs are produced by biosynthetic processes in biological bodies, and materials produced may not be homogeneous in molecular structure. Furthermore, as some changes in the higher structure of the molecule that are difficult to determine by physicochemical analyses can affect biological activity, evaluation of the impact by changes in the manufacturing method on the quality, safety, and efficacy of the product is considered different from that of ordinary chemical drugs. Because biological drugs consist of various kinds of materials such as proteins, glycoproteins, polypeptides, and their derivatives, and their controls also vary, it is difficult to uniformly specify the matters to be addressed in a minor change notification for biological drugs. Accordingly, in the case of biological drugs, changes in the matters described on an approval application form shall, in principle, be addressed in a partial change approval application. However, in cases where it is judged that the quality of the product is ensured by the operating control items or in-process control tests, it may be addressed in a minor change

notification, described on the application form as changes in the process parameters that serve as target values/set values or in the reference values relating to standard batch size.

Partial Change Application	• Changes to raw materials used after the final intermediate or used in a critical step (S) • Changes to critical limits and control methods of raw materials, but only if the changes require special controls (such as a change in an item related to manufacturing of a sterile drug substance) (S) • Changes in control criteria for solvents used in the final purification process, in cases where the solvent has a large possibility of affecting the drug substance (S) • Changes in the names of materials used for packaging materials that affect the quality of the drug product (S) • Changes to the quality and control methods of raw materials, but only if the changes concern aseptic manufacturing or require a special control, for example changes to functional excipients of a modified-release formulation (S)
Minor Change Notification	• The minor change items are specified using unique bracket 『xx』 or "xx" in M1.2 • For changes that are reasonably judged to have no impact on the quality of products, such as changes in the country of origin in relation to bovine spongiform encephalopathy, changes in the compendia, other changes based on the administrative procedures, and changes to narrow specification values/acceptance criteria, it is acceptable to submit a minor change notification (S) (B) • For raw materials derived from humans and animals, if changes are made to the country of origin, etc., to cope with new risks such as infectious factors, or other changes have been made based on the administrative procedures (S) (B) • Changes in the names of materials used for packaging materials that affect the quality of the drug product; for solid oral preparations, a minor change notification is acceptable for changes in the name of a material; if polyethylene, polyethylene, terephthalate, polyvinyl chloride, polyvinylidene chloride, polypropylene, cyclic polyolefin, aluminum foil, cellophane, or multi-film that combines these materials; or glass is used as the name of material for immediate containers (S)

[20]

China (NMPA)

Based on NMPA guidance, the classification of changes is implemented according to the degree of risk and effect of CMC changes on the safety, efficacy, and quality of products. Changes are classified from high to low based on the risk and the degree of impact: major, moderate, and minor.

- For major changes (Supplement, prior approval), the potential risk of impacting efficacy, safety, and quality of the drug is high. It is required to demonstrate through a series of studies that the changes have no influence on safety, efficacy, or quality of products.
- For moderate changes (Notification), the potential risk of impacting efficacy, safety, and quality of the drug is moderate. It is required to demonstrate through corresponding studies that the changes have no influence on safety or efficacy and will not reduce the product quality.

- For minor changes (Annual Report), the potential risk of impacting efficacy, safety, and quality of the drug is low.

Additionally, NMPA requires registration of high-risk excipients and primary container components using a master file that is referenced by the drug product sponsor. NMPA also subjects excipient and primary container suppliers with registered master files to postapproval change management. This creates a challenge for the drug product manufacturer to ensure that change notifications and change categories are aligned between the master file system and the drug product license.

Major	**Raw Material Change** • Changing materials of construction and/or types of packaging materials and containers for inhaled preparations, injections, ophthalmic preparations, etc., (e.g., changing from three-layer coextrusion infusion bags to five-layer coextrusion infusion bags, from polypropylene infusion bottles to upright polypropylene infusion bags, from soda lime glass infusion bottles to five-layer coextrusion infusion bags) (S) • Changes in media components (B) • Change in excipient composition (B) • Replacement or introduction of excipients with potential TSE risk (B) **Raw Material Supplier Change** • Source change for materials of animal origin (B) • Addition/ replacement of excipient supplier (B)
Moderate	**Raw Material Change** • Changing materials of construction and/or types of packaging materials and containers for liquid/semisolid drug products (except inhaled preparations, injections, ophthalmic preparations, etc.), sterile and/or liquid drug substances (e.g., changing from polypropylene bottles for oral liquid preparations to polyester bottles for oral liquid preparations) (S) • Changing materials of construction and/or types of packaging materials and containers for nonsterile solid drug products in the following circumstances: changes among blisters, bottles, and pouches; a change from double aluminum blisters to aluminum-plastic blisters, etc. (S) • Changes in critical media components (e.g., addition, deletion, replacement, increase, reduction, change of supplier) and critical quality attributes of product is not influenced (B) • Change in single-use storage bag, packaging materials and containers, and filter membrane, etc. (B) **Raw Material Supplier Change** • Source change for materials of animal origin. Critical quality attributes of products are not influenced. Non-animal-derived materials, such as tissue- or plasma-derived raw materials, are changed to recombinant products, and animal-derived raw

	materials are replaced to plant-derived raw materials (B) • Source change for materials of nonanimal origin. Critical quality attributes of products are not influenced. Noncomponents of culture media. Not raw materials with complex structure for the manufacturing of polyethylene glycol (PEG) and fatty acid chain (B) • Addition/replacement of excipient supplier. Safety level and specification requirements of excipients after change are not lower than the current excipients. The stability and efficacy of drug product are not reduced after changing excipients. Excipient suppliers are approved pharmaceutical excipient suppliers or registered suppliers in category A (B) **<u>Raw Material Specification Change</u>** • Changing varieties of reaction reagents and solvents where the impurity profile of the drug substance keeps unchanged prior to the last reaction step (S) • Changing the technical grade of an excipient (e.g., replacement of microcrystalline cellulose PH200 with microcrystalline cellulose PH101). The technical grade of an excipient depends mainly on the specification, purpose, and impurity profile of the excipient (S) • Changing the specification of an excipient (except minor change *), where the quality control level is not lowered (S) • Reduction in test item/relaxation of specification criteria (B) • Addition of test item or tightening of limit of specification (B)
Minor	**<u>Raw Material Change</u>** • Changing the materials of construction and/or types of packaging materials and containers for drug substances and nonsterile solid drug products not specified in this guideline. The post-change packaging materials and containers have been used in marketed drugs with the same route of administration and have the same or better applicability (S) • Changes in noncritical media components (e.g., addition, deletion, replacement, increase, reduction, change of supplier) and critical quality attributes of product is not influenced (B) • Change in single-use storage bag, packaging materials and containers, and filter membrane, etc., are equivalent before and after change (including transfer stability studies, etc.). Change does not increase extractable/leachable risk. Sterilization process of packaging materials, containers, and filter membrane is unchanged (B) **<u>Raw Material Supplier Change</u>** • Changing the supplier of an excipient, where the technical grade of the excipient remains unchanged and the quality of the excipient is not downgraded (S) • Source change for materials of animal origin. Critical quality attributes of products are not influenced, and the replacement is for compendial animal-derived raw materials (e.g., newborn calf serum) (B) • Addition/replacement of excipient supplier. Safety level and specification requirements of excipients after change are not lower than the current excipients. The stability and efficacy of drug product are not reduced after changing excipients.

	Excipient suppliers are approved pharmaceutical excipient suppliers, or registered suppliers in category A. Excipients such as inorganic salt and sucrose with simple preparation and stable physical and chemical properties and will not cause changes in the formulation of the final drug product (B) **Raw Material Specification Change** • Improving specifications of the starting material or intermediates (S) • Changing specifications or grades of reaction reagents and solvents used in drug substance manufacturing processes, where the quality of the reaction reagents or solvents is not downgraded (S) • Change in solvent varieties used in the pre-change synthetic process of the drug substance (S) • Improving the specification of an excipient (e.g., tightening quality control limits) or changing the specification of an excipient as a result of the pharmacopoeia version updating or supplementation (S)* • Reduction in test item/relaxation of specification criteria. Change in raw material specification does not allow the drug substance specification to be out of approved range and limits or alter the drug substance impurity beyond the approved range and limits with no new impurities present. Reduction of test items due to inapplicability. Changes are not associated with recurring deviations or stability concerns during manufacture. Test item changes do not affect product key quality attributes (e.g., purity, impurity, critical physicochemical properties) (B) • Addition of test item or tightening of limit of specification. Change in raw material specification does not allow the drug substance specification to be out of approved range and limits or alter the drug substance impurity beyond the approved range and limits with no new impurities present. Changes are not associated with recurring deviations or stability concerns during manufacture. Not test items of human source plasma (B)

[21–23]

WHO (Biologics)

Submission categories for quality changes are based on the potential effect of the quality change on the quality attributes (i.e., identity, strength, purity, and potency) of the biotherapeutic product and on the potential impacts of this on the safety or efficacy of the product [24]. The categories are as follows:

- Major quality change: Has significant potential to impact quality safety and efficacy. The marketing authorization holder should submit a prior approval supplement (PAS) and receive a notification of approval from the national health authority before implementing the change (prior to distribution of the post-change product).
- Moderate quality change: Has moderate potential to impact the quality, safety, or efficacy. The marketing authorization holder should submit a PAS and receive a notification of approval from the notified regulatory agencies (NRA) before implementing the change.

- Minor quality change: Has minimal potential to impact on quality, safety, or efficacy. These changes may be implemented by the marketing authorization holder without submitting a PAS and prior review by the NRA. However, the NRA should be notified of the changes within a specified timeline. The justification and supporting documentation are not needed for such notification but should be made available by the marketing authorization holder upon request from the NRA.
- Quality change with no impact on product quality: Safety or efficacy may be implemented by the marketing authorization holder without submitting a PAS and prior review by the NRA. Information must be retained as part of the manufacturer's GMP records or marketing authorization holder's product records. These changes must comply with the applicable GMP requirements and must be available for review during GMP inspections.

Major Quality Change	**<u>Raw Material Supplier Change</u>** • Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk • Change in manufacture of a biological excipient • Change in supplier for a plasma-derived excipient (e.g., human serum albumin)
Moderate Quality Change	**<u>Raw Material Supplier Change</u>** • Change in supplier of raw materials of biological origin (e.g., fetal calf serum, insulin, trypsin) • Change in source of raw materials of biological origin (e.g., bovine trypsin to porcine trypsin) • Change in source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source • Change in manufacture of a biological excipient that is not a human plasma-derived excipient • Change in supplier for a plasma-derived excipient (e.g., human serum albumin). The new supplier is an approved medicinal product, and no manufacturing changes were made by the supplier of the new excipient since its last approval, and the excipient does not influence the structure/conformation of the active ingredient • Change in supplier for an excipient of nonbiological origin or of biological origin (excluding plasma-derived excipient) **<u>Raw Material Specification Change</u>** • Widening of an approved acceptance criterion used to release an excipient • Change in the standard/monograph (specifications) claimed for the excipient
Minor Quality Change	**<u>Raw Material Supplier Change</u>**

	• Change in supplier of compendial raw materials of biological origin (for example, fetal calf serum, insulin, trypsin) excluding human plasma-derived materials • Change in source of compendial raw materials of biological origin (for example, bovine trypsin to porcine trypsin) excluding human plasma-derived materials • Replacement in the source of an excipient from a TSE risk source to a different TSE risk source (e.g., different animal source, different country of origin). The TSE risk source is covered by a TSE CEP and is of the same or lower TSE risk as the previously approved material • Change in manufacture of a biological excipient that is not a human plasma-derived excipient and there is no change to the specification of the excipient or drug product outside the approved limits • Change in supplier for an excipient of nonbiological origin or of biological origin (excluding plasma-derived excipient). There is no change to the specification of the excipient or drug product outside the approved limits. The TSE risk source is covered by a TSE CEP and is of the same or lower TSE risk as the previously approved material **<u>Raw Material Specification Change</u>** • Deletion of a test used to release an excipient (test demonstrated to be redundant or is no longer a pharmacopeial requirement) • Addition of a test used to release an excipient (acceptance criteria for residual solvents are within recognized or approved acceptance limits) • Replacement of an analytical procedure used to release excipient that is at least equivalent; maintains or improves precision, accuracy, specificity, and sensitivity; and the change is within the range of approved acceptance criteria or has been made to reflect new pharmacopeial monograph • Minor changes to approved analytical procedure used to release an excipient • Change from an in-house analytical procedure to a recognized compendial procedure • Narrowing of an approved acceptance criterion used to release an excipient (the change is within the range of approved acceptance criteria or has been made to reflect new pharmacopeial monograph, acceptance criteria for residual solvents are within recognized or approved acceptance limits, the analytical procedure remains the same or changes in test procedure remain minor) • Change in excipient testing site. There is no change to the specification of the excipient or drug product outside the approved limits
No Impact	• Change in specifications for a compendial raw material, a compendial excipient, or a compendial container closure component to comply with an updated pharmacopeial standard/monograph • Addition of a new GMP-compliant storage warehouse for raw materials

[24]

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