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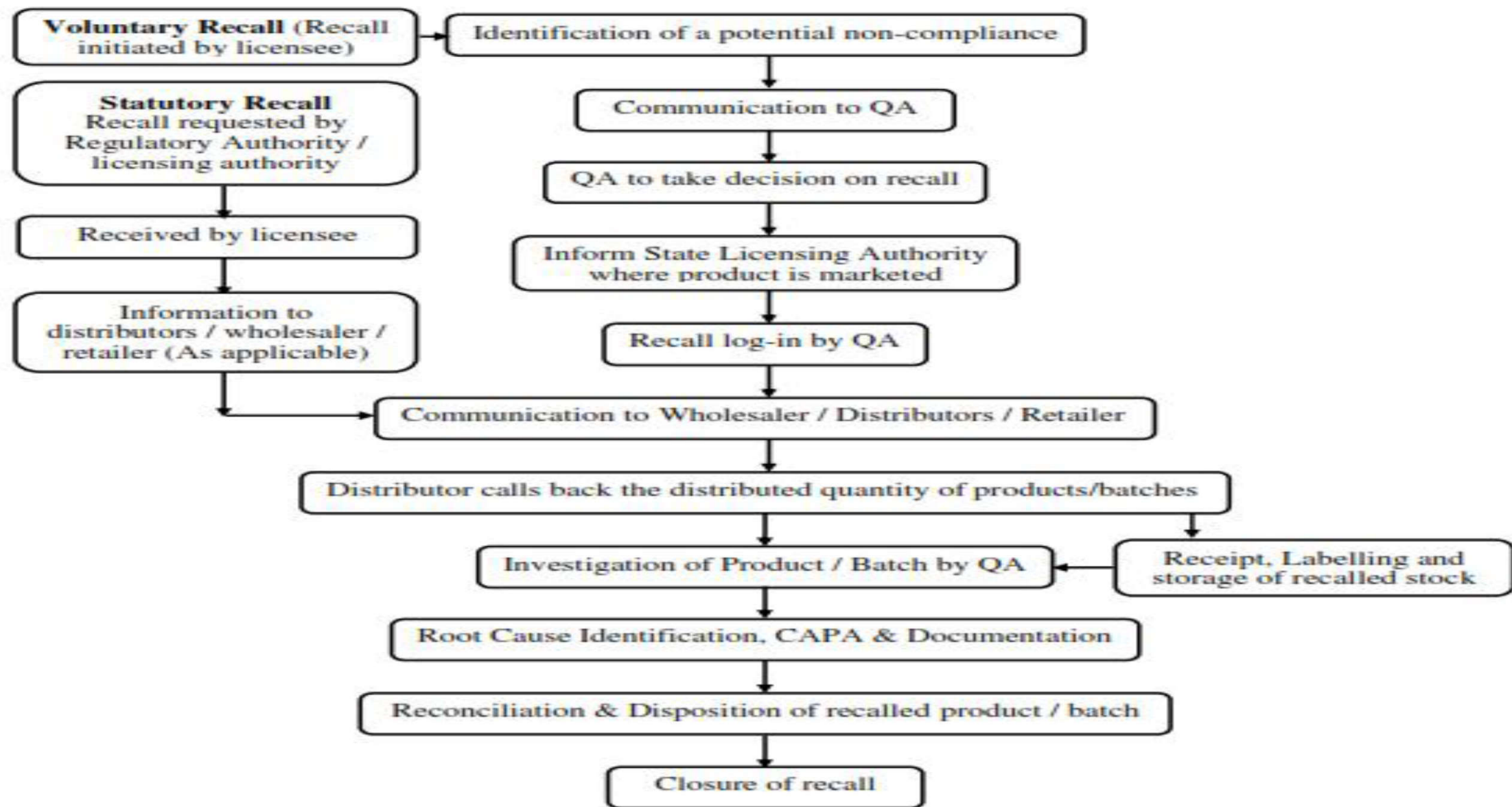


**REGULATORY REQUIREMENT
FOR VALIDATION IN
PHARMACEUTICAL INDUSTRY**

IMPORTANCE OF VALIDATION

- ☐ Quality assurance cost reduction
- ☐ Customer satisfaction
- ☐ Product liability
- ☐ Fewer product recall
- ☐ Fewer batch failures
- ☐ Decreased risk of regulatory non compliance
- ☐ Smooth running of process
- ☐ In process control and end product testing

FLOW CHART FOR PRODUCT RECALL



HISTORICAL BACKGROUND FOR THE REGULATORY BASIS

- [?] The emphasis on validation began in the late 1970s, the requirement has been set at 1963 as cGMP regulations for finished pharmaceuticals.
- [?] Validation is an integral part of Quality Assurance & its meaning is “Action of providing an evidence”.
- [?] Validation is necessarily include process qualification (qualification of raw materials, equipment, system) under the section 21 CFR 211.100 which states:
- “There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity”.

HISTORY

- [?] The **Kefauver-Harris Amendments** to the FD&C Act were approved in 1962 with Section 501(a)(2)(B) as an amendment.
- [?] The result of The amendments Provided an additional powerful regulatory tool to FDA to stop particular manufacturing process when the drug product is deemed to adulteration.
- [?] The Drug Product Quality Assurance Program of the 1960s and 1970s involved first conducting a massive sampling and testing program of finished batches.
- [?] The investigation of clinical failures of several products (including Digoxin, Digitoxin, Prednisolone, and Prednisone) by FDA found significant content uniformity problems that were the result of poorly controlled manufacturing processes

REGULATORY BASIS

- [?] The regulatory basis validation program of process validation is embodied within the regulations & guidelines provided by cGMP & FDA.
- [?] The ultimate legal authority is Sec501(a)(2)(B) by the FD&C Act, which states “Drug is deemed to be adulterated due to the methods/ facilities used for the manufacturing, processing, packing/holding fails to administer in conformity – cGMP”
- [?] Validation-Process validation is not just an FDA or U.S. requirement. Similar requirements included in the World Health Organization (WHO), the Pharmaceutical Inspection Co-operation Scheme (PIC/S), and the European Union(EU).

REGULATIONS FOR VALIDATION UNDER USFDA

- [?] Section 211.100(a): Written procedures/deviations. “There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity.”
- [?] Section 211.110: Sampling and testing of in-process materials and drug products
- “....control procedures shall be established to monitor the output and Validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product”

- [?] 21CFR211.133: Control of Microbiological Contamination " 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."
- [?] FDA must inspect every drug manufacturing establishment at least once every 2 years .

Apotex Inc. 2/21/13



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Warning Letter

WL: 320-13-09

February 21, 2013

Jeremy B. Desai, PhD
President and Chief Operating Officer
Apotex, Inc.
150 Signet Drive
Toronto, ON, Canada M9L 1 T9

Dear Dr. Desai:

During our August 13, 2012 through August 24, 2012, inspection at your pharmaceutical manufacturing facility, Apotex, Inc., located at 150 Signet Drive, Toronto, Canada, and our October 18, 2012 through October 26, 2012, inspection of your pharmaceutical manufacturing facility, Apotex, Inc., located at 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Part 210 and 211. These violations cause your drug product(s) to be

processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's responses of September 14, 2012 and November 16, 2012, and note that they lack sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated October 11, 2012 and December 14, 2012.

Our investigators observed specific violations during the inspections, including, but not limited to, the following:

A. Apotex, Inc., 150 Signet Drive, Toronto, Canada

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

For example, you failed to perform adequate unidirectional airflow pattern studies (i.e., smoke studies) for the aseptic filling line used for the production of (b)(4) Injection. The smoke studies did not include examination of airflow during set-up and at points of process intervention. Moreover, your airflow pattern studies for the class 100 area of the (b)(4) filling line show clear evidence of turbulent airflow in your filling line located in Room (b)(4) both above the (b)(4) just prior to entry into the filling zone and over the stopper bowl adjacent to the filling zone. Although this lack of unidirectional airflow can compromise sterility, you failed to take appropriate action to ensure that your parenteral drug products were protected from these contamination hazards.

An *in situ* air pattern analysis should be conducted in all critical areas under dynamic conditions, to demonstrate unidirectional airflow and sweeping action at critical work areas.

These studies should evaluate the impact of aseptic manipulations (e.g., interventions) and equipment design, document the activities performed, and include written conclusions. In your response to this letter, provide a copy of your new smoke study recordings along with supporting documentation.

According to your September 14, 2012 response, you committed to conduct smoke studies by December 31, 2012. In your response to this letter, provide an update of all airflow pattern studies conducted, your evaluation of the results, and your proposed corrective and preventive actions. In addition, provide your risk assessment for all sterile products within expiry that were manufactured under these unacceptable conditions.

In addition, your firm failed to establish maximum holding times for vials used in media fills prior to incubation

management is essential to support the reliability of your aseptic manufacturing of finished drug products intended for distribution in the United States.

B. Apotex, Inc., 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

For example, (b)(4) Injection (b)(4) lot #(b)(4) failed its sterility test on April 19, 2012. Your firm rejected all manufactured batches of (b)(4) Injection (b)(4) up to the resumption of commercial production on June 28, 2012. However, you did not recall the lots of (b)(4), manufactured on the same filling line, and still within expiry. In your response of November 16, 2012, you indicated that one of the probable root causes was the lubricant used on a (b)(4) for the (b)(4) filling line. In addition, you indicated that the last shipment of (b)(4) was January 21, 2011, and that all distributed batches but that one had expired. Your response was inadequate because it did not address all products within expiry as of the date of the sterility failure.

2. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

For example, your firm failed to record the incubation dates of the microbiological plates in the validation study of the (b)(4) of (b)(4) for (b)(4) Solution, (b)(4) Solution, (b)(4) Solution, and (b)(4) Spray. Your procedure for the validation study requires the incubation of the (b)(4) plates to be (b)(4) to (b)(4) and the incubation of the (b)(4) plates to be (b)(4) to (b)(4). You indicate in your response that you have revised procedures, conducted a risk assessment, and will re-execute the validation of the (b)(4) of (b)(4). Your response is inadequate because the risk assessment did not assess the impact of your failure to document the incubation period on the released batches.

In addition, your firm failed to record and maintain the raw data to support your conclusions regarding the effectiveness of the (b)(4) used in (b)(4) Solution, (b)(4) Solution, (b)(4) Solution, and (b)(4) Spray. Your firm recorded the (b)(4) test results from (b)(4) plates for each time point rather than recording the actual observed colony count for each plate. In your response, you indicated that you will revise procedures, conduct a risk assessment, and re-execute (b)(4) effectiveness testing. However, you failed to include an assessment as to how the lack of raw data supporting (b)(4) effectiveness affects batches that you released to the market.



December 18, 2006

WARNING LETTER
CHI-3-07

Chicago District
Chicago District
550 West Jackson Blvd., 15th Floor
Chicago, Illinois 60661
Telephone: 312-353-5863

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Patrick Soon-Shiong, M.D.
Chairman of the Board and Chief Executive Officer
Abraxis Bioscience, Inc.
11777 San Vincente Blvd, Suite 550
Los Angeles, CA 90049

Dear Dr. Soon-Shiong:

An inspection of Abraxis Pharmaceutical Products (APP), 2020 Ruby Street, Melrose Park, IL, was conducted from May 16 through June 29, 2006. FDA investigators documented significant deviations from current Good Manufacturing Practice (cGMP) Regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211, with regard to the production of pharmaceutical products by this facility. These cGMP deviations were listed on an Inspectional Observations (Form FDA-483) form issued to and discussed with John F. Harmon, Executive Vice President, Global Operations. A copy of the Form FDA 483 is enclosed. These cGMP deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)]

We also have completed review of your August 2, 2006 response to the Form FDA-483 observations. As noted in the individual citations below, the cGMP deficiencies need more timely and comprehensive corrections than the actions you have proposed or taken.

parts 210 and 211, with regard to the production of pharmaceutical products by this facility. These cGMP deviations were listed on an Inspectional Observations (Form FDA-483) form issued to and discussed with John F. Harmon, Executive Vice President, Global Operations. A copy of the Form FDA 483 is enclosed. These cGMP deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)]

We also have completed review of your August 2, 2006 response to the Form FDA-483 observations. As noted in the individual citations below, the cGMP deficiencies need more timely and comprehensive corrections than the actions you have proposed or taken.

cGMP Charges

- 1) Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and failure to validate sterilization processes as required by 21 CFR 211.113 (b).
 - a) You have not conducted bacterial filtration retention validation for all of your aseptically filled products. We note in your response that you have established a [REDACTED] plan to complete such validation for all products by the fourth quarter of 2008. Please indicate if you intend to ship any product that has been manufactured without a validated sterilization process. If so, then please identify the product and provide your justification for releasing such product.

REGULATORY REQUIREMENT FOR VALIDATION IN cGMP



- [?] The first cGMP regulations, based largely on the Pharmaceutical Manufacturers Association's manufacturing control guidelines .
- [?] *the Medicines Act (1968) covers most aspects of cGMP in what is commonly referred to as "The Orange Guide"*
- [?] Validation under document of cGMP covers procedure, process qualification, equipment, & facilities.

- 211.68 :validation of automated process.
- 211.84(d)(2): validation of supplier's test results for components.
- 211.84(d)(3): validation of supplier's test results for container and closures.
- 211.110(a) : validation of manufacturing process to ensure content uniformity& integrity.
- 211.1113(b): validation of sterilization process.
- 211.165 : validation of analytical methods.
- By June 2010, the same GLP/GMP Validation requirements will
- apply to all manufacturers of dietary supplements.

PLANS OF FDA GMP

- [?] The FDA plans to oversee 591 national GMP inspections in 2014 and 2015, reduced from 967 performed last year.
- [?] Consequently the agency plans to perform 30 percent more foreign GMP inspections, increasing last year's total of 604 to a new grand total of 843 inspections.
- [?] Companies will now be chosen for inspection using the agency's risk-based inspection model that equates inspection periodicity to company quality practices and procedures. This risk based model develop specifically for FDA GMP PLANS use, takes into account risk factors; such as, Class I recalls, adverse events, as well as compliance history as it assigns an appropriate inspection cycle.

VALIDATION REQUIREMENT UNDER WHO



- [?] WHO (World Health Organization) cGMP Guidelines: Validation studies are an essential part of current good manufacturing practice (cGMP) and should be conducted in accordance with predefined protocols.
- [?] WHO validation definition: The documented act of proving any procedure, process, equipment, material, activity or system which actually leads to the expected results.

- [?] DQ: Design Qualification IQ: Installation Qualification
- [?] OQ : Operational qualifi. PQ: Performance qualification
- [?] **DQ**: The compliance of the basic design (location plan) with the user requirements & regulatory requirements should be submitted & documented.
- [?] **IQ**: Documentary evidence to prove that the premises & equipment have been built & installed in compliance with their specifications. IQ include:
 - 1.Preventive maintenance.
 - 2 .Equipment info.
 - 3. Calibration.
 - 4.Verification of the equipment.



- **□ OQ:** A series of tests to measure the performance capability of equipment. The OQ for HPLC system is the operation of pump, injector & detector will be tested at this stage.
- **□ PQ:** Process to verify that the system is repeatable & capable for consistently producing a quality product.

VALIDATION REQUIREMENT UNDER EU

- [?] The European Union requirements for validation is an extract from ICH Q8, Q9 and Q10 documented guidelines and helps to study continuous process verification
- [?] **EU Validation Definition:** Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly, To produce a medicinal product meeting its predetermined specifications and quality attributes
- [?] Strategies of validation under EU includes:
 - 1) Traditional process verification
 - 2) Continuous process validation. (CPV)
 - 3) Critical process parameter. (CPP)
 - 4) Critical quality attributes. (CQA)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- 1) Traditional process verification : process validation should focus on the control strategy, which primarily includes critical process parameters and other relevant studies demonstrating that the process is capable of delivering the desired product quality.
- 2) Continuous process validation (CPV): an alternative approach to process validation in which manufacturing process performance is continuously monitored & evaluated.
- 3) Critical process parameter (CPP): a process parameter whose variability has an impact on a critical quality attribute and therefore should be controlled to ensure the process produce the desired quality.
- 4) Critical quality attributes (CQA): a physical, chemical, biological or microbiological property should be within an appropriate limit, range to ensure product quality.

VALIDATION REQUIREMENT UNDER PIC/S

- [?] According to the EU Guidelines to Good Manufacturing Practice for Medicinal Products in Annex 15 the principles of qualification & validation of the PIC/S is given under document PIC/S PI 006-3:
- [?] Doc states: GMP for medicinal products Recommendations on Validation Master Plan Installation and Operational Qualification(Non-Sterile Process Validation Cleaning Validation) can assist with the interpretation and the implementation.
- [?] This document applies primarily to inspectorates of the PIC/S member for whom it is intended as instruction for preparing an inspection, and as an advanced training aid for qualification/validation

PREREQUISITES FOR SUCCESSFUL VALIDATION

- 1. Experience
- 2. Planning
- 3. Resource
- 4. Understanding & communication
- 5. Training
- 6. Sop's instrument & methodologies.
- 7. Validation master plan
- 8. Data analysis
- 9. Validation report

VALIDATION MASTER PLAN

- [?] The complete overview of validation operation, organization structure, content & planning in the form of a document is the VMP.
- [?] VMP should contain following data:
 - 1) Validation policy of company, location & schedule
 - 2) List of product, processes & system to be validated.
 - 3) Installation & qualification for new equipment.
 - 4) Key acceptance criteria.
 - 5) Documentation format used for protocols & report.
 - 6) Time planning & scheduling of project.

- [?] The Validation Master Plan is a top layer document and should not go into specific detail; but present an overall picture of the company facility, organisation and capability.
- [?] It must give a clear and concise overview, to a reviewer, of how the company has integrated all the applicable cGMP requirements into every aspect of its operations.
- [?] It must define validation activities and allot responsibilities for authoring, reviewing, approving, and executing validation documentation and tasks.

VALIDATION REPORT

- [?] The validation report should be approved prior to product distribution and kept permanently on file in quality assurance.
- [?] The validation report should have a conclusion that explains the manufacturing specialist's (preparer's) statement and opinion.
- [?] The validation report should contain the approved validation protocol, tabulated or graphical results, process monitoring (forms), and all analytical results of the validation batches

CONCLUSION

- [?] Regulatory authorities working on strategies to reduce the cost of process validation and incorporate validation consideration during product design and development.
- [?] New technologies under development for 100% analysis of drug products and other innovations in pharmaceutical industry may also have a significant effect on Validation & basic regulatory authority's acceptance.
- [?] The future of process validation is also of great interest, especially with the worldwide expansion of pharmaceutical manufacturing & for harmonizing in international standards and requirements.