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Compilation of key GMP requirements in us and Japan for Tablet Manufacturing

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Abstract

The tablet is most popular dosage form in the world. The objective of this work helps in bringing the awareness about the manufacturing requirements as per USFDA and Japan. GMP covers all aspects of production, from the starting materials, premises, equipment and training and personal hygiene to staff. GMP of tablet manufacturing was designed to ensure that all is well. Implementation of GMP is an investment in good quality medicines. It demonstrates industry and regulatory authority's support for an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of GMP throughout the product lifecycle should facilitate *innovation* and *continual improvement* and strengthen the link between pharmaceutical development and manufacturing activities. It also helps in increasing the process efficiency and product quality by adopting the current, risk-based manufacturing approach and in turn optimizes manufacturing process and improves quality of the end-product.

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INTRODUCTION

"Good manufacturing practice" or "GMP" is part of a quality system covering the manufacture and testing of active pharmaceutical ingredients, diagnostics, foods, pharmaceutical products and medical devices. GMPs are guidelines that outline the aspects of production and testing that can

impact the quality of a product. Many countries have legislated that pharmaceutical and medical device companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation.

GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.[1]

Table 1: GMP as per the countries

COUNTRES	GMP AS PER THE COUNTRIES
INDIA	SCHEDULE M:- Schedule M of drug and cosmetic acts 1940 regarding GMP and requirements of premises, plants Part-I & Part I-B; specific requirements for manufacture of oral solid dosage forms (tablets & capsules)
US FDA	FDA (Food and drug administration) Part 210 — Current Good Manufacturing Practice in Manufacturing & Part 211 discusses GMP requirements in general.
EU	Two directives laying down principles and guidelines of good manufacturing practice (GMP) for medicinal products were adopted by the Commission in 1991, the first for medicinal products for human use (Directive 91/356/EEC),the second one for veterinary use (Directive 91/412/EEC). These guidelines describe GMP requirements in general and not specifically for tablets.
JAPAN	Pharmaceutical affairs law, there has been issued a new MHLW (Minister of health labor and welfare) ordinance relating to standards for manufacturing control and quality control for drugs and devices (MHLW ORDINANCE NO. 179 December 24, 2005) but there are not specific requirements for manufacture of oral solid dosage forms tablets. It depending on products & manufacture to set up for solid dose form like tablet.

34 % of the world pharmaceutical dosage forms are in tablet form. GMP covers all aspects of production, from the starting materials, premises, equipment and training and personal hygiene to staff. Detailed written procedures are essential for each process that could affect the quality of the finished product and manufacturing of tablet. Implementation of GMP is an investment in good quality medicines. This will improve the health of the individual patient and the community, as well as benefiting the pharmaceutical industry and health professionals. It also helps in increasing the process efficiency and product quality by adopting the current, risk-based manufacturing approach and in turn optimizes manufacturing process and improves quality of the end-product.

COMPILATION OF KEY GMP REQUIREMENTS IN US FOR TABLET DOSAGE FORMS

1. ORGANIZATION AND PERSONNEL

- Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform.
- Personnel shall practice good sanitation and health habits. Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.
- Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

TRAINING

- Training must be approached with the seriousness of purpose that it needs and deserves.
- The necessity for training arises whenever there is any deficiency in the knowledge, understanding, attitudes and specific skills possessed by a person as compared with the knowledge, understanding, attitudes and specific skills required for the successful performance of any task assigned to that person.
- The new recruit, or a person newly transferred to a department, is almost certain to display a deficiency

in one of more of these areas, and is thus a prime candidate for training.

2. OPERATOR HYGIENE — BASIC GUIDELINES

- It needs to be understood that good bodily hygiene and a high level of general cleanliness are necessary in those working on the manufacture of pharmaceuticals and similar products.
- Hands, including nails, should be kept clean, always be carefully washed after visits to the toilet, before meals, and before work commences, or recommences after a break. There is considerable risk of infection being passed on by contaminated hands. To reduce the risk of infection through hand contact, the following should be required of all operators:
  a) Do not touch the product, nor objects that may come in contact with the product, with unprotected hands.
  b) Keep the hands well groomed with short, clean nails. Hands must be free of any lesions, wounds, cuts, boils, or any other sources of infection.
  c) Wrist watches, rings, or other jewellery should not be worn on the job.
  d) Hands should be washed before work and as often as the job requires.
  e) Protective gloves should be worn when working with open products and when handling objects that come in direct contact with the product.
- Persons with infectious diseases or with open lesions on the body surfaces should not work in production areas.
- A program for health checkups should operate for all production personnel. It should provide for regular checkups in addition to a general medical examination prior to employment.

3. BUILDINGS AND FACILITIES

- Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, labelling, in-process materials, or drug products, and to prevent contamination.
- Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:
  a) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labelling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;
  b) Holding rejected components, drug product containers, closures, and labelling before disposition;
  c) Storage of released components, drug product containers, closures, and labelling;
  d) Storage of in-process materials;
  e) Manufacturing and processing operations;
  f) Packaging and labelling operations;
- Adequate lighting shall be provided in all areas.
- Adequate ventilation shall be provided.
- Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
- Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.

4. EQUIPMENT PRODUCTION AND PROCESS CONTROLS

- There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
- Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity,

strength, quality, and purity they purport or are represented to possess:

a) The batch shall be formulated with the intent to provide not less than 100 percent of the labelled or established amount of active ingredient;

b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information;

I. Component name or item code;

II. Receiving or control number;

III. Weight or measure in new container;

IV. Batch for which component was dispensed, including its product name, strength, and lot number.

- Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that;

I. The component was released by the quality control unit;

II. The weight or measure is correct as stated in the batch production records;

III. The containers are properly identified.

IV. Each component shall be added to the batch by one person and verified by a second person.

- Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.
- All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.
- Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the Batch Production Record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.
- Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conforms to specifications.
- In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.
- Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.
- When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product, such deviation shall be justified and documented.
- Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.
- Reprocessing shall not be performed without the review and approval of the quality control unit.

LABELING ISSUANCE

- Strict control shall be exercised over labelling issued for use in drug product labelling operations.
- Labelling materials issued for a batch shall be carefully examined for identity and conformity to the labelling specified in the master or batch production records.
- Procedures shall be used to reconcile the quantities of labelling issued, used, and returned, and shall require

evaluation of discrepancies found between the quantity of drug product finished and the quantity of labelling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with 211.192. Labelling reconciliation is waived for cut or roll labelling if a 100% examination for correct labelling is performed in accordance with 211.122(g)(2).

- All excess labelling bearing lot or control numbers shall be destroyed.
- Returned labelling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.
- Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

DRUG PRODUCT INSPECTION

- Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct labeling.
- A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
- Results of these examinations shall be recorded in the batch production or control records.

5. RETURNED AND SALVAGED DRUG PRODUCTS

- Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labelling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

6. SPECIAL REQUIREMENTS FOR SOLID DOSAGE FORM

CHEMICAL WEIGHING

- Many Companies have adopted a central weighing department to service all of the processing areas.
- The centralization of responsibility, the avoidance of duplicating weighing facilities, and lower labour costs. After an item is weighed & properly initiated on the batch sheet by the weighed.
- High-potency drugs such as steroids and alkaloid should be weighed in a separate room equipped with absolute filters to avoid even minimal cross-contamination. This room could also be use for weighing dyes.
- Sinks and drain boards should be conveniently located to facilitate frequent cleaning of measuring equipment. Cabinets should be provided for the storage of utensils.
- Vacuum hoses should be available in the weighing area immediately adjacent to the weighing booths so that the top of deems and other containers can be opened for removal of contents.

TABLET GRANULATION AND COMPRESSING

- The numerous steps in granulation procedure increase the possibilities of cross-contamination, incorrect product identification, and/or mix-ups. To eliminate these possibilities, a separate room or booth is recommended for each step.
- Compartmentalizing the granulating process has, unfortunately, fragmented the operation and increase space, capital, and labour costs.

- Granulation should be considered a unit operation composed of closely integrated manufacturing steps, and process development work should be directed to this area for cost reduction and process improvement.
- Particular attention should be devoted to the cleaning of drying rack and trays, which should be designed for easy cleaning and made of stainless steel or other non-rusting material.
- If the department is not air-conditioned, all windows should be screened against the entrance of insects.
- Room should have special low vapour transmission treatment of walls and should be equipped with air locks.
- The booth walls should extend from floor to ceiling and may be made of tile up to the four-foot or five-foot level, with a glass or transparent partition extending it to the ceiling**.**
- Space should also be provided for in-process testing equipment such as balances and tablet hardness testers.
- There are two type of checks one is automatic and other is physical or manually.
- A major discrepancy between theoretic and actual yields signifies that an error may have been introduced at some stage of the process.

COMPILATION OF KEY GMP REQUIREMENTS OF JAPAN FOR TABLET DOSAGE FORMS

1. GENERAL REQUIREMENTS

- To be provided with facilities and equipment necessary for manufacturing the products including those that have undergone the intermediate process and need to undergo subsequent process to be the products in the manufacturing site.
- To be provided with the hand-washing facilities, toilets and gowning areas.
  - To be ensured that the areas where the manufacturing operations are conducted meet the following requirements:-
  a) Being appropriately illuminated and ventilated, and clean.
  b) Being distinctly segregated from the living quarters and unsanitary areas.
  c) Being provided with sufficient area necessary for conducting the operations without hindrance.
  d) Being provided with the buildings or facilities for controlling dust, insects and rodents, the process prior to the final purification of the products concerned with the active pharmaceutical ingredients provided for the purpose of being used for the manufacturing of drugs and the manufacturing facilities for such process are the well-closed structure.
  e) Being provided with the facilities necessary for disposing of the poisonous gases in case where they are handled according to the products.
- To be ensured that the work room among the work areas for the products concerned with APIs, where the filling operations to the sealing operations in the containers for the intermediate products which have undergone the final purification are conducted, and the work rooms among the work areas for the products other than those concerned with APIs where the weighing operations for the raw materials and the formulating, filling and sealing operations for the products are conducted meet the following requirements,
  a) Not being provided with the entrances directly leading to the outside, buildings and facilities necessary for preventing contamination due to the outside:
  b) Provided with the entrances and windows that can be closed;
  c) Provide the effluent facilities in the work room with the structure necessary for preventing contamination of the work rooms;
  d) Provided the ceiling of the work room with the structure which does not allow dust to fall;
  e) Provided the pipes, ducts and other relevant facilities in the work rooms with the structure which does not allow dust to accumulate on their surfaces, with the proviso that this provision shall not apply in case where such facilities can be easily cleaned.
- **Manufacturing department and quality department** The manufacturing, for each of the manufacturing sites, establish a department concerned with manufacturing control and a department concerned with quality control under the supervision of the drug manufacturing manager.

- **Duties of manufacturing manager are as follows** To supervise the duties of the manufacturing control and quality control, and to manage the manufacturing and quality control duties so that they are conducted properly and efficiently**.** To verify that necessary actions have been promptly taken, to verify the progress of such actions, and to give instructions, where necessary, to take necessary actions such as improvements, in case where quality defects or a potential risk which could affect the quality of the products exists.

2. PERSONNEL

- The manufacturer shall assign an appropriate number of responsible persons according to the organisation, size type of the duties, etc of the manufacturing site.
- The manufacturer shall ensure sufficiently the personnel who have competence for appropriately conducting the manufacturing and quality control duties.
- The manufacturing shall define and document appropriately the scope of the responsibility of the personnel engaged in the manufacturing and quality control duties, and the system for supervising the personnel.

3. BUILDING AND FACILITIES

- To be appropriately cleaned and maintained according to the use to be sterilised where necessary and to be ensured that records thereof are established and maintained, in accordance with the documented procedure.
- To be provided with the facilities necessary for disposing of the poisonous gases in case where they are handled according to the products.
- To be ensured that the work rooms, among the work areas, where the weighing operations for the raw materials or the formulating operations, filling operations or sealing operations for the products are conducted are the buildings which do not allow passage of the personnel other than those conducting operations in such work rooms.
- In case where the products, are easily dispersed and cause hypersensitive reaction in a minute amount or could cross-contaminate and seriously affect other products to be ensured that the work rooms are exclusively used for such products etc and air-handling system is separated from those used for other products.
- Japanese company involves stripping off all street clothes down to underwear, donning freshly laundered plant uniform, and then having that uniform gone over with an adhesive roller to collect any non-viable particles that might be adhering to the outside of the uniform.

4. MANUFACTURING CONTROL

- To establish and maintain documented manufacturing orders describing the instructions, precautions and other matter necessary for the manufacturing process.
- To manufacture the products in accordance with the documented manufacturing orders.
- To verify, for each lot that the packaging and labelling materials of the products are proper and to establish and maintain records concerned with the results of the verification.
- To properly store the products etc for each lot and the packaging and labelling materials for each controlled unit to control their receipt and delivery and to establish and maintain records.

5. QUALITY CONTROL

- To collect sample necessary for testing for lot of the products, etc and from each controlled unit of the packaging and labelling materials and to establish and maintain records of the collection.
- To conduct the testing including those conducted on the manufacturer's own responsibilities using their testing facilities or other testing institutions and such conduct is verified to present no hindrance to the proper testing and hereinafter referred to as such of the collected samples for each lot or for each controlled unit, and to establish and maintain records of the testing.
- Japanese companies react to a product complaints, where invariably the results of the compliant investigation are communicated to the person making

the complaint by a personal visit to the complainant from the company's Vice President of Quality, a recitation of the deficiencies found, and an explanation of what measures the company is implementing to prevent the occurrence happening again a series of events that are common in Japanese culture, but to which no Western company would even dream of doing.

6. CHANGE CONTROL

- The manufacturer shall in case where any change will be made in the manufacturing procedure, etc. which could affect the quality of the products have the person designated beforehand conduct the following duties in accordance with the documents procedure.
- To evaluate effects on the quality of the products due to such change, to be approved by the quality department with respect to the change being made based on the results of the evaluation, and to establish and maintain records of the evaluation and approval.

7. DEVIATION CONTROL

- The manufacturer in case where any deviation from the manufacturing procedure, has occurred, have the person designated beforehand conduct the following duties in accordance with the documented procedure.
- To record the details of the deviation.
- To conduct the following duties in case where any serious deviation has occurred.
- Evaluating effects on the quality of the products due to the deviation, and taking necessary actions.
- Establishing and maintaining records of the results of the evaluation and the action specified in preceding and reporting them in writing to the quality department.

8. HANDLING OF INFORMATION ON QUALITY

- The manufacturer shall in case where they have received the information on the quality, etc of the products have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc., with the proviso that this provision shall not apply in case where the matters concerned with the quality information are not obviously attributable to their manufacturing site.
- To investigate the cause of the matters concerned with such quality information and to take necessary actions in case where improvements are necessary for correcting the manufacturing control and quality control.
- To establish and maintain records describing the details of such quality information, the results of the investigation and the improvements and to promptly report in writing the records to the quality department.

9. HANDLING OF RECALL

- To segregate the products recalled, and to dispose of them appropriately after storing for a certain period.

To establish and maintain records of handling of recall describing the details of the recall, and to report in writing them to the quality department and the manufacturing manager

10. SELF INSPECTIONS

- To conduct the self inspections periodically on the manufacturing control and quality control of the products in their manufacturing site.
- To report in writing the result of the self- inspections to the manufacturing manager.
- To establish and maintain records of results of the self inspections.

11. TRAINING

- To implement as planned the training necessary for conducting the manufacturing control and quality control for the personnel engaged in the manufacturing and quality control duties of the products.
- To report in writing the progress of the training to the manufacturing manager.
- To establish and maintain records of the implementation of the training.

12. CONTROL OF DOCUMENTS AND RECORDS

- To put the date of the establishment or the revision of the documented procedures etc. On them, and to maintain records of the history of previous revisions in case where they are established or revised.

- To maintain the documents and records specified in this ministerial ordinance for 5 years of which shelf life plus 1 year exceed 5 from the date of the establishment. [9-11] Some of the parameters were similar for manufacturing of tablet in Japan to US GMP guidelines however some differences were observed in certain aspects of tablet manufacturing requirements and general. They are as follows:

Table 2: Comparison of Japan GMP and US GMP guidelines

PARAMETERS	JAPAN GMP	US GMP
Organization & Personnel	Responsible persons who have competence for conducting the manufacturing and quality control duties properly and efficiently according to the organisation, size, type of the duties, etc of the manufacturing site are required.	Not clearly defined.
Building & Facilities	Japanese company typical involves stripping off all street clothes down to underwear, donning freshly laundered plant uniform, and then having that uniform to collect any non-viable particles that might be adhering to the outside of the uniform.	US Company typical no stripping off all street clothes is not included but have the provision to clean or collect any non-viable particles.
Equipment	To establish and maintain records concerned with the manufacturing of the products for each lot.	Master production and control records on separate records for each lot it is included in it.
Production & process controls	A records check on equipment/line/work station clearance is specified.	Not mentioned.
Materials control	To store a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products for each lot	Not specified amount mention to be stored for testing a product.
Packaging & labeling control	To properly store the products etc for each lot and the packaging and labeling materials for each controlled unit to control their receipt and delivery and to establish and maintain records	There are no specific action mentioned to control their receipt and delivery and to establish and maintain records
Control laboratory	Japanese companies react to a product complaints, where invariably the results of the compliant investigation are communicated to the person making the complaint by a personal visit to the complainant from the company's Vice President of Quality, a recitation of the deficiencies found, and an explanation of what measures the company is implementing to prevent the occurrence happening again – a series of events that are common in Japanese culture.	Product complaints are handled by quality control & assurance personals only.
Records and reports	Sanitation control standard code, manufacturing control standard code, quality control standard code, and documented procedure in the manufacturing site are mentioned.	No such code is there in manufacturing site.
Training	To report in writing the progress of the training to the manufacturing manager. To establish and maintain records of the implementation of the training.	Specific guidelines are giving, more importance in motivation & management No writing report.
Chemical weighing	No specific information about chemical weighing.	The hood for each 14 × 15 foot booth should have a capacity of 4500 cfm with a face velocity in excess of 150 free per minute
Compressions	No specific information about tablet presses.	Tablet presses however, at least 450 cfm and a velocity of over 3000 feet per minute are needed
Coating	No specific information about hood and booth system.	In large coating operation when the noise level approaches the maximum permitted under the OSHA maximum average of 80 decibels.
Change control	To evaluate effects on the quality of the products due to such change, to be approved by the quality department with respect to the change being made based on the results of the evaluation, and to establish and maintain records of the evaluation and approval.	As such information about change control in not mentioned.

CONCLUSION

GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.

In general, there are a number of similarities in terms of the content of the US and Japan documents.

The Japan GMP gives detailed job descriptions describing the duties and responsibilities of various members of key management staff in the pharmaceutical company. It describes the role and function of the Manufacturing Control Manager, the Quality Control Manager and the Product Security Pharmacist. Japanese Product Security Pharmacist was effectively equivalent to the European "Qualified Person". Japanese pharmaceutical companies, it was found that the concept of GMP compliance as it is understood in the West is almost totally unknown. However Japanese product quality is far better anything encountered in America or Europe.

Hence understanding the similarities and differences among GMP requirements for the tablet manufacturing & general requirement which are used in tablet manufacturing by the regulated countries shall benefit the pharmaceutical companies of both ROW countries & Regulated countries.

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