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Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding high-risk level CSPs. This test is completed without interruption in the following sequence:

1. Dissolve 3 g of nonsterile commercially available Soybean–Casein Digest Medium in 100 mL of nonbacteriostatic water to make a 3% solution.
2. Draw 25 mL of the medium into each of three 30-mL sterile syringes. Transfer 5 mL from each syringe into separate sterile 10-mL vials. These vials are the controls, and they generate exponential microbial growth, indicated by visible turbidity upon incubation.
3. Under aseptic conditions and using aseptic techniques, affix a sterile 0.2-µm porosity filter unit and a 20-gauge needle to each syringe. Inject the next 10 mL from each syringe into three separate 10-mL sterile vials. Repeat the process into three more vials. Label all vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 25° to 35°. Inspect for microbial growth over 14 days as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

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LIMITACIONES:

• No reproduce procesos complejos que frecuentemente se realizan en hospitales. (uso de trasvasadores, llenado de infusores, bombas ….)

• Equivalencia niveles de riesgo USP y GBPP

• No valora técnicas de protección del manipulador (no válido para citotóxicos)

Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding

LAWRENCE A. TRISSEL, JOSEPH A. GENTEMPO, ROGER W. ANDERSON, AND JOEL D. LAJEUNESSE

For at least a dozen years, pharmacists who compound sterile preparations have had guidance from national organizations on quality assurance for the safe compounding of these preparations. The American Society of Health-System Pharmacists (ASHP) and the United States Pharmacopeia (USP) provide a framework for quality assurance and assessment that offers minimum standards that patients have a right to expect of those who prepare their sterile medications.[1,2] USP recently issued a new standard on the compounding of sterile preparations, chapter 797,[3] that was developed from the previous chapter (1206) and is enforceable by regulatory entities.

Purpose. The estimated microbial contamination rate for complex, multiple-step, medium-risk-level compounding was studied.

Methods. The results of evaluations of the aseptic technique of pharmacists and technicians in compounding complex USP medium-risk-level sterile preparations were compiled to estimate the microbial contamination rate. The testing took place in 2002 and 2003 at a single institution and involved reconstitution of sterile dry growth medium and a series of complicated transfers of the medium from vials and ampuls to intravenous bags. The bags were incubated at 25–35 °C for 14 days and observed for microbial growth.

Results. Of 539 evaluations, 28 (5.2%) resulted in preparations that yielded microbial growth. Pharmacists' compounding resulted in a slightly lower contamination rate (4.4%) than that of technicians (6.2%). Inadvertent touch contamination may have been the principal source of the contamination.

Conclusion. A two-year series of 539 evaluations of the aseptic technique of pharmacists and technicians conducted with sterile growth medium and designed to simulate the compounding of USP medium-risk-level sterile preparations yielded an overall contamination rate of 5.2%.

Index terms: Compounding; Contamination; Drugs; Injections; Methodology; Personnel, pharmacy; Pharmacists; Stability; Sterile products; Storage

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Appendix—Procedure for testing medium-risk-level aseptic technique

1. Using a 30-mL syringe and an 18-gauge needle, reconstitute a vial of dry sterile Trypticase soy growth medium (vial 1) with 20 mL of sterile water for injection.
2. Using a 60-mL syringe and an 18-gauge needle, transfer 50 mL of sterile water for injection from a 50-mL vial into a sterile empty 150-mL Viaflex bag.
3. Insert a dispensing pin into a 30-mL vial of sterile liquid Trypticase soy growth medium (vial 2). Using a 10-mL syringe, withdraw 5 mL of growth medium through the dispensing pin. Attach an 18-gauge needle to the syringe, and transfer the growth medium into the Viaflex bag.
4. Using a 10-mL syringe and an 18-gauge needle, withdraw 5 mL of sterile growth medium from the reconstituted vial 1, and transfer it into the Viaflex bag.
5. Using a 20-mL syringe and an 18-gauge needle, withdraw 10 mL of sterile growth medium from a 10-mL vial (vial 3), and transfer it into the Viaflex bag.
6. Using a 10-mL syringe, make a second withdrawal of 5 mL of sterile Trypticase soy growth medium from vial 2 through the dispensing pin. Attach an 18-gauge needle to the syringe, and transfer the growth medium into the Viaflex bag.
7. Using a 10-mL syringe and an 18-gauge needle, make a second withdrawal of 5 mL from the reconstituted vial 1, and transfer it into the Viaflex bag.
8. Carefully open a 10-mL ampul of sterile Trypticase soy growth medium. Using a 20-mL syringe and a 5-µm filter straw, withdraw 10 mL of sterile Trypticase soy growth medium from the ampul. Remove the filter straw, and replace it with an 18-gauge needle. Transfer the growth medium into the Viaflex bag.
9. Using a 10-mL syringe, make a third withdrawal of 5 mL of sterile Trypticase soy agar from vial 2 through the dispensing pin. Attach an 18-gauge needle to the syringe, and transfer the growth medium into the Viaflex bag.
10. Using a 10-mL syringe and an 18-gauge needle, make a third withdrawal of 5 mL from the reconstituted vial 1, and transfer it into the Viaflex bag.
11. Label the bag, incubate it at 25–35 °C for 14 days, and observe the content for cloudy turbidity or discrete colonies that indicate microbial growth.

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4. PROCESS SIMULATION TEST PROCEDURES

4.1 General Comments

4.1.1 The media fill should emulate the regular product fill situation in terms of equipment, processes, personnel involved and time taken for filling as well as for holding.

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5.2 Selection of Growth Medium

5.2.1 The criteria for the selection of growth medium include: low selectivity, clarity, medium concentration and filterability.

5.2.2 *Ability to support growth of a wide range of microorganisms:* The medium should have a low selectivity i.e. be capable of supporting growth of a wide range of microorganisms such as Bacillus subtilis, Staphylococcus aureus, Candida albicans, Aspergillus niger and Clostridium sporogenes (e.g. Soybean Casein Digest).

5.2.3 The selection of the medium has to be based also on the in house flora (e.g. isolates from monitoring etc.).

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5.3 Incubation Conditions

5.3.1 It is generally accepted to incubate at 20-25°C for a minimum of 7 days followed immediately, or after a first reading, by incubation at 30-35°C for a total minimum incubation time of 14 days. Other incubation schedules should be based on supporting validation data.

	procesos a validar	PROCESOS IMPLICADOS		pasos del test
a	Limpieza caucho viales	a	1	Desinfectar el tapón de caucho del vial
b	Transferencia de vial a jeringa	b (ó f) y h	2	Coger dos jeringas de 10 ml de medio de cultivo (a y b) y taponar una (b y c)
c	Transferencia de jeringa a vial	d	3	Transferir la jeringa a a otra jeringa de 20 ml a través del cono. (jeringa c)
d	Transferencia de jeringa a jeringa	b y f	4	Tomar 10 ml de una ampolla de SF y transferirlo por el cono a la jeringa c y homogeneizar.
e	Transferencia de vial a vial.	c	5	Transferir el contenido de la jeringa c al vial/bolsa de vacio.
f	Transferencia del contenido de una ampolla (podría no ser de medio)	g	6	Reconstituir un vial de vitaminas con la jeringa b Transferirlo con la misma jeringa al vial/bolsa vacio
g	Transferencia y reconstitución de un liofilizado (podría no ser medio sino un f.co no ab)	e	7	Completar el vial/bolsa hasta 100 ml con SF por medio de un sistema de transferencia, y homogeneizar.
h	Uso de tapones de jeringa	i y j	8	Transferir 10 ml del vial/bolsa a un vial vacio de 10 ml por medio de un filtro de 5 micras. Cerrar y etiquetar para mandar a analizar
i	Filtración "esterilizante"	i y j	9	Transferir 10 ml del vial/bolsa a un frasco de colirio vacio por medio de un filtro de 5 micras. Cerrar y etiquetar para mandar a analizar
j	Transferencia desde vial a sistema abierto (vial o frasco de colirio)			

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ELABORACION DE UN PROCEDIMIENTO DE VALIDACION DE MANIPULADORES DE MEDICAMENTOS ESTERILES USANDO MEDIOS DE CULTIVO LIQUIDOS, SIGUIENDO LAS RECOMENDACIONES PARA LA VALIDACION DE LOS PROCESOS ASEPTICOS DE LA PHARMACEUTICAL INSPECTION CONVENTION 2009

ALONSO JM, TRUJILLANO A; GARCIA-MOLINA C; RENTERO L
Hospital General Universitario Reina Sofía (Murcia)

Introducción

Elaborar un procedimiento de validación de manipuladores de medicamentos estériles, que cubra los niveles exigibles a las preparaciones que se realizan en un servicio de farmacia hospitalaria.

Material y Métodos

•1 - Revisión bibliográfica de los procedimientos descritos y de las recomendaciones para realizarlos de sociedades y organismos internacionales.
•2 – Puesta a punto del procedimiento.
•3 – Aplicación del mismo en un curso de manipuladores.

Resultados

• La Pharmaceutical Inspection Convention (PIC/s) editó una recomendaciones para la validación de procesos asépticos en 2009, en las que recomendaban emular la situación que se pretende validar en términos de equipos, procesos, personal implicado y tiempo empleado.
• En cuanto a la selección del medio de cultivo recomiendan uno de baja selectividad, claro, filtrable, y a su vez adecuado para la flora detectada a nivel local.
• Para emular de forma general la elaboración de estériles en un servicio de farmacia, se analizaron todos los procesos implicados habitualmente y se diseñó un procedimiento con medios de cultivo que reprodujesen todos estos procesos.

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http://www.ffis.es/Formateca/verVideos.jsp?id=17

Curso_farmacia.mp4

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Pharmacy Compounding-USP <797> Risk Level Assessment

Classification	Requirements	Yes	No
Low-Risk Compounding	■ Simple admixtures compounded using closed system transfer methods ■ Prepared in International Organization for Standardization (ISO) Class 5 (Class 100) laminar airflow workbench (hood) ■ Located in ISO Class 8 (Class 100,000) buffer room (Cleanroom) with ante area ■ Examples include reconstitution of single-dose vials of antibiotics or other small-volume parenterals (SVPs), preparation of hydration solutions		
Medium-Risk Compounding	■ Admixtures compounded using multiple additives and/or small volumes ■ Batch preparations (e.g. syringes) ■ Complex manipulations (e.g. TPN) ■ Preparation for use over several days ■ Prepared in ISO Class 5 (Class 100) ■ Located in ISO Class 8 (Class 100,000) Cleanroom with ante area ■ Examples include pooled admixtures, parenteral nutrition solutions using automated compounders, batch-compounded preparations that do not contain bacteriostatic components		
High-Risk Compounding	■ Non-sterile (bulk powders) ingredients ■ Open system transfers ■ Prepared in ISO Class 5 (Class 100) ■ Located in ISO Class 8 (Class 100,000) Cleanroom with separate ante area ■ Examples include CSPs prepared from bulk, nonsterile components (morphine or other narcotics) or final containers that are nonsterile and must be terminally-sterilized (nuclear pharmaceuticals)		

Table 3

USP <797> Quality Domains	Impact to CSP Quality	Relative Cost
Verification Processes		
Sterility Testing	+++	$$$
Environmental Monitoring	++++	$$
Personnel Training and Education	++++	$$

Personnel Training and Evaluation in Aseptic Manipulation Skills

It is important to realize that many pharmacists and technicians have little or no didactic training in the area of sterile compounding. This section of the chapter requires that all personnel be properly trained by the following means:

- Prior to commencing any compounding, perform thorough didactic instruction in the theory and practice of sterile preparations, with evaluation of technique annually (for low- and medium-risk level) and semiannually (for high-risk level)
- Compounder evaluations should include a formal written exam and practical evaluation of aseptic technique using growth media (media fills)

Soybean–Casein Digest Medium are aseptically transferred by gravity through separate tubing sets into separate evacuated sterile containers. The six containers are then arranged as three pairs, and a sterile 10-mL syringe and 18-gauge needle combination is used to exchange two 5-mL aliquots of medium from one container to the other container in the pair. For example, after a 5-mL aliquot from the first container is added to the second container in the pair, the second container is agitated for 10 seconds, then a 5-mL aliquot is removed and returned to the first container in the pair. The first container is then agitated for 10 seconds, and the next 5-mL aliquot is transferred from it back to the second container in the pair. Following the two 5-mL aliquot exchanges in each pair of containers, a 5-mL aliquot of medium from each container is aseptically injected into a sealed empty sterile 10-mL clear vial using a sterile 10-mL syringe and vented needle. Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

High-Risk Level CSPs

CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated with infectious microorganisms.

High-Risk Conditions—

1. Nonsterile ingredients, including manufactured products for routes of administration—other than those listed under c. in the

Quality Assurance—Quality assurance procedures for high-risk level CSPs include all those for low-risk level CSPs. In addition, a media-fill test that represents high-risk level compounding is performed semi-annually by each person authorized to compound high-risk level CSPs.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding high-risk level CSPs. This test is completed without interruption in the following sequence:

1. Dissolve 3 g of nonsterile commercially available Soybean–Casein Digest Medium in 100 mL of nonbacteriostatic water to make a 3% solution.
2. Draw 25 mL of the medium into each of three 30-mL sterile syringes. Transfer 5 mL from each syringe into separate sterile 10-mL vials. These vials are the controls, and they generate exponential microbial growth, indicated by visible turbidity upon incubation.
3. Under aseptic conditions and using aseptic techniques, affix a sterile 0.2-µm porosity filter unit and a 20-gauge needle to each syringe. Inject the next 10 mL from each syringe into three separate 10-mL sterile vials. Repeat the process into three more vials. Label all vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 25° to 35°. Inspect for microbial growth over 14 days as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

SIMULACIÓN CON MEDIOS DE CULTIVOS

Introduction—are incorporated or a nonsterile device is employed before terminal sterilization.

2. Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see *Table 1*). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
3. Nonsterile preparations are exposed for at least 6 hours before being sterilized.
4. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients (see *Ingredient Selection* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).
5. For a high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 3 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.

All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk CSP solutions subjected to terminal steam sterilization are passed through a filter with a nominal porosity not larger than 1.2 µm preceding or during filling into their final containers. Sterilization of high-risk level CSPs by filtration is conducted entirely with an ISO Class 5 or superior air quality environment (see *Table 1*).

Examples of High-Risk Compounding—

1. Dissolving nonsterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized.
2. Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see *Table 1*). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
3. Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.
4. Assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95% by weight of their active chemical moiety and have not been contaminated or adulterated between uses.

VERIFICATION OF COMPOUN ACCURACY AND STERILIZAT

The compounding procedures and sterilization m correspond to correctly designed and verified writte in the compounding facility. Verification requires designed to demonstrate effectiveness of all procedu accuracy and purity of finished CSPs. For example (see *Test for Sterility of the Product to be Examine Tests* ⟨71⟩) may be applied to specimens of low- a CSPs, and standard nonpathogenic bacterial cultures nondispensable specimens of high-risk CSPs sterilization for subsequent evaluation by sterility t and labeled CSPs are visually inspected for physi expected appearance, including final fill amount. T identities and concentrations of ingredients are acc absence of reliable observations and data to confirm those parameters, samples of CSPs are assayed.

Sterilization Methods

The licensed health care professionals who supe ing are responsible for determining that the sele method (see *Methods of Sterilization* under *Steriliza Assurance of Compendial Articles* ⟨1211⟩) bot maintains the strength, purity, quality, and packa CSPs. The selected sterilization process is expected and appropriate information sources—and, pre wherever possible—to achieve sterility in the General guidelines for matching CSPs and compone sterilization methods include the following:

1. CSPs have been ascertained to remain physicall stable when subjected to the selected sterilizat
2. Glass and metal devices may be covered tightl foil, then exposed to dry heat in an oven at a m of 250° for 2 hours to achieve sterility and dep *Dry-Heat Sterilization* under *Sterilization an ance of Compendial Articles* ⟨1211⟩). Such ite immediately or stored until use in an environ compounding low- and medium-risk CSPs.
3. Personnel ascertain from appropriate informa the sterile microporous membrane filter used solutions, either during compounding or a chemically and physically compatible with th

Photo courtesy of QI Medical

A positive test (center and right) can be caused by touch contamination or a compromised compounding environment, among other possible factors.

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Principles of media fill

- In aseptic processing, the greatest risk comes from the personnel working in the clean room: the operators have to participate in media fills

  Which qualifications to the operators need and when can operators be considered qualified?

- Environmental monitoring activities are required during aseptic filling operations

Are there additional monitoring activities necessary or not?

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■ Farmaindustria quiere que todo se limite a la ficha técnica y en vacío terapéutico

EDITORIAL / OPINIÓN /

Con la venia: La guía de los "expertos de reconocido prestigio"

e que se matice
de la guía de

EDITORIAL DE LA PRESIDENTA DE LA SEF

Mª Teresa Tejerina
Doctora en Medicina. Catedrática del Departamento de Farmacología de la Universidad Complutense de Madrid. Presidenta de la SEF.

¿Volvemos a las Fórmulas Magistrales? ahora Fórmulas Magistrales semi-industriales

Fórmula magistral: medicamento destinado a un paciente individualizado, preparado por un farmacéutico, o bajo su dirección, para cumplimentar expresamente una prescripción facultativa detallada de los principios activos que incluye, según las normas de correcta elaboración y control de calidad establecidas al efecto, dispensado en oficina de farmacia o servicio farmacéutico y con la debida información al usuario en los términos previstos en el artículo 42.5.

ue todo se limite a la ficha técnica y en