○○ Co., Ltd. □□　Plant

Site Master File

Document No. xx-xx

Version No.	Prepared by	Date of prepared	Approved by	Date of approval

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1 General information on the manufacturer

1.1 Contact information on the manufacturer

1.1.1 Name and official address of the manufacturer

Name: ○○ Co., Ltd.

Address: xxx, xxx, xxx City, xxx Prefecture

1.1.2 Name and street address of the manufacturing site

Note: If there is multiple manufacturing places (addresses), write down all the places

Name: ○○ Co., Ltd. □□ Plant

Address: xxx, xxx, xxx City, xxx Prefecture

1.1.3 Contact information of the manufacturer including 24 hrs. telephone number of the contact personnel in the case of product defects or recalls;

Name and title of the contact personnel: □□, Director of ■■ Department, (Supervisor for Drug Manufacture)

Tel: xxx-xxx-xxxx Fax: xxx-xxx-xxxx

E-mail: xxxx@xxxx.co.jp

Telephone number for contact of business hours: xxx-xxx-xxxx (staff's cell phone number, TEL number of guard station or the like)

1.1.4 Identification number of the site as e.g. GPS details, D-U-N-S (Data Universal Numbering System) Number (a unique identification number provided by Dun & Bradstreet) of the site, or any other geographic location system.

D-U-N-S number: 999-999-999

GPS information: ●●●●●●●●●●●●●●

1.2 Authorized pharmaceutical manufacturing activities of the site including those from foreign regulatory authorities

1.2.1 Information about drug manufacturing license

Note: If manufacturing sites has no authorization, describe details.

Photocopy of the valid manufacturing authorization issued by the relevant competent authority: See Appendix 1.

1.2.2 Brief description of manufacture, import, export, distribution and other activities as authorized by or registered to the relevant Competent Authorities including foreign authorities.

(1) Domestic: License for Drug Manufacture: API, intermediates for API, non-sterile dosage forms, non-sterile dosage form manufacturing processes (including primary packaging, secondary packaging, labeling and storage)

(2) Country A: Submitted Drug Establishment Registration to FDA. Drug substance and non-sterile dosage form manufacturing processes, (submitted notification for the manufacture of export only drugs including APIs and dosage forms to the Japanese Authorities)

(3) Country B: Submitted notification for the manufacture of export only drugs for API s (for Italy) to the Japanese Authorities.

1.2.3 Type of products currently manufactured on- site

Non-sterile API, solid dosage forms and injectables

See Appendix 2 for a list.

1.2.4 List of GMP Inspections of the site within the last 5 years

Name /country of the Competent Authority	Dates	Product(s) covered	Results	Type of inspection on-site/desk-top

1.2.5 GMP certificate

Copies of current GMP certificates for the products manufactured at this site are given in Appendix 3.

1.3 Any other manufacturing activities carried out on the site

[If not applicable]

None of the following non-pharmaceutical products is being manufactured at this site.

Medical devices

Chemicals used for non-pharmaceutical products

Cosmetics

Household cleaning products and sanitary goods

Insecticides, herbicides

[If applicable]

The following non-pharmaceutical products are being manufactured at this site.

Chemicals used for non-pharmaceutical products

2 Quality management system of the manufacturer

2.1 The quality management system of the manufacturer

2.1.1 Brief description of the quality management system run by the company and reference to the standards used

The quality management system of ○○ Co., Ltd. □□ Plant is established referring to Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (GMP Ordinance), relevant regulations/notifications, Current Good Manufacturing Practices Regulations in the US (cGMP) and PIC/S GMP GUIDE, Quality Manual of ○○ Co. Ltd. □□ Plant serves as the highest level document in the document system of the site, and various written standards and procedures have been prepared under this manual.

These documents include quality policy, quality management organization, document control, personnel qualifications/hygiene control/education & training, manufacturing control, quality control, hygiene control of premises and equipment, qualification of premises and equipment, validation/maintenance, change control, deviation control, handling of quality information and quality defects, etc., recall procedure, self-inspection, management review .

The Quality Manual refers to the current version of ISO-9000 Series.

2.1.2 Responsibilities related to maintaining of quality system including senior management

The organization related to the quality management system at this manufacturing site is shown in Appendix 5: GMP Organization Chart of ○○ Co., Ltd. □□ Plant. Senior management and other management are responsible for ○○.

Head of Quality Assurance supervises activities related to manufacturing control and quality control, to ensure appropriate and smooth conduct of such activities. Head of Quality Assurance is responsible for change control, deviation control, handling of quality information and quality defects, etc., product recall, and internal audit and so on.

2.1.3 Information of activities for which the site is accredited and certified

This manufacturing plant isISO-9001certified. Photocopy of the certificate is given in Appendix 6.

ISO-9001

Date of certification:

Scope of certification:

Name of certifying bodies:

2.2 Release procedure of finished products

2.2.1 Detailed description of qualification requirements (education and work experience) of the Authorized

Person(s) responsible for batch certification and releasing procedures

Chapter ○ of the Quality Control Standards sets forth the site procedure for appointment of personnel responsible for batch certification and releasing. Personnel having actual experience of quality assurance or quality control for not less than ○ years and having received education/training on the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceutical and Medical Device, GMP Ordinance and other relevant regulations are appointed by the head of Quality Assurance .

2.2.2 General description of batch certification and releasing procedure

(1) Upon completion of manufacture of a lot of the product, the Quality Assurance Department will review the batch manufacturing records including the packaging process and submits the results of review (batch manufacturing control record) to the Authorized Person.

(2) The Quality Control Department will review the batch test/inspection records and submits the results of review (batch quality control record) to the staff in charge of release decision.

(3) The Authorized Person will review the batch manufacturing records, batch manufacturing control records, batch test/inspection records and batch quality control records and enters the results of review into the releasing document.

(4) Please describe if a computerized system is used to control the release, the results of release of all the starting materials and packaging materials used are controlled with the computerized □□ system. The system is designed to alarm any OOS found to the Quality Assurance Department. The staff at the Quality Assurance Department confirms absence of any such event with the □□ system and records the results of such confirmation in the product releasing document.

(5) If the staff at the Quality Assurance Department finds a description in the manufacturing records or the test/inspection records, of any change control or deviation control possibly affect to the lot concerned, or if the staff finds such an event in the □□ system even when no relevant description is found in the manufacturing records nor test/inspection records, it is required for the staff to evaluate the influence of such an event on releasing the lot concerned and to enter such evaluation results into the batch release document.

(6) If the Authorized Person judges absence of any problematic finding affecting to release of the lot concerned as the results of the reviews mentioned above, he/she should enter the judgment into the relevant column of the batch release document, and sign it.

(7) The Authorized Person will enter the release judgment into the computerized ■■ system. Start of distribution operation for any batch of product prior to the status change into "released" in the ■■ system are electronically locked.
At this manufacturing plant, there is ● Authorized Person.

(8) Statement on whether the control strategy employs Process Analytical Technology (PAT) and /or Real Time release or Parametric Release.

[Case A] PAT is not employed in this site.
[Case B] PAT is employed in the manufacture of xxxx.

2.3 Management of suppliers and contractors

2.3.1 A brief summary of the establishment/knowledge of supply chain and the external audit program

Agreements with the marketing authorization holders relating to the management of supply chain are managed in accordance with the procedure of each marketing authorization holder and are reviewed periodically and when necessary.

Selection and approval of suppliers and contractors as well as management of the approved suppliers and contractors is done by classifying each supplier and contractor according to the results of assessment of the risks of the raw materials and packaging materials to product quality. Details of the management to be done in each class are defined in the procedure. Audits will be carried out at the time of selection and on-going bases thereafter. On-site or desk top audit is selected depending on the risk class assigned to each supplier and contractor.

2.3.2 Brief description of the qualification system of contractors manufacturers of API and other critical materials suppliers

Qualification of each new contractor/supplier and on-going assessment of existing contractors/suppliers are carried out in accordance with the procedure described above 2.3.1. However, evaluation of API supplier is done by reviewing the audit report received from the marketing authorization holder of the finished product.

2.3.3 Measures taken to ensure that products manufactured are compliant with TSE (Transmissible animal spongiform encephalopathy) guidelines

Note: If the product is exported to other country, describe the conformance to such exported country's standard for Biological ingredients.

Raw materials used for the manufacture of the product A in this plant are confirmed to comply with the Japanese Standard for Biological Ingredients and their handling are controlled in accordance with the standard. Also the product A is exported to the country A, the plant are also confrimed to

cmply with the country A Standard for Biological Ingridents "Guideline for TSE", and their handling are controlled in accordance with the standard.

2.3.4 Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identifies

The suspected product should be immediately segregated into quarantine status and the unit that detected it issues a deviation report in accordance with the deviation handling procedure. Subsequent steps should be taken in accordance with the same procedure, while investigation should be conducted to check existence of the same problem in other lots and confirm the range of affected lots. If counterfeit/falsified product is identified, such event should be immediately notified to the marketing authorization holder and ask for subsequent actions.

2.3.5 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis

No technical assistance has been given from outside institution concerning manufacture or analysis. The analytical methods for the products being manufactured at this manufacturing site have been developed at the research laboratory of our company or other company and transferred to this site. Primary and secondary reference materials used for analysis have been supplied from those research laboratories.

2.3.6 List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply chains for outsourced manufacturing and Quality Control activities

A part of analytical work is contracted to outside analytical laboratories. A part of the manufacturing processes is outsourced to contractors. The address, contact information, allocation of responsibilities between us and the contractors, and outline of the contracted activities are shown in Appendix 4.

2.4 Quality risk management (QRM)

2.4.1 Brief description of QRM methodologies used by the manufacturer

One or combination of the following methodologies is used for each situation of risk assessment depending on the situation of QRM.

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)

- Risk ranking and filtering
- Supporting statistical tools

2.4.2 Scope and focus of QRM

At this manufacturing site, QRM is applied, in accordance with the policy of ○○ Co., Ltd., to the entire life cycle of the products to control the risk to the efficacy, safety and quality of the products in all GMP-related fields. Therefore, QRM is applied also to the entire supply chain, including supply of raw materials and outsourced activities.

2.5 Product Quality Reviews

Product quality review is done for each product once a year.

Quality Assurance Department is responsible for product quality review and approval.

(i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances;

(ii) A review of critical in-process controls and finished product results;

(iii) A review of all batches that failed to meet established specification(s) and their investigation;

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;

(v) A review of all changes carried out to the processes or analytical methods;

(vi) A review of Marketing Authorization variations submitted, granted or refused, including those for third country (export only) dossiers;

(vii) A review of the results of the stability monitoring programme and any adverse trends;

(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time;

(ix) A review of adequacy of any other previous product process or equipment corrective actions;

(x) For new Marketing Authorizations and variations to Marketing Authorizations, a review of post-

marketing commitments;

(xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc;

(xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

Items on which the necessity of improvements identified, relevant department prepare corrective action plan in accordance with the product quality review procedure and submits the plan to the Quality Assurance Department, where adequacy of the plan is evaluated. The status of implementation of corrective action is checked during internal audit, and it is also evaluated at the next product quality review. Trend analysis is done by converting the reviewed data into graphs as needed. If the number of lots manufactured during the review period is too small, the results in the preceding year(s) are added for review as needed.

3 Personnel

3.1 Organization chart of the site

Given in Appendix 5, as described in Section 2.1.2

3.2 Number of employees in the manufacturing site

Plant Manager: n=1

Production: n=○

Quality control: n=○

Quality assurance: n=○

Purchasing/warehouse: n=○

Engineering: n=○

Technical development (scale-up, validation, technical improvement): n=○

Total: n=○

4 Premises and Equipment

4.1 Premises

[1] Short description of plant

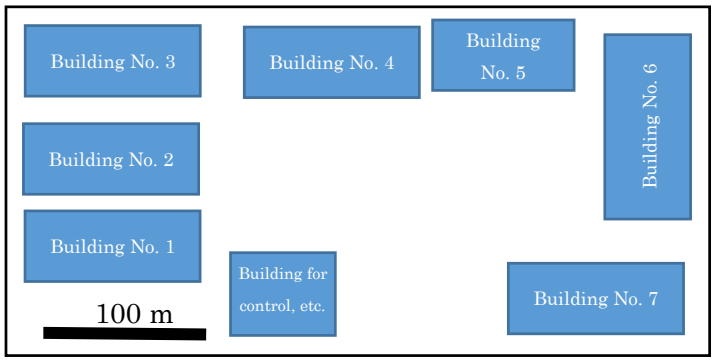
Site area: xxxxx m²

Manufacturing facility: Building No. 1 (For EU: manufacture of API and intermediates for API)
Building No. 2 (solid dosage form)
Building No. 3 (injectables)
Building No. 4 (For Japan: manufacture of API and intermediates for API)

Warehouse: Building No. 5 (warehouse for raw materials/packaging materials)
Building No. 6 (warehouse for finished products)

Laboratories: Building No. 7 (quality control)

Site plan is shown below.



(1) Lay outs of Manufacturing areas

See Appendix 6

Appendix 6-1 (Building No. 1 lay outs, room classification , pressure differential drawing)

Appendix 6-2 (Building No. 2 lay outs, room classification, pressure differential drawing)

Appendix 6-3 (Building No. 3lay outs, room classification, pressure differential drawing)

Appendix 6-4 (Building No. 4lay outs, room classification, pressure differential drawing)

(2) Lay outs of Warehouse

See Appendix 6

Appendix 6-5 (Building No. 5 lay outs, room classification of sampling area, pressure differential drawing, refrigerator, hazardous material storage area)

Appendix 6-6 (lay out of Building No. 6)

4.1.1 Brief description of heating, ventilation and air conditioning (HVAC) systems

4.1.1.1 Cleanliness of the rooms within the facilities of this site is classified into 6 grades.

(1) General area: Without air conditioning, no particulate/microbe monitoring

(2) Semi-controlled area: Air conditioning without high grade filter, no particulate/microbe monitoring

(3) Grade D area

(4) Grade C area

(5) Grade B area

(6) Grade A area

Areas (3) through (6) are controlled in accordance with PIC/S GMP Guidelines Annex 1.

4.1.1.2 Temperature/humidity control

Manufacturing area

Temperature/humidity control is not required for all the raw materials, intermediates or finished products handled at this manufacturing site. However, in view of the convenience of the operators, the control range of room temperature is ○-○°C and humidity is ○-○%RH.

Storage area

Storage area for materials and products to be stored at room temperature is controlled at 1-30°C. Materials and products to be stored in a refrigerated condition are stored in the rooms or refrigerators controlled at 2-8°C. Relative humidity is monitored but not controlled.

However, samples for stability tests are stored in the rooms or chambers where temperature and humidity are controlled in accordance with the conditions of ICH Guideline.

Reference and retention samples are stored in areas of ambient condition, and monitoring of temperature and humidity is done in these areas.

4.1.1.3 Pressure differential control

Pressure differentials with the adjacent different grade rooms in cleanliness-controlled areas such as the manufacturing area and the sampling area are controlled.

Pressure differential is set and controlled so that air flow from lower grade area to higher grade area can be avoided when a door is opened/closed.

Some areas require containment, and an example of the pressure differential cascade is; surrounding area (±) corridor (+) workplace (-), etc.).

4.1.1.4 Number of air change rate, air recycling

Air change rate is controlled only in the classified area, and in accordance with PIC/S GMP Guidelines Annex 1. Air is usually recycled in ○○%. In the areas where organic solvents are handled, 100% fresh air is supplied and the air is exhausted to the environment in accordance with the environmental standards.

4.1.2 Brief description of water systems

Three types of water (tap water supplied by local government, purified water and water for injection) are used at this manufacturing site. Tap water complies with the water quality standards provided by a Ministerial Ordinance issued by Ministry of Health, Labor and Welfare pursuant to Article 4 Paragraph 2 of the Water Supply Act (Law No. 171 in 1957). Purified water is montyly sanitized by hot water and WFI is weekly steriled by steam. Purified water and water for injection comply with the Japanese Pharmacopeia. A schematic diagram of each water system is given in Appendix 7.

4.1.3 Other utilities

Other utilities used for manufacture at this manufacturing site are steam, compressed air and nitrogen gas.

Two types of steam (industrial steam for heating and pure steam generated from purified water) are used. Compressed air is prepared by compression with an oil-less compressor and supplied through a dust-retentive pre-filter and then 0.45 μ or 0.2 μ filter.

Nitrogen gas is prepared from liquid nitrogen. As needed, it is supplied through a 0.2 μ filter.

4.2 Equipment

4.2.1 Listing of major production and control laboratory equipment

Major production and control laboratory equipment are listed in Appendix 8. Critical pieces of equipment are identified with ● mark before their names.

4.2.2 Cleaning and sanitation

Cleaning and sanitation of product contact surfaces is conducted routinely in accordance with the procedure. Master cleaning instructions and records have been established through cleaning validation.

There are two types of equipment in this manufacturing site regarding the cleaning methods, manual cleaning and CIP/SIP. Manually cleaned equipment are either (1) rinsed with water after washing with detergents, or (2) washed with solvents.

4.2.3 GMP critical computerized systems

The computerized system XXX is used at this manufacturing site. This system is used for integrated control of the following jobs.

[1] Warehouse control

(1) Manufacturing control

(3) Laboratory control (including release of raw materials, intermediates and finished products)

(4) Deviation control, change control, handling of information related to quality

(5) Document control

This system is validated and controlled in accordance with “Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs.”

5 Documentation

5.1 Description of documentation system

Two types of documentation systems (electronic system and paper-based system) are used at this manufacturing site. Electronic system is applied to the documents of standards and procedures, including blank forms related to them.

Paper-based control is applied to records. Electronically controlled blank forms are printed out by the personnel having access right to the electronic system and issued to workers in accordance with the procedure. The completed record form will be reviewed by the supervisor in accordance with the procedure and then stored at the predestinated place.

Documents and records are stored in-house and off-site archiving is used.

Off-site Storage : ●● storage Address : ○○ Prefecture ΔΔ City ×× Town.

6 Production

6.1 Type of products

6.1.1 Type of products manufactured at this manufacturing site

Non-sterile API, solid dosage forms and injectables as described in Section 1.2.4.

Details are given in Appendix 2.

6.1.2 Types of investigational medicinal products (IMPs) being manufactured at this site

IMPs manufactured on this site are AAA, BBB and CCC.

6.1.3 Toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitizing properties)

Of the products listed in Appendix 2, two (ΔΔ and □□) have high pharmacological activity. API and dosage forms are manufactured for both of them. No highly sensitizing substance has been handled.

6.1.4 Products manufactured in a dedicated facility/equipment or in a shared facility/equipment

The two products mentioned above (ΔΔ and □□) are manufactured under campaign basis at the same containment facility. Each equipment within this facility is fitted with CIP/SIP function, and cleaning between batches within a campaign and cleaning at product switching has been validated.

6.1.5 Process Analytical Technology(PAT) applications

Example A

No product is now using PAT.

Example B

Product ○○ is using PAT, in accordance with the procedure ….(describe general statement of the relevant technology, and associated computerized systems)

6.2 Process validation

6.2.1 Brief description of general policy for process validation

Process validation is carried out in accordance with the validation procedure to confirm that the defined materials, equipment and manufacturing procedure, critical process parameters, equipment cleaning procedure, involved operators yield a product consistently of the required quality.

For validation at the time of introducing a new product into routine manufacture or at the time of change in facility/process, a master plan is prepared for such product or project and individual validation plan for each validation study included in the master plan is prepared.

After successful completion of initial validation, periodical revalidation should be conducted as the product's life cycle management.

For the processes or process parameters where periodical revalidation is required by some guidelines such as sterility-related parameters, periodical revalidation studies are carried out in accordance with the guidelines. On the other processes or parameters, if the product quality review demonstrate that the processes are under control, additional re-validation studies are not done, and a revalidation report summarizing the reference documents and reports is prepared.

6.2.2 Policy for reprocessing or reworking

A deviation report is issued upon detection of OOS or deviation from process parameters. Then, decision about the need of reprocessing and reworking will be made on the basis of the results of risk assessment involving the relevant departments or units.

The reprocessed or reworked lot should be subjected to the product quality review and added to the stability monitoring program for follow-up.

6.3 Material management and warehousing

6.3.1 Arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage

Upon arrival of raw materials at the warehouse, warehouse personnel check the label, appearance, quantity delivered, etc. and enter information into the computerized system for warehouse control. The raw materials will be stored as “under quarantine” in the storage space. Upon completion of satisfactory sampling and test by the Quality Control Department, the status of the materials is changed into “released” by the Quality Control Department and they will be able to be taken out of the warehouse to be used for processing.

Upon completion of manufacture of a batch of product, the batch information is entered into the warehouse control system. The warehouse staff are not able to take out the lot from the warehouse control system before the status is changed into “released” by the authorized person or the quarantine status in the system is unlocked by the Quality Assurance Department.

6.3.2 Handling of rejected materials and products

If raw materials or finished products failed the test and inspection, status of “rejected,” is assigned to the batch in the computerized system. The batch in this status is retrieved from the storage immediately and a label “rejected” is attached to them. Then, the batch is segregated into the locked rejected material area in the raw material warehouse or rejected product area in the product warehouse. After that, the rejected raw materials are returned to the supplier, and the rejected products are incinerated.

All the events of raw material or finished product rejection are subjected to OOS procedure, and

necessary CAPAs are implemented, according to the deviation handling procedure.

7 Quality control

7.1 Quality control activities carried out on the site

The Quality Control Department of this manufacturing site conducts chemical and microbiological tests of raw materials, other materials used for manufacture (e.g., microbe retentive filter), packaging/labeling materials, water for manufacturing, environmental monitoring samples, critical intermediates, finished products, stability samples, etc., and maintain storage of the stability samples, reference and retention samples. In-process test is conducted by the manufacturing department staff qualified by the Quality Control Department, using the testing methods checked by the Quality Control Department and approved by the Quality Assurance Department.

8. Distribution, complaints, product defects and recalls

8.1 Distribution(to the part under the responsibility of the manufacturer)

8.1.1. Types (wholesale license holders, manufacturing license holders, etc.) and locations of the companies to which the products are shipped from the site

The destination of delivery and the allocation of responsibility for transport of API, bulk products and finished products distributed from this manufacturing site are decided in the agreement with each marketing authorization holder. A list is given below.

○○Drug Company, Drug Wholesaler (License#:○○○○○○○○), ○○ Prefecture ΔΔ City ×× Town

○○Pharmaceutical Co., Drug Manufacturer, ○○ Prefecture ΔΔ City ×× Town

ABC-Pharma. Co., Ltd., License Holder in the USA, ΔΔ City, ○○ State, USA

8.1.2 Description of the system used to verify that each customer/recipient is legally entitled to receive medicinal products from the manufacturer

8.1.3 Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/control

In accordance with the agreement with the marketing authorization holder, at the time of loading the products onto the truck, a data logger for recording temperature should be attached to the products requiring temperature control. The recipient is required, under the agreement, to check the data logger that the temperature has been within the predestinated range. Notification should be made only when any deviation is detected. Absence of such notification means that the temperature has been within the predestinated range.

In case where the manufacturing site assumes the responsibility for transport, education/training (including temperature control) should be provided to drivers under an agreement with the transportation company.

8.1.4 Arrangements for product distribution and methods by which product traceability is maintained

In case where the manufacturing site assumes the responsibility for transport, a written report in the predefined form is sent from the transportation company to the warehouse staff in this site upon completion of transport to the destination. (including report by Email or FAX)

8.1.5 Measures taken to prevent manufacturers/products to fall in the illegal supply chain

Monitor cameras have been installed at the product warehouse of this manufacturing site, and 24 hours security control is provided. The warehouse staff check the report from the driver described in Section 8.1.4 and the notification of receipt issued by the recipient to confirm that correct delivery is done during transportation responsible by this manufacturing site.

8.2 Complaints, product defects and recalls

Brief description of the system for handling complaints, product defects and recalls

Information related to product quality

The information related to product quality notified from the marketing authorization holders is transmitted to the Quality Assurance Department in accordance with the quality agreement and handled according to the procedure in cooperation with other departments related to the event. . If this manufacturing site is responsible to the quality defect, corrective/preventive actions will be taken and follow-up will be continued until completion.

Recall

If the marketing authorization holder judges that recall of the product is necessary as the result of the above information, the Quality Assurance Department will take necessary actions and record them in accordance with the quality agreement and recall procedure.

The products returned to this manufacturing site as the result of recall will be segregated appropriately until their disposition is decided.

9. Internal audit

Short description of the internal audit system

The Quality Assurance Department is responsible for preparing inspection plan, its conduct, and preparation of reports and follow-up of observed issues. These actions are taken and recorded in cooperation with relevant department.

The scope of inspection covers all units described in the organization chart (Appendix 5). An annual plan of self-inspection covering all departments once a year is prepared and carried out according to the plan. Internal audit is carried out by the personnel of this manufacturing site qualified by the Quality Control Department. Internal audit is carried out by a team composed of multiple qualified personnel. The internal audit team should not include any staff of the department being inspected.

The inspection report is delivered to the inspected department and the Plant Manager after approval by the Quality Assurance Department. If any observation is pointed out, a corrective action plan for such issue will be submitted from the inspected department to the Quality Assurance Department and it is also delivered to the Plant Manager. The corrective action plan is followed by the Quality Assurance Department until all the actions are completed. The outline of these steps is subjected to the Management Review.

Appendix 1: Copy of valid manufacturing authorization

Appendix 2 List of dosage forms manufactured

API and intermediates for API	Intermediates for API（API Intermediate○○○○○） Intermediates for API not falling under the category of chemically synthesized highly sensitizing substances or highly physiologically active substances (manufactured in non-dedicated area)
	API (API△△△△△、API□□□□□□) 1. highly pharmacologically active substances (all are chemically synthesized substances; two items with cytotoxicity are manufactured under campaign basis in the area manufacturing only these two items) These items are manufactured also for export. 2. Chemically synthesized API other than those listed above (manufactured in the shared areas) （API●●●●●●）
Solid dosage forms	Tablets (uncoated tablets▲▲▲▲▲, coated tablets■■■■■) and capsules （○△○△○△） are manufactured up to the process of secondary packaging. No modified release product is now being manufactured.
Injectables	Liquids [vials △□△□△(either by aseptic processing or terminal sterilization)] and syringes●▲●▲●▲ (aseptic processing)] and freeze-dried forms (vials) □○□○□○are being manufactured up to the secondary packaging. Two of the liquids have high pharmacological activity, and both of them are manufactured under campaign basis by aseptic process in the area dedicated for the manufacture of these two products.

Appendix 3: Copy of valid GMP certificates

Appendix 4 List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply-chains for these outsourced activities

Contract laboratories

Name: XXXX Co., Ltd. XX Research Institute

Address: XX, XX Town, XX City, XX Prefecture

Contact information: ○○ ○○, Director of XX Department

TEL: XXX-XXX-XXX

Outsourced test item: Atomic absorption spectrophotometry of API○○

Contractor for primary container sterilization

Name: XXXX Co., Ltd. XX Plant

Address: XX, XX Town, XX City, XX Prefecture

Contact information: ○○ ○○, Manager of XX Section

TEL: YYY-YYY-YYY

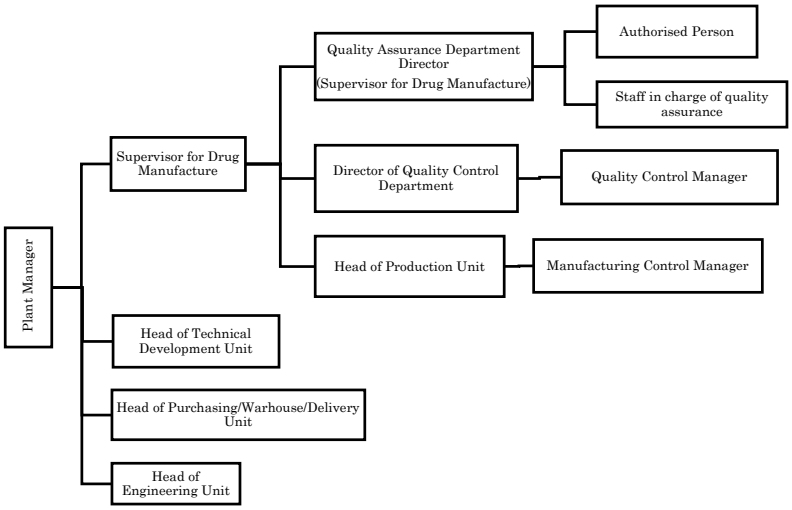
Contract storage : Packaging Materials YY and ZZ

Name: XXX Co. Ltd. XX Warehouse

Address: XX, XX Town, XX city, XX Prefecture

Contact information: ○○ ○○,　Manager of XX Section

Appendix 5: ○○ Co., Ltd. □□ Plant GMP organization chart



Appendix 6-1 through -4: Lay outs of production areas

Lay out of Manufacturing Facility Building No. ○ , room classification in the building, pressure differential drawing

(Note) The drawing should include environmental classification, pressure differential, cleanliness classification of each room and manufacturing activity in it (e.g., blending, filling, storage, and packaging). Specific areas handling highly sensitizing substances or highly pharmacologically active substances also need to be shown clearly.

Appendix 6-5 and -6: Lay out of Warehouse

Lay out of Warehouse Building No. ○ , room classification of sampling area, pressure differential drawing, refrigerator, hazardous material storage area

(Note) Specific areas handling materials with high toxicity, hazardous materials, highly sensitizing substances and highly pharmacologically active substances also need to be shown clearly.

Appendix 7　Schematic drawings of water systems

(1)　Tap water (outline of the system within the site beginning from the entrance of piping into the manufacturing site. Schematic diagram showing storage tanks, branching routes, sampling points, etc.)

(2)　Purified water (schematic diagrams, showing the source water inlet, purification equipment such as

activated carbon filtration column, ion exchanger/RO filter/UF filter/electro dialyzer, storage tank (including vent filter), pumps, piping to the use points, heat exchanger, in-line thermometer/conductivity meter/TOC meter/pressure gauze, sampling points, etc.)

(3) WFI (similar to the above-mentioned purified water system; pretreatment is not needed if purified water is used as the source water)

Appendix 8 List of major manufacturing and laboratory equipment

(1) Manufacturing equipment

Building	Critical equipment	Equipment name
Building No. 1	●	xxxxL reactor
	●	xxxxL reactor with condenser
	●	xx type dryer
	●	xx type blender
Building No. 2	●	xx type mill
	●	xx type blender
	●	Wet granulator
	●	xx type granulator
	●	xx type dryer
	●	Tableting machine
	●	Capsule filling machine
	●	Blister packaging machine
	●	Cartoning machine
	●	Glove box for API dispending
Building No. 3	●	Stainless steel xx L agitation tank for drug solution preparation, with CIP/SIP function
	●	Autoclave, for equipment parts sterilization
	●	Autoclave, for equipment parts and dust-free clothing sterilization
	●	Autoclave, for terminal sterilization of products
	●	Bottle washing machine
	●	Rubber stopper sterilizer
	●	Rubber stopper sterilizer (for isolator)
	●	Tunnel sterilizer
	●	Vial filling machine, capping machine

	●	Syringe filling machine
	●	Isolator (a set of filling line for anticancer drugs)
	●	Cartoning machine

(2) Laboratory equipment

Building	Critical equipment	Equipment name
Building No. 6 Chemical Test Room	●	Precision electronic balance
	●	FTIR
	●	pH meter
	●	Oven for measuring loss on drying
	●	Karl Fischer moisture meter
	●	Gas chromatograph
	●	High performance liquid chromatograph
	●	Elemental analyzer
	●	Refrigerator for reference standard storing
Building No. 6 Microbiological Test Room	●	Autoclave for incubation medium and laboratory tool sterilization
		Autoclave for sterilization of used medium before discarding
	●	Incubator
	●	Incubator
	●	Endotoxin measuring system
	●	Automated nucleic acid testing equipment for microbe identification