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Analysis of GMP for marketing authorization of ATMPs: comparison in the US, the EU, Japan and South Korea

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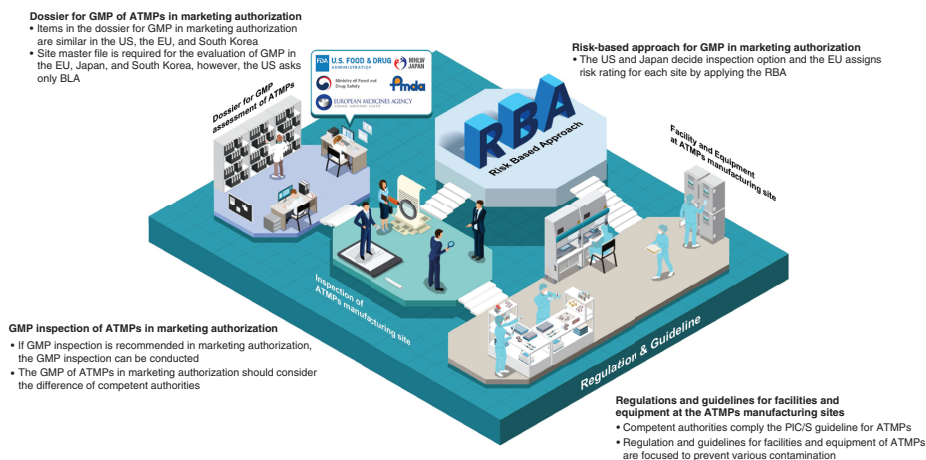
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Aim: This study compared regulatory systems of competent authorities related to GMP for marketing authorization of advanced therapy medicinal products (ATMPs). **Methods:** Dossiers for GMP and regulations and guidelines for facilities and equipment were analyzed using gap analysis. The risk-based approach (RBA) and GMP inspection were evaluated with regulations and guidelines. **Results:** The dossier was similar for the competent authorities. However, whereas a site master file is required in the EU, Japan and South Korea, the US requires only a biologics license application. The regulations and guidelines of facilities and equipment emphasized preventing contamination. There are differences among the competent authorities in GMP inspection and RBAs. **Conclusion:** Differences among the competent authorities in the marketing authorization process related to GMP for ATMPs should be considered.

Graphical abstract:



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Keywords: advanced therapy medicinal products • ATMPs • gap analysis • GMP • good manufacturing practice • marketing authorization • regulation • regulatory system

Advanced therapy medicinal products (ATMPs) have recently emerged as new therapeutic agents for incurable diseases [1–4]. ATMPs are classified as cell therapy, gene therapy, tissue engineering and combined ATMP, depending on their origin, type and use [3]. Overall, 47 cell and 23 gene therapy products have been approved according to the International Society for Cell and Gene Therapy Committee on the Ethics of Cell and Gene Therapy, and recent authorization information (Supplementary Material) [5–12].

ATMPs have different risk analysis, quality, safety and efficacy issues because they involve more complex manufacturing processes and their mechanisms are not well understood, and also because of the variability of starting materials [2,13,14]. The manufacturing of ATMPs requires strict control, using regulations and guidelines for marketing authorization, GMP and a risk-based approach (RBA) to ensure quality, safety and efficacy of the products [1,15,16]. Although many competent authorities are the founding members of the International Conference of Harmonization (ICH) and pharmaceutical inspection cooperation scheme (PIC/S) to provide high-quality products, the regulations in the competent authorities are different, and the difference is a hurdle for global marketing authorization [13,17].

One study analyzed the marketing regulatory oversight of ATMPs in the EU. The study informed the overall regulatory framework for ATMPs and the requirements for ATMP quality and manufacturing. Owing to the diversity and characteristics of ATMPs, a flexible strategy was reported to reduce risk factors and ensure quality, safety and efficacy [15]. Another study compared the GMP regulation of cell therapy with three ICH members: Canada, the USA and the EU. The study focused on manufacturers that should meet the GMP standards in academic facilities as well as industrial facilities, although there are differences in GMP regulatory methods in Canada, the US and the EU [13].

GMP for ATMPs is an important part of new drug development and marketing authorization. The GMP regulation system for ATMPs are different for each competent authority. Recently published studies analyzed the overall regulatory frameworks for ATMPs and compared GMP regulation of cell therapy with three ICH members. However, study of the GMP regulatory system for ATMPs in the context of marketing authorization is still insufficient. For development of ATMPs, it is necessary to determine the regulatory system of each competent authority and the latest development trends for GMP for ATMP marketing authorization. This study was therefore performed to compare the dossier for GMP; regulation and guidelines for facilities and equipment; the RBA for GMP; and GMP inspection for marketing authorization in the USA, the EU, Japan and South Korea.

Materials & methods

This study targeted the GMP for marketing authorization of ATMPs in the USA, the EU, Japan and South Korea and compared their competent authorities. The competent authorities have approved many ATMPs and are the founding members of the ICH and PIC/S [5–12,17]. The ATMPs have different definitions and classifications among the competent authorities, and this study applied the following exclusion criteria. The human cells and tissues and cellular and tissue-based products (HCT/Ps) in the US that are minimally manipulated and intended for homologous use under section 361 of the Public Health Service were excluded because the products do not require premarket approval [18–22]. Regenerative medicine used as an academic or clinical research product in Japan and South Korea was excluded because regenerative medicine does not require market approval [17,23,24]. In addition, although manufacturing sites for investigational ATMPs used for clinical trials should be applied the GMP, investigational ATMPs were excluded in this study [13,25].

The dossier for GMP, regulations and guidelines for facilities and equipment, the RBA for GMP and GMP inspection for marketing authorization were analyzed according to regulations and guidelines of each competent authority (Table 1). Gap analysis was undertaken to compare each competent authority: the GMP dossier for marketing authorization (each competent authority) and regulations and guidelines for facilities and equipment at the manufacturing site (each competent authority and PIC/S). Gap analysis of regulations and guidelines of facilities and equipment was performed on the manufacturing sites, including workroom, work area, laboratory and storage area. The PIC/S guideline is also considered in gap analysis of regulations and guidelines to confirm harmonization and differences among the competent authorities. GMP inspection for marketing authorization was analyzed for the competent authorities. Because each competent authority has a different RBA and GMP inspection, the RBA and GMP inspection were evaluated without gap analysis.

The regulations were searched using the legislation platforms of each competent authority, including e-Code of Federal Regulations (CFR; www.ecfr.gov) and EUR-Lex (eur-lex.europa.eu), the National Law Information Center (www.law.go.kr) and E-laws (<https://elaws.e-gov.go.jp>). The guidelines and other information were collected from competent authority websites, including the FDA (www.fda.gov/), EMA (www.ema.europa.eu/en), Pharmaceutical and Medical Devices Agency (PMDA; www.pmda.go.jp/index.html), Ministry of Health, Labour and Welfare (MHLW; www.mhlw.go.jp/index.html) and Ministry of Food and Drug Safety (MFDS) websites (www.mfds.go.kr/index.do).

Table 1. Regulations and guidelines for GMP for marketing authorization.

Jurisdiction	Regulation	Guideline	Others
FDA (US)	• 21 CFR 211 – CGMP for Finished Pharmaceuticals • 21 CFR 314 – Applications for FDA approval to market a new drug • 21 CFR 600 – Biological products general • 21 CFR 601 – Licensing • 21 CFR 1271 – HCT/Ps	• Guidance for Industry – Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) • Guidance for industry-sterile drug products produced by aseptic processing-current good manufacturing practice • Compliance Guidance Manual Chapter – 45 Biological Drug Products • SOPP 8401: Administration Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA) • SOPP 8410: Determining when Pre-License/Pre-Approval Inspections are Necessary	• FDA form-356h – Application to market a new or abbreviated new drug or biological for human use • FDA form-483 – Notice of Inspectional Observation
EMA (European)	• Regulation (EC) No. 1394/2007 • Regulation (EC) No. 726/2004 • Directive 2001/83/EC • Directive 2003/94/EC	• Procedural Advice on the evaluation of advanced therapy medicinal products in accordance with Article 8 of Regulation (EC) No 1394/2007 • Guidelines on GMP Manufacturing Practice specific to Advanced Therapy Medicinal Products • Compilation of Union Procedures on Inspections and Exchange of Information • Explanatory Notes on the preparation of a Site Master File • European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure	–
PMDA/MHLW (Japan)	• Act of Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices • Enforcement Rule of Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices • Regulation for structural equipment for pharmacy, etc. • Ordinance on standards for manufacturing management and quality control of regenerative medicinal products, etc.	• Confirmation of the status of pre-approval GMP compliance inspection for new drug • Submission Documents for Application of Drug Compliance Inspection • Guidelines for aseptic manufacturing of products for regenerative medicinal products • Guidance on GCTP/GQP/regulations for buildings and facilities compliance division director notice 1009 No. 1 • Guideline for manufacturing of aseptic medicinal products	• GMP Inspection by PMDA
MFDS (South Korea)	• Advanced Regenerative Medicine and Advanced Biopharmaceuticals Safety and Support Act • Enforcement Decree of Advanced Regenerative Medicine and Advanced Biopharmaceutical Safety and Support Act • Enforcement Rule of Advanced Biopharmaceuticals Safety and Support • Regulations on the Biopharmaceutical Product Approvals and Reviews • Regulations on the 'human cell,' etc. and advanced biopharmaceutical approval and safety, etc. • Decree on facility standards for manufacturing business and importers of drugs, etc. • Annex I manufacturing of sterile medicinal products of Regulation on good manufacturing practice to medicinal products	• Guidelines on good manufacturing practice specific to advanced biopharmaceutical • Guideline on good manufacturing practice to cell therapy	–

CFR: Code of Federal Regulations; CGMP: Current GMP; EC: European Commission; GCTP: Good gene, cellular, and tissue-based products manufacturing practice; GQP: Good quality practice; MFDS: Ministry of Food and Drug Safety; MHLW: Ministry of Health, Labor and Welfare; PMDA: Pharmaceuticals and Medical Devices Agency; SOPP: Standard operating procedures and policies.

Results

Dossier for the GMP of ATMPs for marketing authorization

Procedures for evaluation of GMP may be conducted at the manufacturing site for marketing authorization to ensure compliance with applicable requirements. For GMP related to marketing authorization, inspection teams may also ask for information related to the manufacturing site and operations. The inspection team verifies the details relating to the manufacture and control of a product that were provided in a marketing authorization application (MAA). The MAA is a procedure to ensure the quality, safety and efficacy of ATMPs. When marketing authorization is performed to approve ATMPs, the MAA dossier of ATMPs is submitted to the competent authority and follows the common technical document format [26,27].

In the EU, the inspection team requests a site master file and verifies the details relating to the manufacture and control of the ATMPs that were provided in the MAA. The site master file contains information related to the overall GMP, including general information on the manufacturer, quality management system of the manufacturer,

personnel, premises, equipment and production [28,29]. The ATMPs MAA in Article 7 of Regulation (EC) No. 1394/2007 specifies that this MAA shall comply with Article 6 of Regulation (EC) No. 726/2004 [21,30]. Following Article 6 of Regulation (EC) No. 726/2004, the application for the ATMPs authorization shall be included entirely in the documents, as referred to in Article 8(3), 10, 10a, 10b or 11, and Annex I of Directive 2001/83/EC [31]. Quality document overlapped with GMP in Article 8 of the Directive 2001/83/EC is included in 'Evaluation of the potential environmental risks posed by the medicinal product'; 'Description of the manufacturing method'; 'Description of the control methods employed by the manufacturer'; 'A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of GMP by conducting audits, in accordance with point (f) of Article 46'; and 'A document showing that the manufacturer is authorized in his own country to produce medicinal products' [2,19]. Guidelines on GMP specific to ATMPs are also provided to apply the RBA in the GMP to comply with the GMP and to ensure quality according to the specific risk of ATMPs and the manufacturing process [32].

In the USA, GMP for marketing authorization of HCT/Ps is conducted with verification of sections of a biologics license application (BLA), including facility and equipment information, batch record and other information, and does not require additional documents such as a site master file [33]. Application in the US should be submitted through the BLA to the Center of Biologics Evaluation and Research. The BLA of the HCT/Ps uses FDA Form 356h, 'Application to Market a New or Abbreviated New Drug or Biologic for Human Use' [18,34,35]. This form regulates 21 CFR parts 314 and 601 and includes 20 items [34]. The items for GMP are included in 'Chemistry section,' 'Establishment description' and 'Field Copy Certification.' The 'Chemistry section' is composed of the following three subitems: 'Chemistry, manufacturing, and controls information'; 'Samples'; and 'Methods validation package' [34].

In Japan, a GMP dossier for marketing authorization is required to submit to the PMDA and includes an inspection application and MAA. The inspection application comprises a checklist related to regenerative medicinal products and manufacturing sites. Additional documents for GMP are required, including standard operating procedures, testing and control of products, status of process validation and status of standards for biological ingredients. If the site master file is at least equal to the additional documents, these documents can be replaced with the site master file [36,37]. The regenerative medicinal products MAA is regulated in 21, 23 of Article 137 of the Order for Enforcement of the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) [38]. The GMP dossier in Article 137 of the PMD Act is included in 'Copy of the manufacturing and marketing authorization for the medicinal products' and 'Data on manufacturing methods and specification and testing methods, etc' [38].

In South Korea, the site master file related to GMP for marketing authorization is contained in the MAA. For marketing authorization of advanced biopharmaceuticals in South Korea, the application is explained in the regulations that contain Article 23 of the Advanced Regenerative Medicine and Advanced Biopharmaceuticals Safety and Support Act (i.e., Advanced Regenerative Bio Act) and Article 5 of the Regulations on the Biopharmaceutical Product Approvals and Reviews [23,39,40]. The GMP dossier is included in 'Data on manufacturing and quality control standards and testing method' and 'Data necessary for evaluating the implementation status of manufacturing and quality control standards' in Article 23 of the Advanced Regenerative Bio Act [23]. Number 2 additionally consisted of subitems 'Site master file', 'Data on the facility and environmental management related to the product', 'Data on quality control (guarantee) system', 'Copy of product standards and manufacturing and quality control records related to the product' and 'Data on validation related to the product' [40].

A gap analysis of the dossier for GMP was conducted for marketing authorization (Table 2). The South Korea dossier does not include the 'Manufacturing method' and 'Site certification'. All items should be submitted for GMP in the USA and the EU. Because the Japanese dossier is different in composition, it is excluded from the gap analysis. The site master file is required for the evaluation of GMP in the EU, Japan and South Korea; however, the USA only requires BLA.

Regulations & guidelines for facilities & equipment at the ATMP manufacturing sites

The USA, EU, Japan and South Korea are members of the ICH and PIC/S. PIC/S tries to provide high-quality, safe products and international marketing authorization by supplying and sharing ATMPs GMP guidelines. GMP guideline for ATMPs was recently published in the PIC/S to provide global harmonization of GMP for ATMPs [41,42]. To confirm the harmonization and differences between the competent authorities and the PIC/S

Table 2. Gap analysis of the GMP dossier for marketing authorization with the USA, the EU and South Korea.

Items	Competent authorities [†]		
	USA (FDA)	EU (EMA)	South Korea (MFDS)
Establishment description	O	O	O
Manufacturing method	O	O	X
Manufacturing control	O	O	O
Quality control	O	O	O
Environmental assessment	O	O	O
Validation data	O	O	O
Site master file	X	O	O

O: Mentioned in regulation or guideline; X: No data.

[†]As the dossier for GMP in Japan is different from other competent authorities, it is excluded from Table 2.

MFDS: Ministry of Food and Drug Safety.

Table 3. Gap analysis of the regulations and guidelines of facilities and equipment at the ATMPs manufacturing sites.

Manufacturing site	Regulation/guideline				
	PIC/S [†]	US [‡] (FDA)	EU [§] (EMA)	Japan [¶] (PMDA/MHLW)	South Korea [#] (MFDS)
Workroom					
Prevention of mix-up and cross-contamination	O	O / O	X / O	O / O	X / O
Water facility	O	O / X	X / O	O / O	O / O
Changing room and ancillary area	O	O / X	X / O	O / O	O / O
Cleaning and sanitation	O	O / O	X / O	X / O	O / O
Air handling unit	O	O / O	X / O	O / O	O / O
Equipment and instrument for testing and inspection	X	X / X	X / X	O / O	O / X
Working area					
BSC	X	X / X	X / O	X / O	X / O
Isolator system	O	X / O	X / O	X / O	X / O
Fill/blow/seal system	O	X / O	X / X	X / O	X / O
RABS	X	X / X	X / X	X / O	X / X
Working room for weighing raw material and filling/packaging the container	O	O / X	X / O	O / O	O / X
Working room for drying, sterilizing, and storing the container	X	X / X	X / X	O / O	O / X
Laboratory					
Microbiology laboratory	X	X / O	X / X	X / X	O / X
Animal laboratory	X	O / X	X / X	X / X	O / X
Sterile laboratory	X	O / X	X / X	O / X	O / X
Quality control laboratory	X	X / X	X / O	X / X	X / O
Storage area					
	O	O / O	X / O	O / O	O / O
Facilities for ATMPs					
	X	X / X	X / X	O / O	X / X

O: Mentioned in regulation or guideline, X: no data.

[†]Guideline used: Guide to good manufacturing practice for medicinal products annexes.[‡]Regulation used: 21 CFR parts 211, 600 and 1271. Guidelines used: Guidance for industry-current good tissue practice (CGTP) and additional requirements for manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/PTs); Guidance for industry-sterile drug products produced by aseptic processing-current good manufacturing practice.[§]Regulation used: Directive 2003/94/EC. Guidelines used: Guidelines on good manufacturing practice specific to advanced therapy medicinal products.[¶]Regulation used: Regulation for structural equipment for pharmacy, etc., Ordinance on standards for manufacturing management and quality control of regenerative medicinal products, etc. Guideline used: Guidelines for aseptic manufacturing of products for regenerative medicinal products, Guideline for manufacturing of aseptic medicinal products, Guidance on GCTP/GQP/regulations for buildings and facilities compliance division director notice 1009 No. 1.[#]Regulation used: Regulation on the 'human cell', etc. and advanced biopharmaceutical approval and safety, etc.; Decree on facility standards for manufacturing business and importers of drugs; Annex I manufacturing of sterile medicinal products of Regulation on good manufacturing practice to medicinal products. Guideline used: Guidelines on good manufacturing practice specific to advanced biopharmaceutical, Guideline on good manufacturing practice to cell therapy.

ATMPs: Advanced therapy medicinal products; BSC: Biosafety cabinet; MHLW: Ministry of Health, Labor and Welfare; MFDS: Ministry of Food and Drug Safety; PIC/S: Pharmaceutical Inspection Co-operation Scheme; PMDA: Pharmaceuticals and Medical Devices Agency; RABS: Restricted access barrier system.

guidelines, a gap analysis for the facility and equipment at the ATMPs manufacturing sites was conducted to identify and analyze the four competent authorities and PIC/S (Table 3).

In the EU, the GMP of ATMPs is regulated by medical products for human use by Directive 2003/94/EC. Because Directive 2003/94/EC regulates general information on facilities and equipment at the manufacturing site, specific regulations are not provided [30,43,44]. The GMP guidelines for the ATMPs are supplied. The guideline contents include the prevention of mix-up and cross-contamination, cleaning agents and disinfectants, air handling units, laboratories and storage areas [32].

In the USA, the HCT/Ps GMP should comply with 21 CFR Parts 211, 600 and 1271 subpart D – Current Good Tissue Practice (CGTP), which regulates HCT/Ps to prevent the introduction, transmission or spread of communicable disease [19,45,46]. The USA applies supplement 21 CFR Part 1271 subpart D called Guidance for Industry – CGTP and Additional Requirements for Manufacturers of HCT/Ps. This guidance is in the form of questions and answers [47]. GMP guidance for sterile drugs is also applied to HCT/Ps because terminal sterilization is often impossible for HCT/Ps [48].

Regenerative medicinal products and advanced biopharmaceuticals in Japan and South Korea have applied specific regulations for facilities and equipment at manufacturing sites [49–51]. The facilities and equipment regulations in South Korea are applied to medicinal products, including advanced biopharmaceuticals, whereas those in Japan are only applied to regenerative medicinal products. Japan and South Korea regulations cover workrooms, working areas, laboratories and storage areas [49–51]. The Japanese guidelines are also designed for aseptic manipulation of regenerative medicinal products at the manufacturing site and to supplement the regulations. The water facility, fill/blow/seal system and storage area apply the GMP guidelines for medical products in Japan [52–54]. South Korea additionally applies the GMP guidelines for cell therapy as well as advanced biopharmaceuticals [55].

Although fill/blow/seal system in the EU are checked ‘No’ in gap analysis, guidelines for facilities and equipment required by PIC/S guidelines are harmonized in the competent authorities (Table 3). The fill/blow/seal system in the EU are guided in Annex I of Part I of the GMP guidelines published in Volume 4 of Eudralex. However, unless a specific reference is made in the Guidelines on GMP specific to ATMPs, other documents that are contained in Volume 4 are not applicable to ATMPs [32]. Therefore, the fill/blow/seal system were checked ‘No’ in the gap analysis. Further, all competent authorities must consider preventing mix-up, cross-contamination and contamination of particles and microbes through the gap analysis [56]. All competent authorities have regulations or guidelines for the prevention of mix-up and cross-contamination, changing room and ancillary area, cleaning and sanitation and air handling unit. Although the EU does not have requirements regarding fill/blow/seal or restricted access barrier systems, these cabinets are also important for preventing contamination, which can maintain the grade of the clean area [46,52,57]. In addition, Japan’s guidelines suggest a requirement facility for ATMPs, including an area for handling cells and microbes, animal management facilities for use and management facilities of equipment and instruments used in ATMPs manufacturing or testing [52].

Risk-based approach for GMP in marketing authorization

The RBA in ATMP manufacturing sites is applied to ensure the quality of the manufacturing process and ultimately the safety of the patient [44]. Whereas the USA, EU and South Korea provide guidelines for the RBA at the ATMPs manufacturing site, Japan only provides the presentation file in PMDA, a competent authority in Japan. These guidelines include risk-based planning, management scope and frequency by applying the RBA program, but the Japanese presentation file indicates whether on-site inspections are conducted [29,32,33,58].

The EU and South Korea have similar GMP guidelines specific to ATMPs, including the RBA [32,53]. According to the guidelines, the RBA brings flexibility in manufacturing sites, and manufacturers can design appropriate measures to minimize the potential risks to ensure quality and compliance with GMP. When applying the RBA at the ATMPs manufacturing sites, manufacturers comply with relevant regulations and ensure adequate risk management [15,32,53].

In the EU, the quality risk management tool based on the RBA is additionally used to determine the frequency, depth and breadth of the ATMPs manufacturing site inspection to maintain a high level of safety (Table 4) [29]. Risk ranking for inspection at the sites is assigned by the tool, which includes an intrinsic and compliance-related risk. The intrinsic risk refers to the complexity of manufacturing sites, processing, products and the criticality of products or services, such as analytical testing. The intrinsic risk is scored based on indicators. For example, large sites are graded as more complex, and sterile sites always have high complexity (Figure 1) [29]. For compliance-related risk, the classification and number of deficiencies based on the late routine inspection at the site are determined to estimate the GMP compliance status. If a high risk is issued in the compliance-related risk, the ATMPs manufacturing site requires nonroutine reinspection, and manufacturing authorization may be revoked or varied. Overall risk, which

Table 4. Summary for the risk-based approach for GMP in marketing authorization.

Category	USA (FDA)	EU (EMA)	Japan (PMDA/MHLW)
Application of the RBA	Decide inspection options, Level I and Level II inspection ■ Level I inspection (full) – Three critical element[†] – At least four key systems[‡] ■ Level II inspection (abbreviated) – Three critical element – Two key systems	Assign risk ranking for each site ■ Intrinsic risk: – Complexity: 1 (low)–3 (high) – Criticality: 1 (low)–3 (high) ■ Compliance related risk: – Critical deficiencies ≥ 1 or major deficiencies ≥ 5: high – 1–5 major deficiencies: medium – No major or critical deficiencies: low ■ Overall risk rating – Low risk: A – Medium risk: B – High risk: C	Decide inspection options, on-site and desk-top inspection ■ The items to be evaluated at risk analysis: – Sorts of product – Manufacturing process – Dosage form – Inspection history by foreign inspectorates – Past GMP noncompliance – Past recall history – Inspection by PMDA – Site information
Frequency of inspection	■ Basic biennial schedule (If necessary, more frequent inspections)	■ Overall risk-based rating: – Risk rating A: 2–3 years – Risk rating B: 1–2 years – Risk rating C: <1 year	–
Expenditure of inspection time	–	■ Aseptically prepared ≥ 10 days ■ Cell therapy product ≥ 7 days ■ Gene therapy product ≥ 7 days	–
Scope of the next routine inspection	–	■ Four section of the next routine inspection – Focus, depth – Required duration – Required number of inspectors – Specific competence or expertise	–

[†]Three critical elements: standard operating procedures, training and records.

[‡]Seven key systems: quality, facilities and equipment, materials, production, packaging and labeling, laboratory control and donor eligibility systems.

ATMPs: Advanced therapy medicinal products; PMDA: Pharmaceuticals and Medical Devices Agency; MFDS: Ministry of Food and Drug Safety; MHLW: Ministry of Health, Labor and Welfare.

Table 5. Factors for setting the expenditure of inspection time and the scope of next inspection in the EU.

Category	Factors
Expenditure of inspection time	■ The type of inspection ■ The complexity of the site ■ The complexity of the manufacturing process ■ The complexity of the product and its therapeutic significance ■ The patient exposure ■ The compliance history of the site
Scope of next routine inspection	■ Overall compliance status and history of the facility ■ Results of product testing by OMCLs ■ Number and significance of quality defects ■ Marketing authorization variations affecting the site ■ A failure to implement a marketing authorization variation on time ■ Compliance information from trusted authorities outside the EU

OMCL: Official medicines control laboratory.

combines intrinsic and compliance-related risk, represents the overall risk rating at the ATMPs manufacturing site [29].

Risk ratings in the EU affect routine inspection frequency and time expenditure. The routine inspection frequency is recommended by the overall risk rating [29]. For example, two manufacturing sites are graded as risk rating B, and the routine inspection frequency is 1 to 2 years. One has five major deficiencies, and the other has only one major deficiency. The manufacturing site with five major deficiencies is inspected closer to the 1-year frequency, and the other is inspected closer to the 2-year frequency. The expenditure of time, which is the time required for inspecting the manufacturing site, is adjusted depending on certain factors (Table 5) [29]. In particular, cell therapy and gene therapy included in ATMPs require at least 7 days for overall inspection. For aseptic preparation, at least 10 inspection days are required. The scope of the next routine inspection is not decided by the risk rating. Instead, the quality risk management methodology requires factors for the next routine inspection scope (Table 5). The scope should be updated regularly when new information is received before the next routine inspection [29].

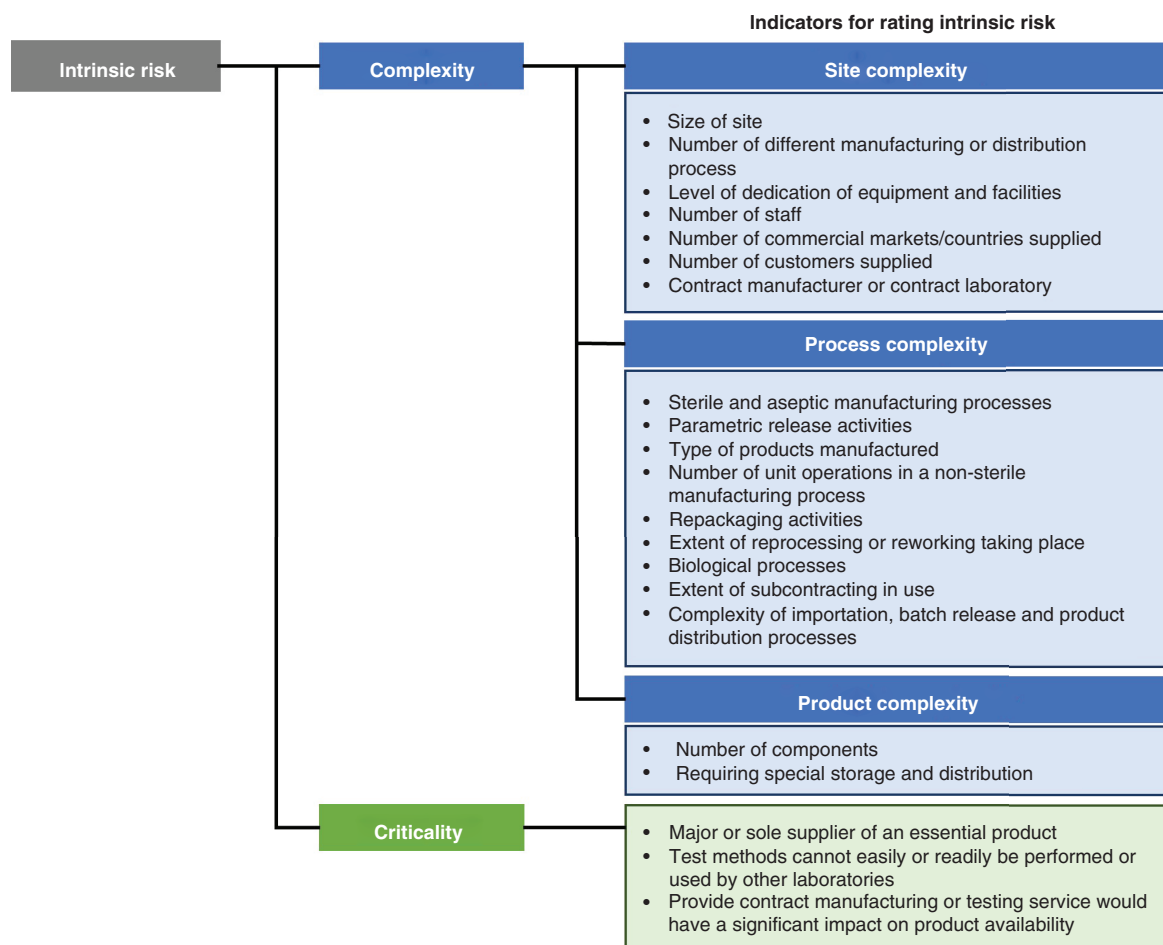


Figure 1. Indicators for rating the intrinsic risk in the EU.

In the USA, the RBA is referred to as a risk-based program or system-based risk management approach [33]. The risk-based program identifies seven key systems and three critical elements for conducting inspections at the ATMPs manufacturing sites (Table 4). Facilities and equipment system among the seven key systems includes verifying the appropriate physical environment used in the production of HCT/Ps. The system should comply with 21 CFR parts 211, 600, and 1271 [33].

For GMP inspection at the HCT/Ps manufacturing site, the risk-based program decides inspection options: Level I (full) and Level II (abbreviated) inspection [33]. Two levels of inspection enable the efficient evaluation of compliance and an in-depth audit of the critical elements. The inspection-level identification depends on the conditions (Table 6). By applying Level I inspection, the manufacturing site should prepare all critical elements in at least four key systems [33]. The four key systems in HCT/Ps manufacturing sites should include quality, production and donor eligibility systems. Level II inspection should comprise a streamlined evaluation that includes two key systems: the quality system and the other rotated during successive inspections [33].

In Japan, RBA is applied to select the GMP inspection method – that is, an on-site or desk-top inspection. If the on-site inspection is conducted using the RBA, data are accumulated by inspection information, such as the site's rank after finishing the inspection. The items are evaluated in the risk analysis (Table 4) [58].

GMP inspection of ATMPs for marketing authorization (if recommended)

GMP inspection can be conducted for marketing authorization by competent authorities if GMP inspection of the manufacturing site is recommended to ensure compliance with the applicable requirements. The purpose of conducting a GMP inspection in the marketing authorization procedure is to verify specific GMP-related issues identified during the review of a marketing authorization [13,59]. The ATMPs manufacturing site requires flexible

Table 6. Conditions for selecting GMP inspection level in the USA.

Inspection	Conditions
Level I	■ Initial GMP inspection ■ History of compliance problems ■ Compliance follow-up inspection ■ Firm under a Consent Decree of Permanent Injunction ■ Firm under Notice of Intent to Revoke and/or other administrative actions ■ Implementing significant changes ■ Conducting two previous inspections under a Level II inspection
Level II	■ Satisfactory history of compliance, e.g., at least two successive NAI or VAI inspections ■ One of the two previous routinely inspections is a Level I inspection ■ No specific trends that have a significant impact on products safety or quality in inspection preparation procedures

NAI: No action indicator; VAI: Voluntary action indicator.

inspection because there are differences in manufacturing processes, facilities and equipment depending on the products. Therefore, RBA programs are applied to efficiently assess ATMPs and manufacturing process risks [1].

In the EU, ATMPs are inspected following a centralized system for marketing authorization [26,29,31,44]. The Committee for Medicinal Products for Human Use (CHMP) determines the need for GMP inspection during the marketing authorization process for ATMPs at manufacturing sites in the EU or a country outside the EU. Supervisory authorities and GMP inspectors of EU member states are designated for the GMP inspection [29,30,60,61]. The inspectors are composed of the EU member states where the manufacturing site is located or the product is imported. After deciding whether to conduct an inspection and designating the supervisory authority for GMP inspection, GMP inspection is conducted using the corporate GXP application and the quality risk management tool based on the RBA. After the GMP inspection, the relevant report is sent to the CHMP. The CHMP checks and returns the inspection report to the authorities to explain the reasons for nonacceptance, revision, reinspection or other remedial actions. The next routine inspection is planned in consultation with supervisory authorities (Figure 2B) [29,60–62]. The routine inspection for manufacturing sites located in the EU is performed by national competent authorities. If the manufacturing site is found to be correctly controlled during routine inspection, the national competent authorities issue GMP certification for the site. Routine inspection is an independent process from the MAA, and the CHMP is not responsible for routine inspection [29].

In the USA, after submitting the HCT/PS MAA, a prelicense inspection (PLI) or preapproval inspection (PAL) can be determined and performed by the Division of Manufacturing and Product Quality for marketing authorization [33,63–65]. The PLI or PAL is conducted to ensure that the BLA is submitted and in compliance with the requirements at the manufacturing site. All manufacturing sites should be inspected for Level I inspection of the risk-based program. If the manufacturing site is found to require inspectional observation during the PLI or PAL, FDA Form 483, ‘Notice of Inspectional Observation’, is issued. Manufacturers should submit and resolve a corrective plan for FDA Form 483 (Figure 2A) [33,65,66]. Depending on the GMP inspection findings, the site is issued a no-action indicator (NAI), a voluntary action indicator (VAI) or an official action indicator (OAI) [33]. The NAI means that no action is required, and the firm is considered to operate in a state of control. However, VAI or OAI means that the firm must develop a corrective action plan. Especially for an OAI, warning letters that include license revocation, license suspension, seizure, injunction and prosecution may be issued to the firm. In addition, GMP inspection is routinely performed on a biennial schedule by a biologics team. Afterward, the risk-based program is scheduled to determine whether a Level I or Level II inspection will be necessary (Figure 2D and Table 5) [33].

For GMP inspection in Japan, the Office of Manufacturing Quality for Drugs (OMQD) performs and manages inspection for new drugs. The GMP/Good gene-, cellular- and tissue-based products manufacturing practice (GCTP) inspection team of the OMQD evaluates the manufacturing site of regenerative medicinal products [67]. GMP inspection involves two methods determined by RBA. One is a desktop inspection that evaluates only the GMP dossiers. The other is an on-site inspection by the GMP/GCTP inspection team [36]. On-site inspection can also be selected if the manufacturing site does not receive on-site inspection for 2 years [68]. Whereas the desktop inspection only requires inquiry and notification of the result, the on-site inspection has other processes, including the issuance of observation and correction plan/report for observation (Figure 2C) [36].

In South Korea, the Biopharmaceutical Quality Management Division manages the GMP of advanced biopharmaceuticals [69]. However, the GMP inspection for advanced biopharmaceuticals is not specified in the regulations

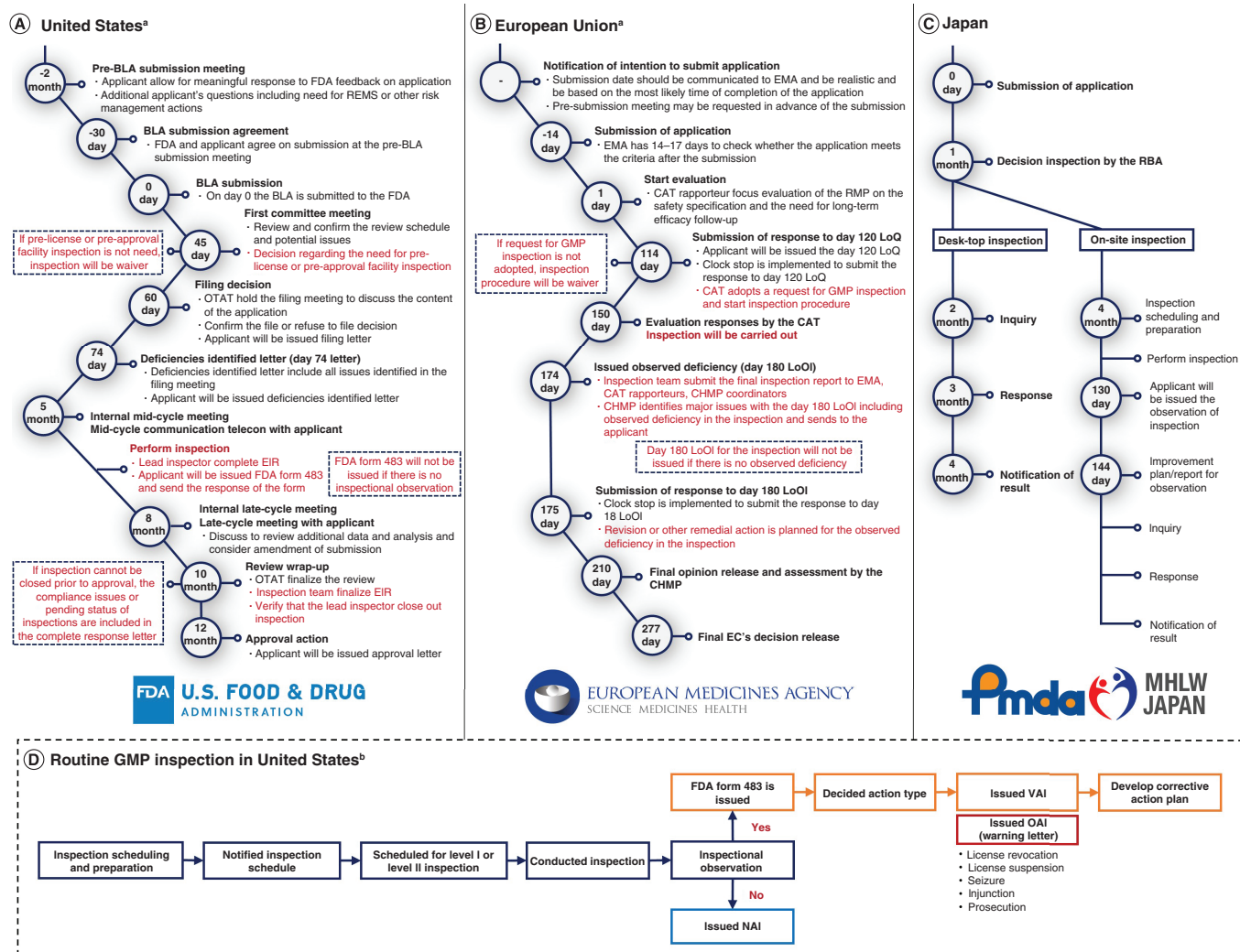


Figure 2. The ATMP GMP inspection procedure for marketing authorization in the USA, EU and Japan. (A) The GMP inspection for marketing authorization procedure is indicated by red text; case control in the GMP inspection is indicated with dotted boxes. **(B)** Routine GMP inspection in the US is conducted as necessary after marketing authorization is complete and is separate from marketing authorization.

BLA: Biologics license application; CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; EC: European Commission; EIR: Establishment inspection report; LoOI: List of outstanding issues; LoQ: List of questions; NAI: No action indicator; OAI: Official action indicator; OTAT: Office of Tissues and Advanced Therapies; RBA, Risk-based approach; REMS: Risk evaluation and mitigation strategies; RMP: Risk management plan; VAI: Voluntary action indicator.

and guidelines of the MFDS. In Appendix 12 of “Enforcement Rule of Advanced Biopharmaceuticals Safety and Support”, only the required duration for the dossier evaluation is provided [39]. In this regulation, the required duration for evaluating ‘Data on manufacturing and quality control standards and testing method’ and ‘Data necessary for evaluating the implementation status of manufacturing and quality control standards’ is 115 and 90 days, respectively [39].

Discussion

This study investigated and compared the regulations and guidelines of GMP for marketing authorization for ATMPs in the USA, EU, Japan and South Korea. The GMP dossier for marketing authorization and regulations and guidelines for facilities and equipment at the ATMP manufacturing sites were analyzed using gap analysis. The RBA for GMP and the GMP inspection for marketing authorization were evaluated by analyzing regulations and guidelines.

The gap analysis showed that the items in the GMP dossier for marketing authorization were similar in the USA, EU and South Korea (Table 2). The manufacturing method in the gap analysis was not included in South Korea. This item can be found in the specification and test method, which is another dossier item for assessing products [39,40]. The site master file is required in the EU, Japan and South Korea; however, the USA requires only the BLA. Whereas the EU inspection team requires the site master file before inspecting the manufacturing site, Japan requires the submission of additional documents with the MAA, which can be replaced by the site master file, and the MAA in South Korea contains the site master file as an item of the MAA [29,36,40,65].

GMP guidelines for ATMPs were recently published in the PIC/S to provide global harmonization of GMP for ATMPs to provide high-quality, safe products. This guideline is meant to provide specific guidance on the full scope of ATMP. The premises and equipment and the production aspects are mentioned in the PIC/S GMP guidelines for ATMPs [41,42]. If the GMP guidelines of the competent authorities are harmonized by the PIC/S guidelines, manufacturers may easily achieve international marketing authorization. It was confirmed that the competent authorities comply with the PIC/S guidelines for ATMPs to harmonize the GMP guidelines globally in the gap analysis. Regulations and guidelines for facilities and equipment at ATMPs manufacturing sites are focused on preventing mix-up, cross-contamination and the transmission risk of relevant communicable disease agents because terminal sterilization is often impossible for ATMPs (Table 3) [19,27,66]. The workroom is universally composed of a closed and an open system to prevent cross-contamination, although the terms are not defined in exactly the same way. The closed system is an area to maintain sterile materials and products, and the open system is an area to support the closed system and store nonsterile materials. Depending on these systems, an appropriate-grade clean area should be available, according to ISO 14644-1 [32,48,52,53].

The ATMP manufacturing field is experiencing rapid technological changes to address the specific challenges of ATMPs [70,71]. Therefore, the EU suggests that the RBA is necessary to implement the most appropriate measures considering the risks of manufacturing processes and products [32,53]. A study evaluated the impact of the RBA by conducting site monitoring in Japan. The average number of on-site monitoring visits in the study decreased from approximately five to one. This result indicates that the RBA promotes effective monitoring of the sites, and the on-site monitoring frequency decreases [72]. The competent authorities suggested and applied the guidelines for the RBA depending on the interest of the RBA. Whereas the EU basically assigns the risk ranking for each site by applying the RBA, the USA and Japan decide on inspection options by applying the RBA. In addition, because ATMPs usually use viable cells, genes or tissues and sometimes allogeneic material, donor eligibility system in the US is included in the GMP inspection related to review of the procedures performed in screening, testing and determining donor eligibility [33]. The EU also decides the frequency, expenditure, time of inspection and scope of the next routine inspection based on the results of the RBA and characteristics of ATMPs [29].

GMP inspection is typically conducted as a routine inspection. However, if GMP inspection is recommended for marketing authorization, it can be conducted during the marketing authorization process to verify the details related to manufacturing and control of the ATMPs. In the EU, a centralized system is applied for GMP inspection for marketing authorization because ATMPs are authorized via the centralized (European) procedure. Accordingly, CHMP decides whether the inspection is conducted, and the inspection team in the EU member states performs the inspection [61]. In the US, if GMP inspection is necessary, PLI is performed with marketing authorization. GMP inspection for marketing authorization should apply Level I (full) inspection [33,65]. The manufacturing sites in Japan are inspected by desktop inspection or on-site inspection after the RBA results. If a desktop inspection is conducted, inspectors verify the inspection application and the details relating to the manufacture and control of the ATMPs, which were provided in the MAA without inspecting the manufacturing site [36].

Conclusion

The GMP for ATMPs is an important aspect of new drug development and marketing authorization. To promote effective development of ATMPs, this study considered the dossier of GMP, regulations and guidelines for facilities and equipment, the RBA and GMP inspection in the USA, the EU, Japan and South Korea. The GMP regulatory system of ATMPs was similar for the competent authorities. However, there were some differences of the GMP regulatory system of ATMPs. Therefore, differences in the marketing authorization process among the competent authorities related to GMP for ATMPs should be considered.

Summary points

- Items in the GMP dossier for marketing authorization are similar among the competent authorities.
- A site master file is required for the evaluation of GMP in the EU, Japan and South Korea; however, the USA require only a BLA.
- Competent authorities comply with the PIC/S GMP guideline for ATMPs.
- Regulations and guidelines for facilities and equipment at ATMP manufacturing sites are focused on preventing mix-up, cross-contamination and transmission risk of relevant communicable disease agents because terminal sterilization is often impossible for ATMPs.
- The competent authorities suggested and applied the guidelines, including risk-based planning, management scope and frequency in the RBA program.
- The US and Japan decide on inspection options, and the EU assigns a risk rating for each site by applying the RBA for marketing authorization.
- If a GMP inspection is recommended for marketing authorization, it can be conducted during the marketing authorization process to verify the details related to manufacturing and control of the ATMPs.
- Differences in the marketing authorization process among the competent authorities related to GMP for ATMPs should be considered.

Author contributions

H Shin and E Kim were responsible for study conception and design; H Shin was responsible for acquisition of the data and data analysis; H Shin and E Kim were responsible for drafting and revision of the manuscript.

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