4. Monitoring of Personnel. Daily personnel monitoring data and associated trends should be reviewed and can in some cases strongly indicate a route of contamination. The adequacy of personnel practices and training should also be considered.

5. Product pre-sterilization bioburden. Trends in product bioburden should be reviewed (counts and identity). Adverse bioburden trends occurring during the time period of the test failure should be considered in the investigation.

6. Production record review. Complete batch and production control records should be reviewed to detect any signs of failures or anomalies which could have a bearing on product sterility. For example, the investigation should evaluate batch and trending data that indicate whether utility/support systems (e.g., HVAC, WFI) are functioning properly. Records of air quality monitoring for filling lines should show a time at which there was improper air balance, an unusual high particulate count, etc.

7. Manufacturing history. The manufacturing history of the product or similar products should be reviewed as part of the investigation. Past deviations, problems, or changes (e.g., process, components, equipment) are among the factors that can provide an indication of the origin of the problem.

XII. BATCH RECORD REVIEW: PROCESS CONTROL DOCUMENTATION

Sections 211.100, 211.186, and 211.188 address documentation of production and control of a batch, including recording various production and process control activities at the time of performance. Section 211.100 (b) requires a documented record and evaluation of any deviation from written procedures.

Section 211.192 states that "All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup."

Maintaining process and environmental control is a daily necessity for an aseptic processing operation. The requirement for review of all batch records and data for conformance with written procedures, operating parameters, and product specifications prior to arriving at the final release decision for an aseptically processed batch calls for an overall review of process and system performance for that given cycle of manufacture. All in-process data must be included with the batch record documentation per Section 211.188. Review of environmental monitoring data as well as other data relating to the acceptability of output from support systems (e.g., HEPA / HVAC, WFI, steam generator) and proper functioning of equipment (e.g., batch alarms report; integrity of various filters), should be viewed as essential elements of the batch release decision.

While interventions and/or stoppages are normally recorded in the batch record, the manner of documenting these occurrences varies. In particular, line stoppages and any unplanned interventions should be sufficiently documented in batch records with the associated time and duration of the event. In general, there is a correlation between product (or container-closure) dwell time in the aseptic processing zone and the probability of contamination. Sterility failures can be attributed to atypical or extensive interventions that have occurred as a response to an undesirable event during the aseptic process. Written procedures describing the need for line clearances in the event of certain interventions, such as machine adjustments and any repairs, should be established. Such interventions should be documented with more detail than minor events. Interventions that result in substantial activity near exposed product/container-closures or that last beyond a reasonable exposure time should, where appropriate, result in a local or full line clearance

Any disruption in power supply, however momentary, during aseptic processing is a manufacturing deviation and must be included in batch records (211.100, 211.192).

APPENDIX 1: ASEPTIC PROCESSING ISOLATORS

An emerging aseptic processing technology uses isolation systems to minimize the extent of personnel involvement and to separate the external cleanroom environment from the aseptic processing line. A well designed positive pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control, appears to offer an advantage over classical aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should not adopt a "false sense of security" with these systems. Manufacturers should be also aware of the need to establish new procedures addressing issues unique to these systems.

A) Maintenance

1. General

Isolator systems have a number of special maintenance requirements. While no isolator unit forms an absolute seal, very high integrity can be achieved in a well-designed unit. However, a leak in any of certain components of the system can constitute a significant breach of integrity. The integrity of gloves, half-suits, seams, gaskets, and seals require daily attention and a comprehensive preventative maintenance program. Replacement frequencies should be established in written procedures that require changing parts before they breakdown or degrade.

2. Glove Integrity

A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity. The choice of durable glove materials, coupled with a well-justified replacement frequency, are two aspects of good manufacturing practice that should be addressed. With every use, gloves should be visually evaluated for any macroscopic physical defect. Mechanical integrity tests should also be performed routinely. This attentive preventative maintenance program is necessary to prevent use of gloves lacking integrity that would place the sterile product at risk. When such a breach is discovered, the operation should be terminated.

Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly and the operator should also wear a second pair of thin gloves.

B) Design

1. Airflow

The design of an aseptic processing isolator normally employs unidirectional airflow that sweeps over and away from exposed sterile materials, avoiding any turbulence or stagnant airflow in the area of exposed sterilized materials, product, and container-closures. In most sound designs, air showers over the critical zone once, and then is systematically exhausted. Air handling systems should employ HEPA and/or ULPA filters in series.

2. Materials of Construction

As in any aseptic processing design, suitable materials should be chosen based on durability, as well as ease of cleaning and sterilization. For example, rigid wall construction incorporating stainless steel and glass materials is widely used.

3. Pressure Differential

Isolators that include an open exit portal represent a potential compromise in achieving complete physical separation from the external environment. A positive air pressure differential adequate to achieve this full separation should be employed and supported by qualification studies. Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from approximately 0.07" to 0.2" water gauge. The appropriate minimum pressure differential specification established by a firm will be dependent on the system's design and, when applicable, its exit port. Air balance between the isolator and other direct interfaces (e.g., dry heat tunnel) should also be qualified.

The positive pressure differential should be coupled with appropriate protection at the product egress point(s) in order to overcome the potential for ingress of any airborne particles from the external environment by induction. Induction can result from local turbulent flow causing air swirls or pressure waves that can push extraneous particles into the isolator. Local Class 100 protection at an opening can provide a further barrier to induction of outside air into the isolator.

4. Clean Area Classifications

The interior of the isolator should, at minimum, meet Class 100 standards. The classification of the environment surrounding the isolator should be based on the design of the product interfaces, such as transfer ports and discharge points, as well as the number of transfers into and out of the isolator. A Class 10,000 or Class 100,000 background is appropriate depending on isolator design and manufacturing situations. The area surrounding the isolator should be justified. An isolator should not be located in an unclassified room.

C) Transfer of Materials/Supplies

The ability to maintain integrity and sterility of an isolator is impacted by the design of transfer ports. Various adaptations, of differing capabilities, allow for the transfer of supplies into and out of the isolator.

1. Introduction:

> Multiple material transfers are generally made during the processing of a batch. Frequently, transfers are performed via direct interface with a decontaminating transfer isolator or dry heat depyrogenation tunnel with balanced airflow. Such provisions, if well designed, help ensure that microbiological ingress does not result from the introduction of supplies. Properly operated RTPs (rapid transfer ports) are also generally considered to be an effective transfer mechanism. The number of transfers should be kept to a minimum because the risk of ingress of contaminants increases with each successive material transfer.

Some transfer ports can have significant limitations, including marginal decontaminating capability (e.g., ultraviolet) or a design that would compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA-filtered laminar airflow cover in the area of such a port should be implemented.

2. Discharge:

Isolators often include a "mousehole" or other exit port through which product is discharged, opening the isolator to the outside environment. The mousehole represents a potential route of contamination. Sufficient overpressure should be supplied and monitored on a continuous basis at this location to ensure that isolation is maintained.

D) Decontamination

1. Surface Exposure

Written procedures for decontamination of the isolator should be established. The decontamination process should provide full exposure of all isolator surfaces to the chemical agent. For example, in order to facilitate contact with the sterilant, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle.

2. Efficacy

A decontamination method should be developed which renders the inner surfaces of the isolator free of viable microorganisms. Decontamination can be accomplished using a number of vaporized agents, although these agents possess limited capability to penetrate obstructed or covered surfaces. Process development and validation studies should include a thorough determination of cycle capability. The characteristics of these agents generally preclude the reliable use of statistical methods (e.g., fraction negative) to determine process lethality. An appropriate, quantified BI challenge should be placed on various materials and in many locations throughout the isolator, including difficult to reach areas. Cycles should be developed with an appropriate margin of extra kill to provide confidence in robustness of the decontamination processes. For most production applications, demonstration of a six-log reduction of the challenge BI is recommended.

The uniform distribution of the defined concentration of decontaminating agent should also be evaluated concurrent with these studies. Chemical indicators may also be useful as a qualitative tool to show that the decontaminating agent reached a given location.

3. Frequency

While isolators vary widely in design, their interior and content should be designed to be frequently decontaminated. If an isolator is to be used for multiple days between decontamination cycles, the frequency adopted should include a built-in safety margin

and be well justified. This frequency, established during validation studies, should be reevaluated and increased if production data indicate any deterioration of the microbiological quality of the isolator environment.

A breach of isolator integrity (e.g., power failure, glove/seam tear, other air leaks, valve failure, out of specification pressure) should lead to a decontamination cycle. Breaches of integrity should be investigated and any product that may have been impacted by the breach rejected.

E) Filling Line Sterilization

In order to ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile liquid stream should be sterilized. In addition, loose materials or equipment to be used within the isolator should be chosen based on their ability to withstand steam sterilization (or equivalent method). It is expected that any materials that can be subjected to a steam sterilization cycle will, in fact, be autoclaved.

F) Environmental Monitoring

An appropriate environmental monitoring program should be established which routinely ensures acceptable microbiological quality of air, surfaces, and gloves (or half-suits) as well as particulate levels, within the isolator. Air quality should be monitored periodically during each shift. As an example, the exit port should be monitored for particulates to detect any unusual results.

G) Personnel

While cleanroom apparel requirements are generally reduced, the contribution of human factor to contamination should not be overlooked. Isolation processes generally include periodic or even frequent use of one or more gloves for aseptic manipulations and handling of component transfers into and out of the isolator. Contaminated gloves can lead to product non-sterility. This concern is heightened because locations on gloves, sleeves, or half suits can be among the more difficult to reach places during surface sterilization. Meticulous aseptic technique standards must be observed (211.113).

APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY

Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. This manufacturing technology includes economies in container-closure processing and reduced human intervention, and is often used for filling and packaging of ophthalmics and, less frequently, for injectables. This section discusses some of the critical control points of this technology. Except where otherwise noted below, the aseptic processing standards discussed elsewhere in this document should be applied to Blow Fill Seal technology.

A) Equipment Design and Air Quality

A BFS machine operates by 1) heating a plastic polymer resin; 2) extruding it to form a parison (a tubular form of the hot resin); 3) cutting the parison with a high temperature knife; 4) moving the parison under the blow-fill needle (mandrel); 5) inflating it to the shape of the mold walls; 5) filling the formed container with the liquid product; 6) removing the mandrel; 7) sealing. Throughout this operation sterile-air is used, for example, to form the parison and inflate it prior to filling. In most operations, the three steps which pose greatest potential for exposure to particle contamination and/or surrounding air are those in which: the parison is cut; the parison is moved under the blow-fill mandrel; and the mandrel is removed (just prior to sealing).

BFS machinery and its surrounding barriers should be designed to prevent potential for extraneous contamination. As with any aseptic processing operation, it is critical that contact surfaces be sterile. A validated steam-in-place cycle should be used to sterilize the equipment path through which the product is conveyed. In addition, any other surface (e.g., above or nearby) that has potential to contaminate the sterile product needs to be sterile.

The classified environment surrounding BFS machinery should generally meet Class 10,000 standards, but special design provisions (e.g., isolation technology) can justify an alternate classification. HEPA-filtered or sterile air provided by membrane filters is necessary in the critical zone in which sterile product or materials are exposed (e.g., parison formation, container molding/filling steps). Air in the critical zone should meet Class 100 microbiological standards. A well-designed BFS system should also normally achieve Class 100 particulate levels.

Equipment design should incorporate specialized measures to reduce particulate levels. In contrast to non-pharmaceutical applications using BFS machinery, control of air quality (i.e., particulates) is critical for sterile drug product manufacture. Particles generated during the plastic extrusion, cutting, and sealing processes provide a potential means of transport for microorganisms into open containers prior to sealing. Provisions for carefully controlled airflow could protect the product by forcing generated particles outward while preventing any ingress from the adjacent environment. Furthermore, designs separating the filling zone from the surrounding environment are important in ensuring product protection. Barriers, pressure vacuums, microenvironments, and appropriately directed high velocities of sterile air have been found useful in preventing contamination (Ref. 13). Smoke studies and multi-location particulate data are vital when performing qualification studies to assess whether proper particulate control dynamics have been achieved throughout the critical area.

In addition to suitable design, an adequate preventative maintenance program should be established. For example, because of its potential to contaminate the sterile drug product, the integrity of the boiling system (e.g., mold plates, gaskets) should be carefully monitored and maintained.

B) Validation/Qualification

Advantages of BFS processing are known to include rapid container/closure processing and minimized interventions. However, a properly functioning process is necessary to realize these

advantages. Equipment qualification/requalification and personnel practices should be given special attention. Equipment sterilization, media fills, polymer sterilization, endotoxin removal, product-plastic compatibility, forming/sealing integrity, and unit weight variation are among the key issues that should be covered by validation/qualification studies.

Appropriate data should ensure that BFS containers are sterile and non-pyrogenic. This can generally be achieved by validating that time-temperature conditions of the extrusion process destroy the worst-case endotoxin load on the polymeric material.

The plastic polymer material chosen should be pharmaceutical grade, safe, pure, and pass USP criteria for plastics. Polymer suppliers should be qualified and monitored for raw material quality.

C) Batch Monitoring and Control

In-process monitoring should include various control parameters (e.g., container weight variation, fill weight, leakers, air pressure, etc.) to ensure ongoing process control. Environmental monitoring is particularly important. Samples should be taken during each shift at specified locations under dynamic conditions. Due to the generation of high levels of particles near the exposed drug product, continuous monitoring of particles can provide valuable data relative to the control of a blow-fill-seal operation.

Container-closure defects can be a major problem in control of a BFS operation. It is necessary for the operation to be designed and set-up to uniformly manufacture leak-proof units. As a final measure, inspection of each unit of a batch should employ a reliable, sensitive final product examination capable of detecting a defective unit (e.g., "leakers"). Significant defects due to heat or mechanical problems, such as mold thickness, container/closure interface deficiencies, poorly formed closure, or other deviations should be investigated in accord with Sections 211.100 and 211.192.

APPENDIX 3: PROCESSING PRIOR TO FILLING/SEALING OPERATIONS

The purpose of this appendix is to supplement the guidance provided in this document with information on products regulated by CBER or CDER that are subject to aseptic processing from early in the manufacturing process, or that require aseptic processing through the entire manufacturing process, due to their inability to be sterilized. The scope of this appendix includes aseptic processing activities that take place prior to the filling and sealing of the finished drug product. Special considerations include those for:

A) Aseptic processing from early manufacturing steps

Due to their nature, some products undergo aseptic processing at some or all manufacturing steps preceding the final product closing step. There is a point in the process after which a product can no longer be rendered sterile by filtration, and the product is handled aseptically in all subsequent steps. Some products are formulated aseptically because the formulated product cannot be

sterilized by filtration. For example, products containing aluminum adjuvant are formulated aseptically because once they are alum adsorbed, they cannot be sterile filtered.

When a product is processed aseptically from early steps, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages are carefully controlled at each step of the process to maintain sterility of the product.

Procedures that expose the product or product contact equipment surfaces to the environment, such as aseptic connections, should be performed under unidirectional airflow in a Class 100 environment. The environment of the room surrounding the Class 100 environment should be class 10,000 or better. Microbiological and particulate monitoring should be performed during operations. Microbial surface monitoring should be performed at the end of operations, but prior to cleaning. Personnel monitoring should be performed in association with operations.

Process simulation studies should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product during manufacturing. The process simulation, from early process steps, should demonstrate that controls over the process are adequate to protect the product during manufacturing. These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment. The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators. However, process simulations do not need to mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.

It is also important that process simulations incorporate storage of product or transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of bulk tanks or other containers should be simulated as part of the media fill. Please refer to Section IX.A for more guidance on media simulation studies. Process simulation studies for the formulation stage should be performed at least twice per year.

B) Aseptic processing of cell-based therapy products (or of products intended for use as cell based therapies)

Cell-based therapy products represent a subset of the products for which aseptic manipulations are used throughout the process. Where possible, closed systems should be used during production. Cell-based therapy products often have short processing times at each manufacturing stage, even for the final product. Often, it is appropriate for these products to be administered to patients before final product sterility testing results are available. In situations where results of final sterility testing are not available before the product is administered, additional controls and testing should be considered. For example, additional sterility tests can be performed at intermediate stages of manufacture, especially after the last manipulation of the product prior to administration. Other tests that may indicate microbial contamination, such as microscopic examination, gram stains, and endotoxin testing should be performed prior to product release.

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RELEVANT GUIDANCE DOCUMENTS

Some relevant FDA guidances include:

- Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Product, 1994
- Guideline for Validation of Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices, 1987
- Guide to Inspections of Lyophilization of Parenterals, 1993
- Guide to Inspections of High Purity Water Systems, 1993
- Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories, 1993
- Guide To Inspections of Sterile Drug Substance Manufacturers, 1994
- Pyrogens: Still a Danger; 1979 (Inspection Technical Guide)
- Bacterial Endotoxins/Pyrogens; 1985 (Inspection Technical Guide)
- Heat Exchangers to Avoid Contamination; 1979 (Inspection Technical Guide)

For more information on FDA guidance, see our website at www.fda.gov.

DRAFT GLOSSARY

Air lock- A small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.

Alert Limit- An established microbial or particulate level giving early warning of potential drift from normal operating conditions and which trigger appropriate scrutiny and follow-up to address the potential problem. Alert Limits are always lower than Action Limits.

Action Limit- An established microbial or particulate level which when exceeded should trigger appropriate investigation and corrective action based on the investigation.

Aseptic Processing Facility- Building containing cleanrooms in which air supply, materials, and equipment are regulated to control microbial and particulate contamination.

Aseptic Processing Room- A room in which one or more aseptic activities or processes is performed.

Asepsis- State of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product.

Bioburden- Total number of microorganisms associated with a specific item prior to sterilization.

Barrier- Physical partition that affords aseptic manufacturing zone protection by partially separating it from the surrounding area.

Biological Indicator (BI)- A population of microorganisms inoculated onto a suitable medium (e.g., solution, container/closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The challenge microorganism is selected based upon its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.

Clean Area- An area with defined particulate and microbiological cleanliness standards (e.g., Class 100, Class 10,000 or Class 100,000).

Cleanroom- A room designed, maintained, and controlled to prevent particulate and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

Clean Zone- See Clean Area.

Component- Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.

Colony Forming Unit (CFU)- A microbiological term which describes the formation of a single macroscopic colony after the introduction of one (or more) microorganism(s) to microbiological growth media. One colony forming unit is expressed as 1 CFU.

Critical areas - Areas designed to maintain sterility of sterile materials. Sterilized product, container/closures, and equipment may be exposed in critical areas.

Critical surfaces - Surfaces which may come into contact with or directly impact on sterilized product or containers/closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation and sterility is maintained throughout processing.

Decontamination- A process which eliminates viable bioburden via use of sporicidal chemical agents.

Depyrogenation- A process used to destroy or remove pyrogens (e.g., endotoxin).

D value - The time (in minutes) of exposure to a given temperature that causes a one-log or 90% reduction in the population of a specific microorganism.

Dynamic- Conditions relating to clean area classification under conditions of normal production.

Endotoxin- A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.

Gowning Qualification- Program which establishes, both initially and on a periodic basis, the capability of an individual to don the complete sterile gown in an aseptic manner.

HEPA filter- High Efficiency Particulate Air filter with minimum 0.3 micron particle retaining efficiency of 99.97%.

HVAC- Heating, Ventilation, and Air Conditioning.

Intervention- An aseptic manipulation or activity that occurs at the critical zone.

Isolator - A decontaminated unit, supplied with HEPA or ULPA filtered air, which provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding clean room air and personnel).

Laminarity- Unidirectional air flow at a velocity sufficient to uniformly sweep particulate matter away from a critical processing or testing area.

Operator- Any individual participating in the aseptic processing operation, including line set-up, filler, maintenance, or other personnel associated with aseptic line activities.

Overkill sterilization process - A process that is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1 minute.

Pyrogen- Substance which induces a febrile reaction in a patient.

Sterilizing grade filter- A filter which, when appropriately validated, will remove all microorganisms from a fluid stream, producing a sterile effluent.

Terminal sterilization- The application of a lethal agent to sealed, finished drug products for the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10^{-6} (i.e., a probability of a non-sterile unit of greater than one in a million).

ULPA filter- Ultra-Low Penetration Air filter with minimum 0.3 micron particle retaining efficiency of 99.999 %.

Validation- Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Worst case- A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

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以降 P.335-P.341は雑誌/図書等に掲載された論文となりますので、「研究成果の刊行に関する一覧表」をご参照ください。

「研究成果の刊行に関する一覧表」

培地充てん試験法の許容値と充てん本数および製品品質保証レベル
川村邦夫, 阿部寛
PDA J GMP Validation Japan. Vol. 4 No. 2, Page134-140(2000)

資料 9

生物由来医薬品のGMP対応

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目　　次

1.原　則（前提条件）

1-1GMPの原則とは何か

GMP三原則

(1) Keep it clean.（清潔が第一）
(2) Check and double check.（確認は、念には念を）
(3) Write it down - keep good record.
（書くことから、記録は始まる）（c-GMP草案）

GMPの根拠となる品質保証の概念

(1) 品質、有効性、安全性を設計し、製品に作り込まなければならない。
(2) 最終製品を試験検査するだけでは、品質を保証することは出来ない。
(3) 製造工程を各段階毎に管理し、目的とする品質を有する最終製品が製造出来る見込みを得ることを検証しなければならない。（C-GMP）

三原則を実現するための工夫

(1) Keep it clean.（清潔が第一）とはどの様なことか？

○ 微生物汚染のない清潔な環境で医薬品を製造する。
○ 5S（整理・整頓・清掃・清潔・躾）を実行する。
○ 作業を行う前に実技と知識について、教育訓練を行う必要がある。
○ 内容医薬品が環境に暴露されている作業は、清浄な環境で行う。
○ 他の原料・医薬品と交叉汚染や混同のない環境で医薬品を製造する。
○ 洗浄しやすい設備が最も望ましい。洗浄しにくいといい加減になる。
○ 汚染されたものをそのまま放置すると後でまずいことが起きる。

(2) Check and double check.（確認は、念には念を）とは何か？

○ 製造作業を秤量、調製、充てん閉そく、包装表示に区分する。
○ 人は同時に２つのことを行うと何時か必ずミスをする。
● 人の記憶は時間の経過とともにあやふやになる。　＊（3）と共通
○ 指示事項からの逸脱があれば、原因を調査し、記録を残す。
○ 作業で、何かまずい事が起こったら、必ず責任者に報告する。
○ 医薬品の品質保証を確実に行うために、品質ユニット（品質保証部門）の照査が必要である。
○ 医薬品の品質に重大な影響を及ぼす要因については、Zero Defect（6∂：6シグマ）管理を行う。
○ 設備・計測器を定期的に点検しないと品質保証面で事故が起きる。

(3) Write it down - keep good record.
（書くことから、記録は始まる）とは何か？

○ 過去の事故例を教訓として、同じ過ちを繰り返さないように管理基準を設けルール化しておく。
○ ロット番号は、カルテに記載されるので、使用した原料と製造記録、試験記録及び工程管理記録を調査来るように確実に保存する。
○ GXP基準（ICH）を遵守し、定められた通りの手順で作業を行い、その結果を確実に記録する。（説明責任：PL／FOI）

GMPの根拠となる品質保証の概念とは何か？

○ 開発段階で約束したと同じ品質の医薬品を製造する。
（コンプライアンス；法令の遵守）

○ 技術検討・設備検討とバリデーションは別のプログラムで実施する。

○ 設備の適格性の確認後、プロセスバリデーションを実施する。

○ バリデーションは、製造工程、製造を支援するシステム、洗浄等の作業に区分して実施する。

○ 設備・作業条件を変更する場合、品質が変わらないことをあらゆる角度で確認する。

1-2 GMP上実施すべきことの明確化

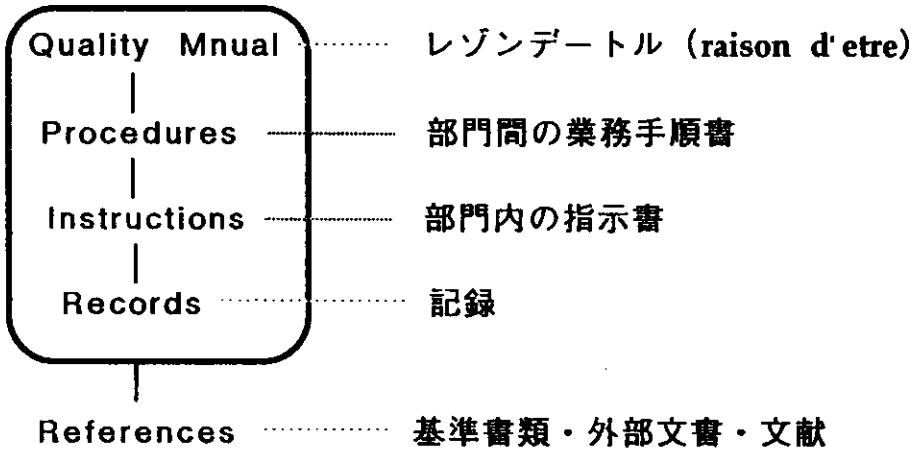
最低限必要な事項は何か？

1）交叉汚染の管理
2）設備・計測機器の管理
3）品質試験管理
4）変更時の記録
5）文書化（情報と記録の管理）
6）ロットの承認

（ICH-APIGMP：i-GMP）

1-3文書化 ---- SOPの作成手順

ア　文書・記録の体系図



留意点：組織の大きさにより、いくつかの手順書体系が必要となる。
例えば、GXP基準（GLP、GCP、GMP、GPMSP）毎に作成する。
記録は、様式（テンプレート）を作成する。
実例（モック）を作成する。
Q&Aを作成する。

イGMPにおける文書・記録の分類例

1.区分

生産管理（Production）、品質管理（Quality control）、
品質管理(Quality Management、Quality Assurance)

2.文書名

Quality Mnual	GMP品質マニュアル
Procedures	製品標準書（原薬、製剤の品目毎に作成する） 製造管理基準書 （原薬、製剤の製造場所毎に作成する） 製造衛生管理基準書（作業内容毎に作成する) 品質管理基準書（製造所毎に作成する） バリデーション、苦情処理、回収処理、自己点検、教育訓練、変更管理、出荷判定 （企業毎に作成する）
Instructions	マスター製造指図書 作業指導書 （設備の取り扱い方、薬品の取り扱い方）
Records	
Documentation	報告書 変更管理報告書、自己点検報告書、 教育訓練報告書、逸脱管理報告書
Statement	設定理由書 標準的仕込み量 試験法の真度、精度、サンプリング法の根拠
Raw data	生データ 設備の定期点検記録、原料の出納記録、 ロット製造記録、安定性試験記録
Complete record	（試験検体のサンプリングから試験実施結果を得るまでの全ての記録） 機器のチャート、サンプリング記録、検体受け渡し記録、試験実施時のデータシート、 試験機器点検・校正の記録、 標準品・試液試薬の記録、

註：1）全ての業務の開始に先だって事前に作成することが不可欠な文書
Quality Mnual、 Procedures

2）経緯、目的、検討内容と結果、考察、結論について詳細な記載が必要な文書
Documentation

3）設定理由が必要とされている文書
Statement