衛生福利部食品藥物管理署委辦計畫

「再生醫療製劑 GMP 評鑑符合性管理制度之推動與趨勢研析」

再生醫療製劑 GMP 訓練活動(3)、(4)

日　期　：民　國　108　年　5　月　28　日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講 師 資 料

林怡廷 經理/輝瑞生技股份有限公司 生產部
蘇文琳 博士/恩典科研股份有限公司 資深顧問

時 間 表

時 間	內 容	講 師
8:30-9:00	報 到	
9:00-9:10	長 官 致 詞	TFDA 風管組代表
9:10-10:30	潔淨室清潔與消毒作業 (一): 清潔/消毒方法的選用	輝瑞生技 林怡廷 經理
10:30-10:50	休 息	
10:50-12:10	潔淨室清潔與消毒作業 (二): 消毒劑的確效與效能試驗	輝瑞生技 林怡廷 經理
12:10-13:10	午 餐	
13:10-14:30	原物料管理(一): 美國藥典 vs. 歐洲藥典	恩典科研 蘇文琳 博士
14:30-14:50	休 息	
14:50-16:10	原物料管理(二): EU GMP Guideline 對 raw materials、starting materials 的要求	恩典科研 蘇文琳 博士
16:10-16:30	交流討論 / 課後評估	

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潔淨室清潔與消毒作業 (一): 清潔/消毒方法的選用

林怡廷
輝瑞生技股份有限公司

課程大綱

- 相關法規
- 潔淨室等級分類
- 基礎微生物
- 什麼是清潔與消毒
- 消毒劑的選擇
- 工具的選擇
- 清潔與消毒的原則
- 清潔與消毒的方法
- 清潔與消毒的頻率

相關法規

- PIC/S GMP Chapter 3
  - 廠房設施及設備的定位、設計、建造、調適及維護皆應適合於其所要執行的作業。其配置與設計應將產生錯誤的風險降到最低並容許有效的清潔及維護保養，以避免交叉污染、聚積粉塵或污垢，總之應以避免對產品品質有任何不利影響為目標。
  - 3.2 廠房設施應謹慎維護，以確保其修理及維護作業不會危害於產品品質。廠房應予清潔，適當時並依詳細的書面程序消毒之。
  - 3.9原料與直接包裝材料、半製品/中間產品或待分/包裝產品暴露的環境，其內部表面(牆壁、地板及天花板)應平滑、無裂縫及無開口接縫，且不得脫落微粒物質，並應容易且有效地清潔，如有必要，還可消毒。

相關法規

- PIC/S GMP:
  - 61.潔淨區的衛生處理特別重要，應依書面程序徹底清潔。使用消毒劑者，應採用一種以上的消毒劑。為了檢測抗藥性菌株的產生，應進行定期監測。
  - 62.消毒劑與清潔劑應監測其微生物的污染；稀釋液應保存在預先洗淨的容器中，且除非經過滅菌，應只在界定的期間內儲存。使用於A級及B級區的消毒劑與清潔劑，使用前應是無菌的。

清潔與消毒的目的

- 控制生產環境中的汙染源，維持良好的生產環境
- 需搭配汙染防治計畫，其中包含：
  - 完善的廠房設計和維護
  - 建立文件系統
  - 經過驗證的消毒程序
  - 可靠的製程控制
  - 良好的內務管理
  - 良好的人物流、權限管控
  - 有效的培訓，資格和評估計劃
  - 材料和設備的品質保證
  - 風險管理

潔淨室（Cleanroom）

- 一個被設計、維持與管制的房間以防止藥物產品被微粒子與微生物污染。此被指定的房間可一再地符合適當的清淨度分級

潔淨區域之空氣等級及微生物品質的建議行動水準摘要如下表

表 1 – 空氣等級[a]

潔淨區域等級(0.5μm微粒子數/立方呎)	ISO等級標準[b]	≥0.5μm微粒子數/立方公尺	浮游微生物行動水準[c] (cfu/立方公尺)	落菌培養皿微生物行動水準[c,d] (直徑 90mm; cfu/4小時)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

[a] 所有等級均係基於活動期間暴露之原物料/物品之鄰近區域的量測數據。

[b] ISO 14644-1 等級標準提供多類產業潔淨室之統一微粒子濃度值。ISO 5 級之微粒子濃度與 100 級相等，且與歐盟之 A 級近乎相等。

[c] 這些數值代表環境品質的建議水準。業者可以依作業的特性訂定適當的替代性微生物行動水準。

[d] 採用落菌培養皿試驗是一個選項。

[e] 正常情況下，100 級區(ISO 5 級區)環境之樣本應無微生物生長。

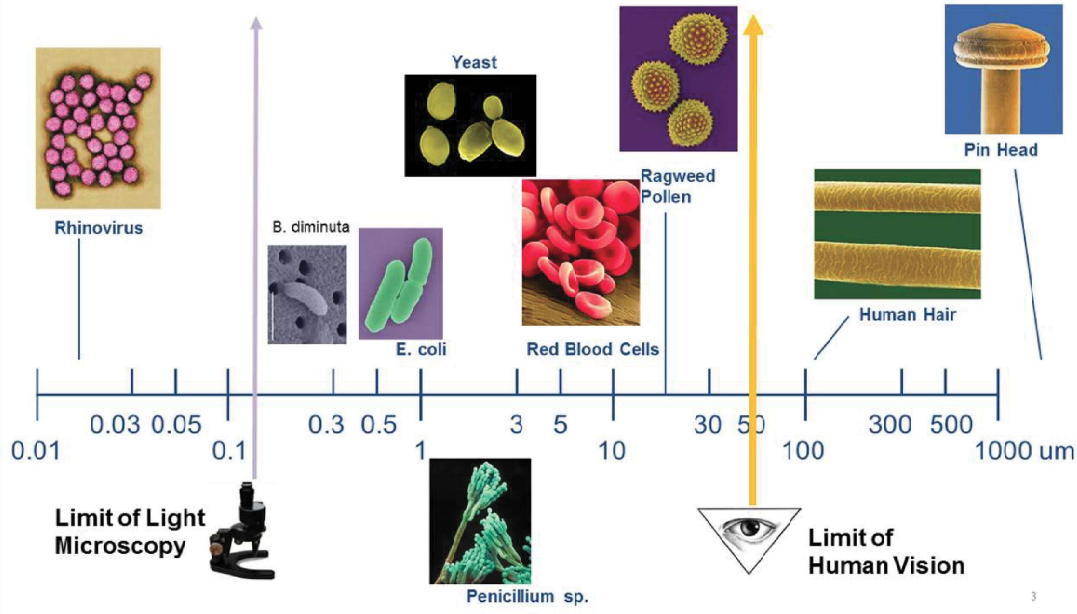
空氣等級(PIC/S)

等 級	每立方公尺等於或大於下述粒徑之微粒的最大容許量			
	靜態		動態	
	0.5 μm	5.0 μm	0.5 μm	5.0 μm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520 000	29,000
D	3,520,000	29,000	未界定	未界定

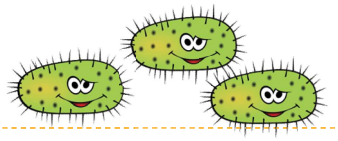
- **重要區域**(Critical area)**(100級區，ISO第5級區)**重要區域是指已滅菌藥物、容器、及封蓋所暴露的區域；為保持產品無菌，該區的環境條件必需加以特別設計。在此類區域內進行的活動，包括充填前、充填中、及封蓋作業中的無菌原物料操作(例如：無菌組裝、無菌有效成分之添加)。

什麼是微生物學?

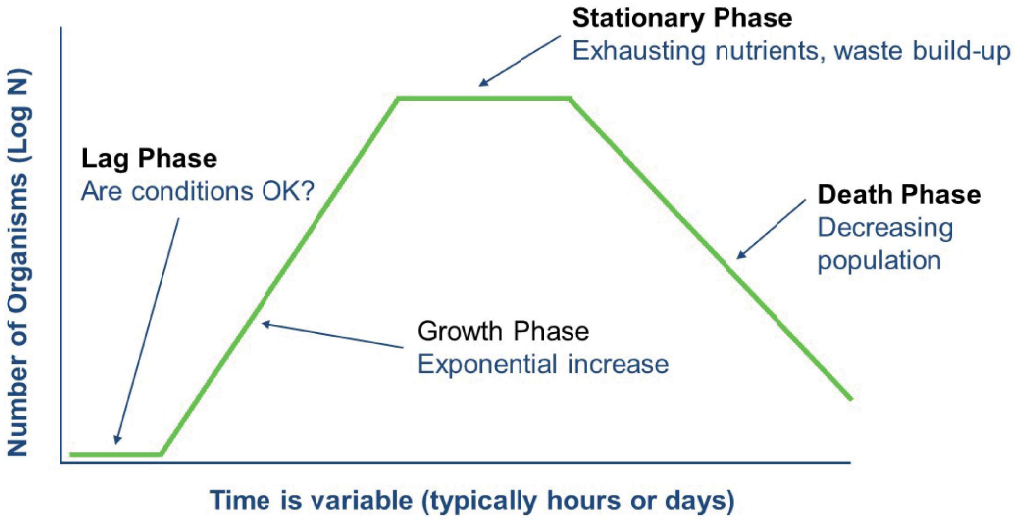
- 研究微小的生物/地球上最古老的生物



微生物如何移動?



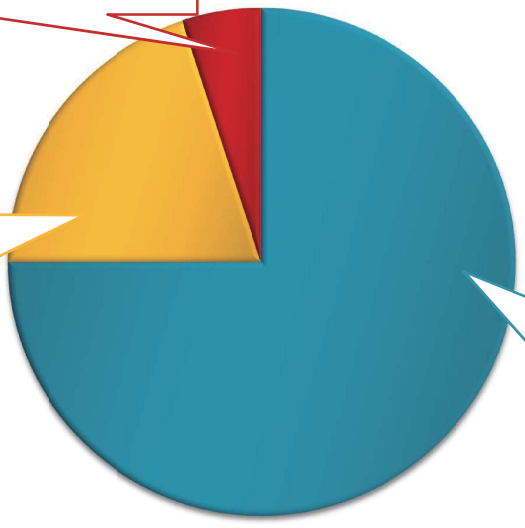
微生物生長週期



潔淨室中微生物的來源

5-10% water/liquid source
Gram negative rod Organisms such as *Pseudomonas* and *Acinetobactor* species

人是潔淨室最大的汙染源



15-20% air/soil source
Organisms such as large Gram positive rods, spore formers, Bacillus and fungi

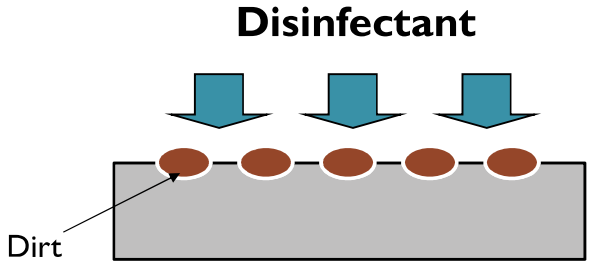
70+% People Organisms, such as, *Staphylococcus*, *Micrococcus* and *Propionibacterium* spp.

無菌生產的廠房設計

- 將無菌生產區與外界區隔來避免汙染的可能性
- 適當的級區進出管控能幫助降低產品微生物汙染風險

清潔 Cleaning

- 應用非破壞性的機械作用來鬆動和去除表面上的污垢，顆粒，微生物和殘留物
- 清潔可以讓後續的消毒更有效：
  - 大部分的微生物以從表面移除
  - 妨礙消毒劑與微生物作用的阻礙物被移除
  - 影響消毒劑有效性的物質被移除
  - 減少可能干擾未來消毒和/或乾燥或剝落並釋放到環境中的殘留物。



消毒 Disinfection

- 使用化學藥劑破壞微生物細胞壁
- 影響消毒劑有效性的因素：
  - 使用的有效成分
  - 空氣和表面溫度
  - 細胞壁的滲透
  - 接觸時間
  - 表面材料
  - 表面的生物負荷菌
  - 化學藥劑的濃度
  - pH值。

去汙染等級

消毒劑的選擇

- Sanitizers:
  - Alcohols (namely, isopropanol and ethanol) are chemicals agents that should be employed when disinfecting items that have been brought into the PA as they are quick to evaporate and leave minimal residue.
  - While alcohols have relatively good biocidal activity on vegetative cells, their rapid rate of evaporation significantly reduces their effectiveness. Alcohols have no effect on spores.

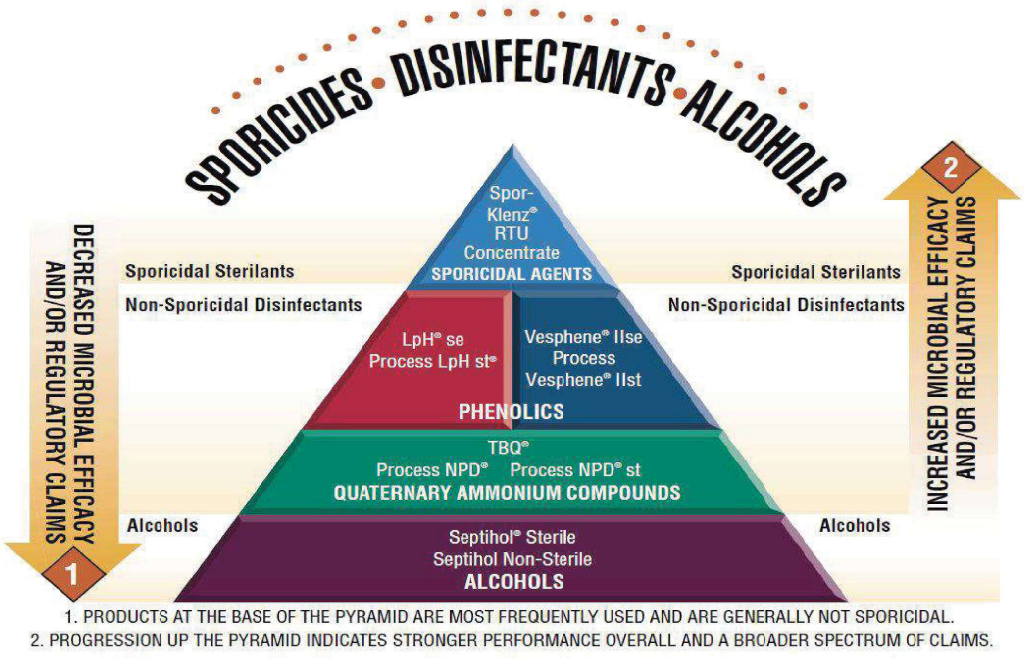
消毒劑的選擇

- Disinfectants:
  - Phenols and quaternary ammonia compounds provide broad-spectrum kill of vegetative cells. These chemicals characteristically leave residues on surfaces. Immediately following their use, such residues should be removed, for example, via IPA wipe-down.

消毒劑的選擇

- Sporicides:
  - Sodium hypochlorite (bleach) and hydrogen peroxide/peracetic acid compounds are widely used sporicidal agents. Hydrogen peroxide can also be used (normally at 6%) to provide activity against molds and some spore-forming organisms.
  - Peroxides are more active than alcohols and break down into water and oxygen, leaving no residue. Sporicidal chemicals should be employed when a disinfecting procedure requires the reduction of spore-forming organisms. Unfortunately, with the exception of hydrogen peroxide these chemicals leave some amount of residue.

消毒劑的選擇



消毒劑的選擇

Type	Examples	Effective Against		
		Bacteria	Fungi	Bacterial Spores
Alcohols	IPA 70%	√		
Phenolics Quats	LpH® Decon-Quat	√	√	
Halogens*	Sodium hypochlorite (Bleach)	√	√	√
Peroxides*	Spor-Klenz® Decon-Spore®	√	√	√

*These disinfectants are also considered sporicides because they can kill bacterial spores.

消毒劑的選擇

- 為確保消毒劑，消毒劑和殺菌劑不會成為污染源，應在A級區和鄰近B級區使用前對其進行無菌過濾或滅菌。

消毒劑的選擇

- 消毒劑的無菌處理：
  - 無菌過濾至A/B級區
  - 在A級區以無菌原料和無菌容器配製
  - 購買無菌等級的消毒劑
  - 配製後以濕熱滅菌釜滅菌

消毒劑的選擇

- 避免消毒劑/殺孢劑造成表面的劣化
  - 腐蝕 Corrosion：
    - 與金屬表面有關，可以採取生鏽或點蝕的形式。
    - 化學試劑對金屬中雜質的侵蝕。
    - 常見於含氯產品。
  - 與表面的化學不相容性 Chemical incompatibility ：
    - 當化學試劑與表面基材反應並且可能通過熔化，軟化或立即變色使表面劣化。
    - 當用於較軟和較低等級的金屬以及多孔和無孔基材時，可以用過乙酸和過氧化氫化合物看到化學試劑與基質的不相容性。

消毒劑的選擇

- 避免消毒劑/殺孢劑造成表面的劣化
  - 乾燥 Drying：
    - 表面基材的干燥可能發生在多孔和無孔軟基材上，如乙烯基，樹脂玻璃，Kydex，Mipolam和環氧樹脂
    - 當化學試劑進入孔隙或輕微瑕疵並過度乾燥表面時，會發生這種類型的劣化。。
  - 褪色或染色 Discoloring or staining：
    - 清潔劑中的染料污染表面。
    - 通常使用酚類或碘類可以看到染色或變色。

消毒劑的選擇

- 避免消毒劑/殺孢劑造成表面的劣化
  - 仔細評估化學試劑的活性和非活性成分
  - 定期去除可能導致表面變質的殘留物
  - 仔細評估藥劑的混合或表面殘留物的混合
  - 防止表面過度暴露於化學試劑

清潔與消毒的工具

拖把

拖把布

無塵布

水桶

清潔與消毒的工具

- 在A級區和相鄰的B級區域使用之前，應徹底清潔清潔設備並使其無菌。
- 清潔設備的滅菌可以通過蒸汽滅菌或使用無菌的一次性系統以及其他方法來實現。

清潔與消毒用具的選擇

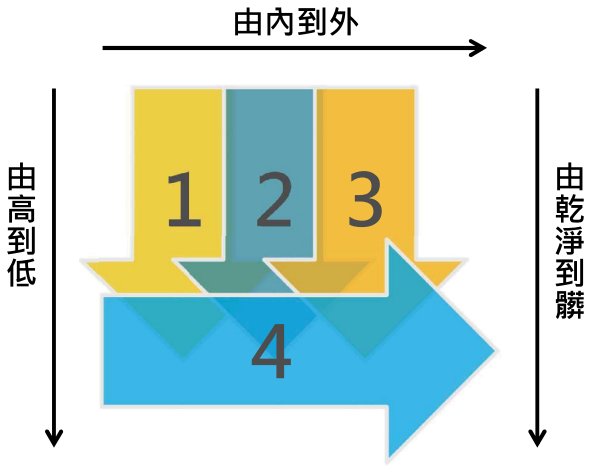
- 需依照潔淨室等級做選擇
- 是否可以被清潔、消毒或滅菌
- 是否會在去汙染過程中造成負面影響
- 是否會在不同級區之間移動

無菌清潔與消毒

- 維持潔淨室環境的重要性
- 不同等級的消毒劑用途
- 清潔用具的管理
- 清潔與消毒程序
  - 由上而下
  - 由內而外
  - 由乾淨到髒

清潔和消毒的原則

- 應建立無菌室清潔與消毒的頻率
- 應避免在清潔過程中造成污染



清潔與消毒的順序

由遠離出口的地方往出口清潔

清潔與消毒的方法

1. 使用無菌的清潔劑清潔
2. 移除表面多餘的液體和汙染物
3. 使用無菌的拖把、無塵布擦乾表面
4. 使用無菌的消毒劑消毒

- 無菌室、工作臺面和設備的清潔頻率取決於廠房的設計、潔淨室的等級、製程和相關的風險。

清潔與消毒的手法

- Spraying
  - 可讓清潔/消毒劑均勻分布在表面
  - 缺乏物理性動作來清潔表面
  - 高殘留性

清潔與消毒的手法

- Mopping
  - 物理性的清潔表面
  - 常用於清潔牆面和地板

清潔與消毒的手法

- Wiping
  - 以無塵布沾取清潔/消毒劑，擦拭表面
  - 物理性的清潔表面

清潔與消毒的手法

- Fogging or Gassing
  - 沒有清潔作用
  - 非常有效的消毒方法
  - 較長的作業時間和消毒劑作用時間
  - 可以消毒到設備死角

設備表面、工作表面的清潔與消毒

- 設備表面：非產品接觸的設備表面
- 工作表面：工作檯面、推車和前置作業區域
- 以消毒劑或殺孢劑消毒
- 須確認清潔/消毒劑、無塵布或清潔工具不會造成表面殘留
- 在消毒劑/殺孢劑的有效作用時間後，可以用70% IPA去除殘留

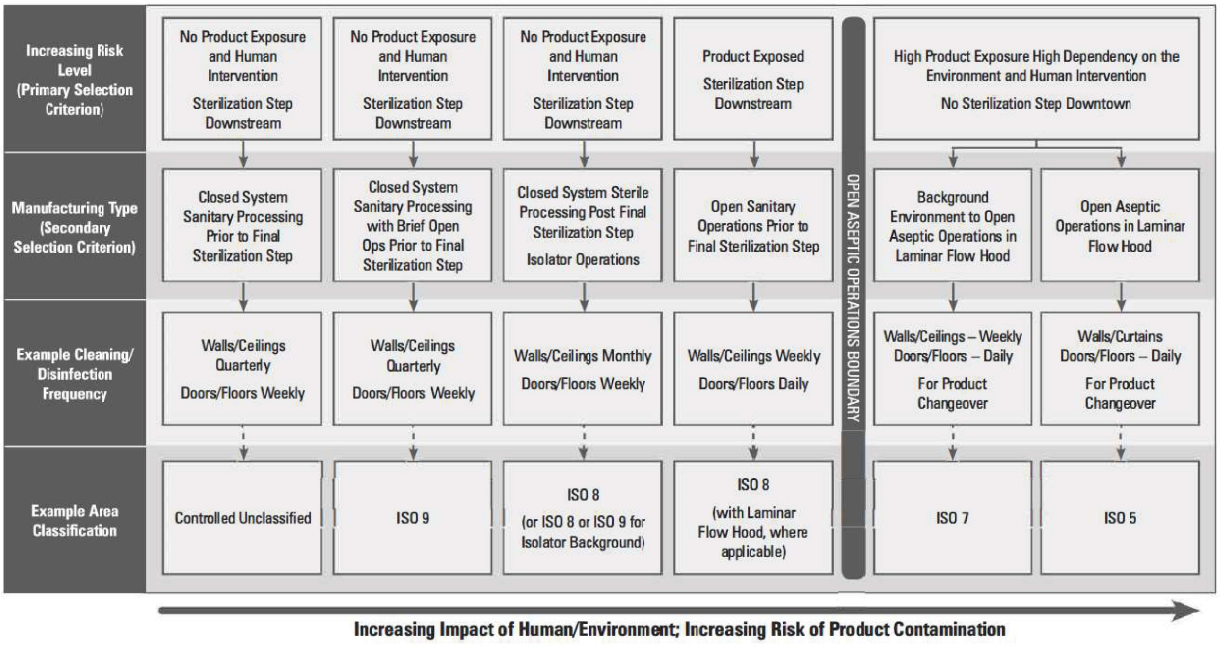
清潔與消毒的頻率

- 依據環境監測結果及/或風險評估來定義清潔/消毒的頻率
- 設備的清潔和消毒頻率取決於潔淨室等級以及環境和設備中污染的控制程度。
- 應對所有設備進行清潔，以確保表面沒有明顯粒子和殘留物。
- 表面消毒應確保將微生物含量降至可接受的表面監測水平以下

清潔與消毒的頻率

- 決定清潔與消毒頻率的方式：
  - 潔淨室等級：
    - 依照潔淨室等級定義清潔頻率，如：A級區每天清，C/D級區每周或每月清。
    - 未將產品汙染風險納入考量。
  - 環境監測數據：
    - 僅基於EM數據建立清潔和消毒頻率可導致程序隨時間不斷變化。
    - 基於持續令人滿意的環境監測結果降低已建立的清潔頻率。
  - 風險評估：
    - 該方法採用前兩種方法的要素，但也考慮了產品暴露於環境和人員的風險以及在分類區域中進行的製造類型。

以風險評估訂定清潔頻率



消毒劑的抗性與輪替

- USP <1702>:
  - The development of microbial resistance is less likely, as disinfectants are more powerful biocidal agents than antibiotics and are applied in high concentrations against low populations of microorganisms, so the selective pressure for the development of resistance is less profound.
- 消毒劑與殺孢子劑輪替使用，以更有效地降低環境負荷菌。

108TPDA04017

潔淨室清潔與消毒作業 (二): 消毒劑的確效與效能試驗

林怡廷
輝瑞生技股份有限公司

課程大綱

- 消毒劑的評估
- 消毒劑有效性驗證
  - In Suspension Study
  - Carrier Surface Study
  - In Situ Study
- 清潔與消毒相關缺失

消毒劑特性評估

- 被清潔物質的溶解度
- 能控制的微生物種類
- 能移除的汙染物種類
- 能應用的表面
- 容易使用
- 容易去除 (殘留的影響)
- 考量毒性和安全性
- 對產品的汙染
- 使用的級區



供應鏈

- 效期、儲存條件、丟棄條件
- 包裝方式
- 提供相關的技術文件，如：MSDS、COA、無菌試驗
- 供應商建議的使用方法
- 供應商的可靠度
- 過去或其他公司的使用經驗

消毒劑有效性驗證

Qualifying Disinfectant

決定測試菌種

↓

決定表面材質

↓

決定消毒劑效期

↓

方法確效

↓

效能試驗

- In suspension Study
- Carrier Surface Study
- In Situ Study

Disinfectant Qualification

- Qualification testing of a new antimicrobial chemical agent should include both laboratory and in situ testing.
- Chemical analysis of the actives may be provided by the vendor or, alternatively, performed in-house or by a qualified contract laboratory using the vendor's method.

Disinfectant Qualification

- The antimicrobials chemical agents used for testing should be close to or beyond their stated in-use expiration date.
- Testing should be done in replicate on multiple lots of the antimicrobial chemical agent where applicable.

Disinfectant Qualification

- Additional qualification may be performed if changes in product formulation or packaging or site investigations deem it necessary. Information supporting the qualification includes the following seven areas:
  - Description of packaging, label, and container type
  - Description of ingredients and concentrations
  - Lot or batch number
  - Efficacy testing results
  - Irradiation or other sterilization verification certification
  - Safety data sheet information
  - Disposal information

Disinfectant Qualification

- 使用濃度、配製方法
- 樣品的效期需與現場使用方法、效期一致
- 有效接觸時間
- 選擇適當的指標菌種
  - 標準菌種 (ATCC, BCRC)
  - 環境指標菌種
- 開封後使用期限
- 測試表面材質需與製造現場一致

Efficacy Test

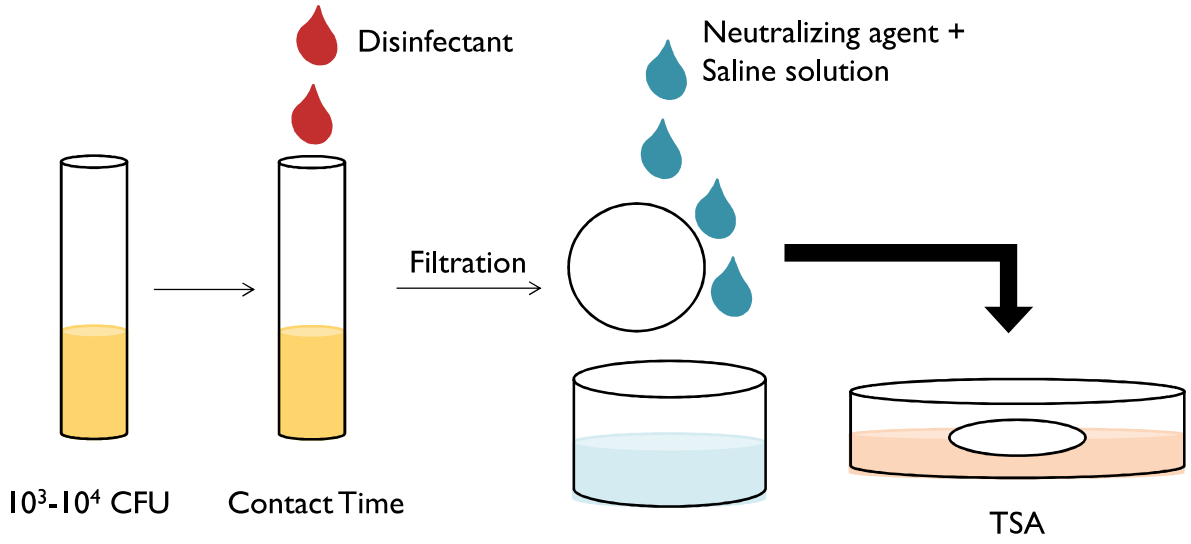
- The demonstration of antimicrobial chemical agents to provide their respective kills is a function of
  1. the concentration of microorganisms present,
  2. the type of microorganisms,
  3. the choice of agent,
  4. the concentration of the agent,
  5. the porosity or texture of the surface to be cleaned,
  6. the method of application,
  7. and the contact time.

Efficacy Test

- Contact or dry times in qualification studies should not exceed:
  - 120 seconds for alcohols
  - 10 minutes for disinfectants and sporicides

In-suspension study

- Quickly screen various chemical agents to determine which may be the most effective.



In-suspension study

- a panel of six to ten microorganisms, including bacteria, yeast, and mold, should be used.
- Selection of organisms should be based on the type of environmental isolates recovered from the facility (environmental isolates are preferred).

Commonly Used Neutralization Agents

Antimicrobial Chemical Agent	Neutralizing Agent
Alcohols	Dilution or polysorbate 80
Sodium hypochlorite	Sodium thiosulfate
Quaternary ammonium compounds	Polysorbate 80 and lecithin
Phenolic compounds	Dilution or polysorbate 80 and lecithin
Hydrogen Peroxide/Peracetic Acid and Hydrogen Peroxide	Catalase

Carrier surface study

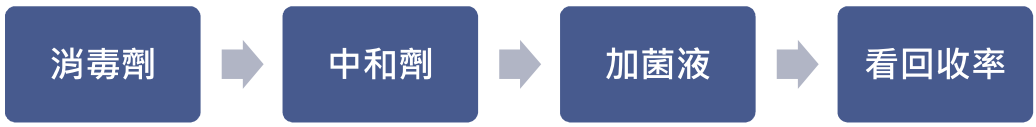
- Provide a verification of the ability of the antimicrobial chemical agent to reduce the microorganism levels that may be present on the types of material surfaces present within the facility.
- The carrier’ s measurements not exceed 1.5 inches (38 mm) * 1.5 inches (38 mm) so as to avoid false positives during handling of the carrier.

Carrier surface study

- Three or more replicates are recommended.
- A panel of 6 to 10 microorganisms that include bacteria, yeast, and mold should be used. The organisms chosen should be based on the type of environmental isolates recovered from the facility.
- Inoculate the preparation using 10^3–10^5 CFU of the appropriate challenge organism.
- Inoculate a minimum of two coupons (sterile) with each of the challenge organisms and prepare a positive control and a negative control

Preparatory Testing

- Recovery Study:
  - 確認消毒劑與中和劑作用後不影響後續的培養



- Neutralizing Media Study:
  - 確認中和劑的毒性不影響後續的培養

Preparatory Test

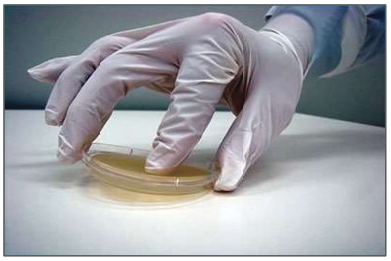
- Challenge microorganisms control:

準備菌液 → 培養計數

- w/o coupons

Sampling methods

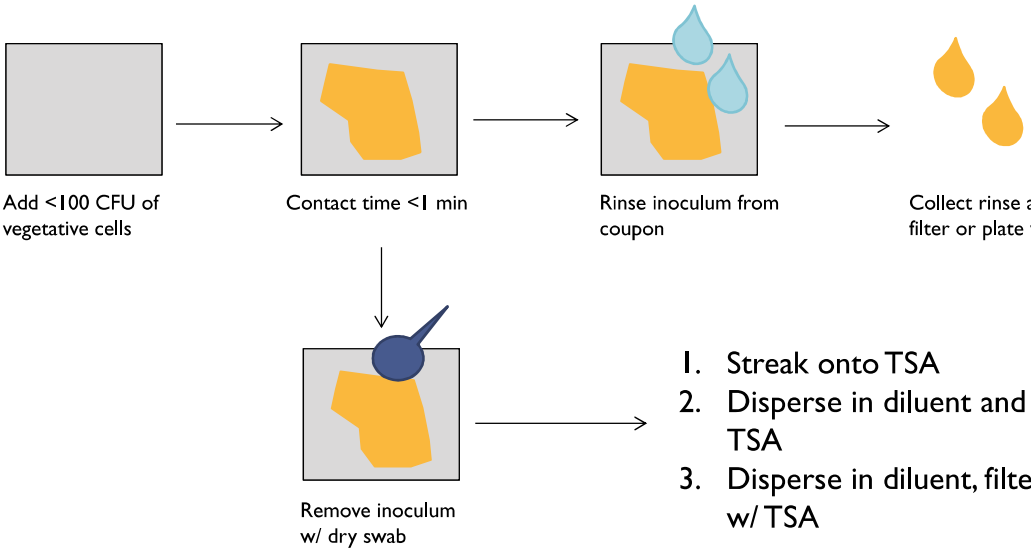
Contact plates



Swabbing

Rinse sampling

Carrier Surface Study-Recovery Qualification



1. Streak onto TSA
2. Disperse in diluent and plate w/ TSA
3. Disperse in diluent, filter, and plate w/ TSA

Incubate TSA plates at 30-35 ℃ for 3-5 days

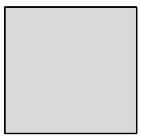
Carrier Surface Study

菌液 → 加消毒劑 → 加中和劑 → 回收培養

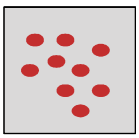
10^3-10^5 CFU　　終止消毒　　三重複

- Negative Control: Disinfectant without challenge organism
- Positive Control: Challenge organism without disinfectant

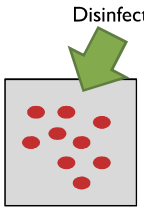
Carrier Surface Study



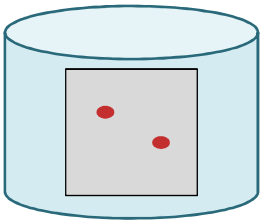
Test carrier



Contamination of test carrier (10^3-10^5 CFU)



Disinfectant applied in the concentration at which it is used in practice and left at appropriate time



Beaker of neutralizing solution before being rinsed.
Micro-organism present in the rinse solution are investigated, followed by enumeration.

Typical Challenge Organisms

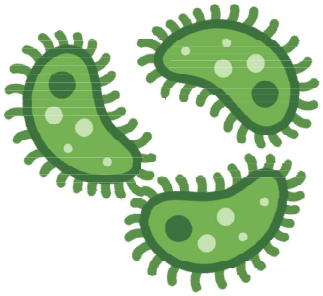
AOAC Challenge Organisms	Typical Environmental Isolates
Bactericide: *E. coli*, ATCC 11229; *S. aureus*, ATCC 6538; *P. aeruginosa*, ATCC 15442 ATCC 9027	Bactericide: *M. luteus*, *S. epidermidis*, *Coynebacterium jeikeium*, *P. vesicularis*
Fungicide: *C. albicans*, ATCC 10231 or 2091; *Penicillium chrysogenum*, ATCC 11709; *A. brasiliensis*, ATCC 16404	Fungicide: *P. chrysogenum*, *A. brasiliensis*
Sporicide: *B. subtilis*, ATCC 19659 ATCC 6633	Sporicide: *B. sphaericus*, *B. thuringiensis*

USP <1072>

Acceptance Criteria

Antimicrobial Chemical Agent	Organism Type	Suggested Contact Time[1]	Suggested Minimum Reduction[2]
Sanitizer	Non-spore formers	max. 90 sec	>1 Log
Disinfectant/Sporicide	Non-spore formers	1–5 min	>1 Log
Disinfectant/Sporicide	Mycoplasma	1–5 min	>1 Log
Sporicide	Mold spores	1–5 min	>1 Log
Sporicide	Bacterial spores	1–5 min	>1 Log

- 高強度消毒劑 (殺孢劑) ：
  - 至少要能減少2-log 的孢子菌
  - 至少要減少3-log營養菌絲
- 中強度消毒劑：
  - 至少要能減少2-log 的黴菌
  - 至少要減少3-log營養菌絲



Acceptance Criteria

Organism Type	Test Method	Test Type	Contact Time (minutes)	Log Reduction Pass Criteria
Vegetative bacteria	EN 1276:1997	Suspension	5	5
Vegetative bacteria	EN 13697:2001	Surface	5	4
Vegetative fungi	EN 1650:1998	Suspension	15	4
Vegetative fungi	EN 13697:2001	Surface	15	3
Bacterial spores	EN 13704:2002	Suspension	60	3

In Situ Study

- The true test of the effectiveness of a cleaning and disinfection program is the monitoring data collected from the manufacturing area.

In Situ Study

- These in-situ data may include the following:
  - Nonviable (total particulate data)
  - Viable data for surfaces and ambient air
  - Personnel-monitoring data
  - Microbial identification of representative isolates from the environment
  - Residual testing of surfaces
  - Product quality (in-process bioburden and sterility testing)

In Situ Study

- Environmental Monitoring Before and After the Start-up of a Facility or Area
  - An initial cleaning is performed. An initial cleaning entails the removal of soil using a broom or vacuum.
  - Increased viable monitoring of air and surfaces is performed to attain baseline.
  - Facility cleaning and disinfection are performed.
  - After the cleaning and disinfection are completed and surfaces are dry, the increased viable monitoring of surfaces should be repeated.

In Situ Study

- Environmental Monitoring Before and After Cleaning and Disinfection During Routine Operation
  - Increased viable surface and air monitoring is performed after operations have occurred and just before cleaning and disinfection take place.
  - Cleaning and disinfection are performed.
  - Increased monitoring is performed again after cleaning and disinfection.

清潔與消毒相關的缺失

清潔與消毒相關的缺失

- Efficacy study using sporicidal disinfectant completed for the Filling and Finish Area did not demonstrate effectiveness in controlling potential microbial contamination showing a minimum x log bioburden reduction.
  - A sporicidal agent shall demonstrate at least a 2 log reduction of bacterial and mold spores and a 3 log reduction of vegetative organisms.

清潔與消毒相關的缺失

- In Disinfection efficacy study performed per protocol the disinfectants were applied by spraying a thin layer of disinfectant directly on to coupons, and waiting for the specified residence times of X before the efficacy log reduction was demonstrated. However, to clean production areas the disinfectant agent is applied using mops for ceilings, walls and floors and sprayed on lint free cloth and wiped on equipment.
  - Application of disinfectants in Plant must be demonstrated in Laboratory disinfection validation testing.

清潔與消毒相關的缺失

- The disinfectants used in Class A and Class B areas are prepared in Class C area.
  - Use of sterile disinfectant is required for Aseptic Processing Areas. (Bioburden data)
  - Continuous monitoring for disinfectant used in grade C/D area.
- The Manufacturing Areas Environmental Monitoring Data Annual Trending Report 2017" identified Bacillus species, spore forming organisms, as the most common isolates from the manufacturing environment. The schedule for routine sanitization does not include periodic use of a sanitizer shown to be effective against spore forming organisms.
  - A sporicidal agent is required at a defined frequency. Use trending data to assist in setting the frequency.

清潔與消毒相關的缺失

- Your cleaning program is deficient. While operator entries in sanitization records state that all required sanitization steps were completed in cleanrooms, many steps were actually skipped, and various pieces of equipment were not sanitized.
  - Procedures must be clear and precise with adequate training provided. All procedures must be consistently followed.

清潔與消毒相關的缺失

- Your operators did not ensure the mop makes proper contact with the floor. Mops were not wetted frequently to ensure adequate coverage. For example, an operator cleaned the walls surrounding Line AH for several minutes without rewetting the mop.
  - Clean and dirty disinfectant solutions shall be segregated during application, i.e.,3-bucket system. Mopping should be applied for a number of overlapping passes, i.e, 3 passes.

清潔與消毒相關的缺失

- The efficacy study demonstrated effectiveness of "perform sterile Concentrate OXY 2%" after five hours contact time. The contact time in your current cleaning procedure using the sporicide is 60 minutes.
  - Plant sanitization procedures must follow the laboratory validation parameters for contact time.

清潔與消毒相關的缺失

- Cleaning and disinfection records of the filling room and the filling line with its enclosure, document one operator as doing the cleaning and disinfection and the second as the checker and/or verifier when in fact, both operators execute the cleaning.
  - The checking/verification is to be done by a colleague independent to the executed operations.

清潔與消毒相關的缺失

- Cleaning and disinfection records of the filling room and the filling line with its enclosure, do not specifically indicate the start and ending time of the cleaning and disinfection of the different areas/ sections of the filling room and the filling line with its enclosure.
  - Documentation should include start and ending times for cleaning and disinfection.

再生醫療製劑(ATMP)之原料要求

- ✓ USP <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products
- ✓ Guidelines of 22.11.2017 Good Manufacturing Practice for Advanced Therapy Medicinal Products
- ✓ EP 5.2.12 Raw Materials of Biological Origin for the Production of Cell-Based and Gene Therapy Medicinal Products

2019/05/28

(108) 再生醫療製劑 GMP 訓練活動
108TPDA04017

EUROPEAN
COMMISSION

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

2019/05/28 2

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

Document History	
Adoption by the European Commission	22 November 2017
Date for coming into operation	ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

These Guidelines are specific to ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference thereto is made in these Guidelines.

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ General principles (1/2)
  - the quality of starting and raw materials is a key factor to consider in the production of ATMPs
  - specifications related to the product will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile
  - prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ General principles (2/2)

- the use of antimicrobials may be necessary to reduce bioburden associated with the procurement of living tissues and cells
- the use of antimicrobials does not replace the requirement for aseptic manufacturing
- when antimicrobials are used, they should be removed ASAP, unless the presence thereof in the finished product is specifically foreseen in the marketing /clinical trials authorizations
- ensure that antibiotics or antimicrobials do not interfere with the sterility testing, and that they are not present in the finished product

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Raw Materials, RM (1/7)

- should be of suitable quality having regard to the intended use
- should take into consideration *the Ph. Eur 5.2.12 general chapter on raw materials of biological origin for the production of cell based and gene therapy medicinal products*
- should be of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research grade are available
- risks of using research grade materials should be understood, including the risks to the continuity of supply when larger amounts of product are manufactured
- the suitability of such RMs for the intended use should be ensured by means of testing, including functional test, safety test

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Raw Materials, RM (2/7), specifications for raw materials, including:
  - description of the RMs, including reference to designated name and any other information required to avoid risks of error
  - for RMs of biological origin, the identification of the species and anatomical environment from which materials originate should also be described
  - for critical RMs, e.g. sera, growth factors, enzymes, cytokines, quality requirements to ensure suitability for intended use as well as acceptance criteria
  - quality requirements agreed with suppliers should be kept
  - instructions for sampling and testing
  - storage conditions and maximum period of storage
  - transport conditions and precautions

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Raw Materials, RM (3/7)
  - RMs for authorized ATMPs, these quality requirements should be agreed with the supplier(s)
  - for investigational ATMPs, the technical specifications for the critical RMs should be agreed with the suppliers whenever possible
  - the assessment whether a specific RMs is critical should be done by the manufacturer having regard to the specific risks (or, as appropriate, the sponsor or marketing authorization holder
  - the decisions taken should be documented
  - the agreed specifications should cover aspects of the production, testing and control, and other aspects of handling and distribution as appropriate
  - the specifications set should be in compliance with the terms of the marketing authorization or clinical trial authorization

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Raw Materials, RM (4/7)
  - the ATMP manufacturer should verify compliance of the supplier's materials with the agreed specifications
  - the level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials
  - reliance on the certificate of analysis of the supplier is acceptable if all the risks are duly understood and measures are put in place to eliminate the risks or mitigate them to an acceptable level (e.g. qualification of suppliers)
  - for RMs that are authorized as medicinal products in the EU (e.g. cytokines, human serum albumin, recombinant proteins), the certificate of analysis of the supplier is not required
  - the use of authorized medicinal products is encouraged

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Raw Materials, RM (5/7)
  - the risk of contamination of RMs of biological origin during their passage along the supply chain must be assessed, with particular emphasis on viral and microbial safety and Transmissible Spongiform Encephalopathy ("TSE")
  - compliance with the latest version of the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required
  - where there is a potential mycoplasma contamination risk associated with a RMs, the ATMP manufacturer should filter the material prior to use (0.1 μm filter), unless the supplier of the RM has certified that the raw material has been tested and is mycoplasma free

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Raw Materials, RM (6/7)

- the risk of contamination from other materials that come into direct contact with manufacturing equipment or the product (such as media used for process simulation tests and lubricants that may contact the product) should also be taken into account
- RMs in the storage area should be appropriately labelled
- labels for critical RM should bear at least the following information:
  (i) the designated name of the product and the internal code reference;
  (ii) a batch number given at receipt;
  (iii) storage conditions;
  (iv) the status of the contents (e.g. in quarantine, on test, released, rejected);
  (v) an expiry date or a date beyond which retesting is necessary

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Raw Materials, RM (7/7)

- when fully computerized storage systems are used, all the above information need not necessarily be in a legible form on the label
- the use of automated systems (e.g. use of barcodes) is permissible
- only RMs that have been released by the person responsible for quality control should be used
- the ATMP manufacturer should put in place appropriate measures to ensure that critical RMs can be traced in order to facilitate recall of products if necessary

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Starting Materials, SM (1/13)

- the donation, procurement and testing of human tissues and cells used as SMs should be in accordance with Directive 2004/23/EC
- for blood-derived cells, compliance with Directive 2002/98/EC regarding donation, procurement and testing is likewise acceptable
- the accreditation, designation, authorization or licensing of the supplier of starting materials as provided for under the legislation above-referred should be verified
- when the cells/tissues used are outside the scope of the Directive 2004/23/EC or Directive 2002/98/EC (e.g. cell-lines/cell banks established outside the EU, or cells procured before the entry into force), the ATMP manufacturer should take appropriate steps to ensure the quality, safety and traceability, in accordance with the terms of the marketing authorization/clinical trial authorization.

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Starting Materials, SM (2/13)

- the ATMP manufacturer should establish quality requirements for the SMs (specifications) which should be agreed with the supplier(s)
- these agreed specifications should cover aspects of the production, testing and control, storage, and other aspects of handling and distribution as appropriate
- depending on the product's characteristics, testing in addition to that foreseen in the Directive 2004/23/EC or Directive 2002/98/EC may be required
- the agreed specifications should be in compliance with the terms of the marketing authorization or clinical trial authorization

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- Starting Materials (3/13), specifications for starting materials, including:
  - description of the starting materials, including any relevant information required to avoid risks of error
  - for starting materials of human origin, the identification of the supplier and the anatomical environment from which the cells/tissues/virus originate should also be described (or, as appropriate, the identification of the cell-line, master cell bank, seed lot)
  - quality requirements to ensure suitability for intended use as well as acceptance criteria
  - contracts and quality requirements agreed with the suppliers should be kept
  - instructions for sampling and testing
  - storage conditions and maximum period of storage
  - transport conditions and precautions

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- Starting Materials, SM (4/13)
  - the ATMP manufacturer should verify compliance of the supplier's materials with the agreed specifications
  - the level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials
  - blood/tissue establishments authorized and supervised in accordance with Directive 2002/98/EC or Directive 2004/23/EC do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing provided for under the national law of the Member State where the blood/tissue establishment is located
  - it is recommended that the agreement between the ATMP manufacturer and the blood/tissue establishment foresees the possibility for the ATMP manufacturer to audit the blood/tissue establishment

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Starting Materials, SM (5/13)

- if the agreed specifications foresee requirements which imply that the blood/tissue establishment should carry out activities in addition to those authorized and supervised by the competent authority in accordance with Directive 2002/98/EC or Directive 2004/23/EC (e.g. additional testing), adequate supervision in respect of the additional requirements should be carried out
- in addition to the specifications for the SMs, the agreement between the ATMP manufacturer and the supplier (including blood/tissue establishments) should contain clear provisions about the transfer of information regarding the SMs, in particular, on tests results performed by the supplier, traceability data, and transmission of health donor information that may become available after the supply of the SM and which may have an impact on the quality or safety of the ATMPs manufactured therefrom

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Starting Materials, SM (6/13)

- the risk of contamination of the SM during their passage along the supply chain must be assessed, with particular emphasis on viral and microbial safety and Transmissible Spongiform Encephalopathy (“TSE”)
- compliance with the latest version of the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required
- only SMs that have been released by the person responsible for quality control should be used
- where the results from the test(s) required to release the SMs take a long time (e.g. sterility test), it may be permissible to process the starting materials before the results of the test(s) are available

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Starting Materials, SM (7/13)

- the risk of using a potentially failed material and its potential impact on other batches should be clearly assessed and understood
- in such cases, the finished product should only be released if the results of these tests are satisfactory, unless appropriate risk mitigation measures are implemented
- SMs in the storage area should be appropriately labelled, at least the following information:
  - (i) the designated name of the product and the internal code reference;
  - (ii) a batch number given at receipt;
  - (iii) storage conditions;
  - (iv) the status of the contents (e.g. in quarantine, on test, released, rejected);
  - (v) an expiry date or a date beyond which retesting is necessary

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

✓ Starting Materials, SM (8/13) -- Processing of SMs

- when fully computerized storage systems are used, all the above information need not necessarily be in a legible form on the label; the use of automated systems (e.g. use of barcodes) is permissible
- the quality of ATMPs is dependent on the quality of the starting materials, thus, cells and tissues of human origin must comply with the donation, procurement and testing requirements provided for under Directive 2004/23/EC or Directive 2002/98/EC
- the further processing/manufacturing thereof should take place in a GMP environment
- where steps like washing or preservation are needed to make the cells/tissues available, this can also take place at the tissue/blood establishment under the requirements of Directive 2004/23/EC or Directive 2002/98/EC

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Starting Materials, SM (9/13) -- Processing of SMs
  - in exceptional cases, it may be acceptable that the manufacture of an ATMP starts from already available cells or tissues where some initial processing/manufacturing steps have been performed outside of the GMP environment, provided it is impossible to replace such material with GMP-compliant material
  - the use of cells that have been separated/isolated and preserved outside a GMP environment for the manufacture of an ATMP should remain exceptional and it is only possible if a risk analysis is performed to identify the testing requirements necessary to ensure the quality of the SMs
  - the overall responsibility for the quality – as well as the impact thereof on the safety and efficacy profile of the product – lies with the ATMP manufacturers, even if the activities have been outsourced

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Starting Materials, SM (10/13) -- Processing of SMs
  - the release of such cells/tissues for use in the manufacturing process should be done by the person responsible for quality control after verifying the quality and safety thereof
  - additionally, the competent authorities should agree to the control strategy in the context of the assessment of the marketing authorization application/clinical trial authorization application
  - in the case of vectors and naked plasmids used as SMs for the manufacturing of gene therapy medicinal products, the principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Starting Materials, SM (11/13) -- additional considerations for xenogeneic cells and tissues
  - the use of xenogeneic cells/tissues in the manufacture of ATMPs poses additional risks of transmitting known and unknown pathogens to humans, including the potential risk of introducing new infectious diseases
  - the selection of donor animals must therefore be strictly controlled
  - source/donor animals should be healthy and should be specific pathogen free (SPF) and be raised in SPF conditions, including health monitoring
  - the donor/source animal should have been bred in captivity (barrier facility) specifically designed for this purpose
  - in the manufacture of ATMPs, it is not acceptable to use xenogeneic cells and tissues from wild animals or from abattoirs
  - cells and tissues of founder animals similarly should not be used

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7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Starting Materials, SM (12/13) -- additional considerations for xenogeneic cells and tissues
  - appropriate measures should be implemented to identify and prevent incidents that negatively affect the health of the source/donor animals or that could negatively impact on the barrier facility or the SPF status of the source/donor animals
  - in addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored and recorded
  - specialist advice should be obtained in establishing the monitoring program
  - instances of ill-health occurring in the herd should be investigated with respect to the suitability of in-contact animals for continued use (in manufacture, as sources of SMs and RMs, in quality control and safety testing)

7. STARTING AND RAW MATERIALS

GUIDELINES OF 22.11.2017 GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCT

- ✓ Starting Materials, SM (13/13) -- additional considerations for xenogeneic cells and tissues
  - the decisions taken must be documented
  - a look-back procedure should be in place which informs the decision making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced cells/tissues have been used or incorporated
  - this decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation
  - the withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the program for defined periods

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ATMP DEFINITION IS SLIGHTLY DIFFERENT BY REGULATORY BODIES

- In the EU, ATMP is defined as:
  - -- Somatic Cell Therapy Medicinal Product (SCTMP)
  - -- Tissue Engineered Product (TEP)
  - -- Gene Therapy Medicinal Product (GTMP)
  - -- a combined ATMP
- US FDA's Office of Cellular, Tissue and Gene Therapies (OCTGT) defines ATMPs as:
  - -- Cellular therapy products, including cellular immunotherapies and other types of both autologous and allogeneic cells for certain therapeutic indications, including adult and embryonic stem cells
  - -- Human gene therapy refers to products that introduce genetic material into a person's DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition

DEFINITION AND SCOPE
RM V.S. AM

5.2.12 **Raw Materials of Biological Origin** for the Production of Cell-Based and Gene Therapy Medicinal Products

- RM of biological origin used for the production of cell-based/gene therapy medicinal products
- Plastics and chemically synthesized RMs, such as basal media, synthetic peptides or polynucleotides, are not within the scope of this chapter.

<1043> **Ancillary Materials** for Cell, Gene, and Tissue-Engineered Products

- Reagents and Materials, required for the manufacturing of cell, gene and tissue-engineered products, include plasma- or serum-derived products, biological extracts, antibiotics, cytokines, culture media, antibodies, polymeric matrices, separation devices, density gradient media, toxins, conditioned media supplied by "feeder cell layers", fine chemicals, enzymes, and processing buffers.

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

1. SCOPE
2. RISK ASSESSMENT
3. GENERAL REQUIREMENTS
   - 3.1. Origin
   - 3.2. Production
   - 3.3. Characterization
   - 3.4. General Quality Requirements
     - 3.4.1. IDENTIFICATION
     - 3.4.2. TESTS
     - 3.4.3. ASSAY
   - 3.5. Storage
   - 3.6. Labelling
4. SERA AND SERUM REPLACEMENTS
   - 4.1. Definition
   - 4.2. Production
   - 4.3. Identification
   - 4.4. Tests
   - 4.5. Assay
5. PROTEIN PRODUCED BY RECOMBINANT DNA TECHNOLOGY
   - 5.1-5.5
6. PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL
   - 6.1-6.5
7. VECTORS

INTRODUCTION – 1/1

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

This general chapter is published for information.

- It contains sections on the quality requirements of raw materials used for the production of cell-based and gene therapy medicinal products for human use.
- It is the responsibility of the manufacturer of a raw material to qualify (prove to be suitable for the intended use) the raw material in accordance with the given requirements.
- It is ultimately the responsibility of the user of a raw material to ensure it is of suitable quality for the specific use.

INTRODUCTION – 2/3

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

This general chapter is published for information.

- quality of the raw materials ⇔ development stages of ATMP
  - ✓ the inherent evolution of the quality profile of the product during its pharmaceutical and clinical development
  - ✓ patient safety in early phase clinical development
- aim to have an appropriate qualification strategy for the raw materials when used for the production of ATMP
- changes in raw materials during the lifecycle of ATMP may affect quality of final product and thus require additional studies to demonstrate comparability

INTRODUCTION – 3/3

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

This general chapter is published for information.

- a risk-based approach is used to evaluate the impact of the RM on the quality, safety and efficacy of ATMP
- RMs are used in order to consistently yield an active substance or medicinal product of a specified quality
  - e.g. biological activity, purity/impurity profile, the risk of adventitious agents (bacteria, viruses, etc.) and stability
- from a risk perspective, the use of raw materials free from human or animal substances is preferred
- the biological nature of a raw material used for ATMP production places special requirements on its quality
- examples of the critical quality attributes specific to each class of raw material are given in this general chapter

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DEFINITION AND SCOPE

AM V.S. RM

<1043> **Ancillary Materials** for Cell, Gene, and Tissue-Engineered Products

- Reagents and Materials, required for the manufacturing of cell, gene and tissue-engineered products, include plasma- or serum-derived products, biological extracts, antibiotics, cytokines, culture media, antibodies, polymeric matrices, separation devices, density gradient media, toxins, conditioned media supplied by "feeder cell layers", fine chemicals, enzymes, and processing buffers.

5.2.12 **Raw Materials of Biological Origin** for the Production of Cell-Based and Gene Therapy Medicinal Products

- RM of biological origin used for the production of cell-based/gene therapy medicinal products
- Plastics and chemically synthesized RMs, such as basal media, synthetic peptides or polynucleotides, are not within the scope of this chapter.

SCOPE – 1/2

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

- This general chapter applies to raw materials of biological origin used for ATMP, and these RMs are
  - not intended to form part of the active substance
  - extracted from various biological sources or produced by recombinant DNA technology
- This general chapter applies to the following classes of RMs
  - Sera and serum replacement
  - Protein produced by recombinant DNA technology
  - Proteins extracted from biological material
  - vectors

SCOPE – 2/2

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

- the principles of this general chapter may also be applied to other classes of biological raw materials where appropriate
- the following are not within the scope of this general chapter:
  - ✓ medical devices
  - ✓ plastics and chemically synthesized raw materials, such as basal media (purely composed of chemicals)
  - ✓ synthetic peptides or synthetic polynucleotides

RISK ASSESSMENT – 1/2

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

- a risk assessment must consider
  - ✓ the biological origin and the traceability of the RM
  - ✓ the production steps at which the RMs are applied
  - ✓ the ability of the manufacturing process to control or remove the RM from the final product
- evaluation of the impact of the RM on the quality, safety and efficacy of ATMP must be performed by the user of the RM
- no single measure or combination of measures can guarantee the quality, functionality and safety of a RM for its intended use

RISK ASSESSMENT – 2/2

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

when evaluating the risk posed by the RM to the final product, the exposure of a patient to residual amounts of RMs with potential harmful effects should be considered in relation to the clinical benefit/risk of the final product

GENERAL REQUIREMENT – 1/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

ORIGIN

- the origin of RM and if relevant any biological substances used for the production of RM must be known
- special attention must be paid to the sourcing, including pooling, of the substances used for the production of RM
- RMs are divided into 3 categories:
  - ✓ RMs of human or animal origin
  - ✓ RMs produced using substances of human or animal origin
  - ✓ RMs free from substances of human or animal origin
- traceability of all RMs is required
- due to the inherent risk of transmitting adventitious agents
  - ✓ minimize the use of RM of human or animal origin
  - ✓ take appropriate measures

GENERAL REQUIREMENT – 2/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

ORIGIN

- Materials derived from human blood or tissue
  - ✓ donors are carefully evaluated and adequately tested for infectious transmissible agents
  - ✓ comply with appropriate EU and/or national legislation applicable to transfusion and transplantation
  - ✓ with traceability from the donation to the RM and to the final product
  - ✓ viral risk assessment is required (general chapter *5.1.7 Viral safety*)
  - ✓ to minimize the risk of TSE, suitable measures are taken (general chapter *5.2. 8 Minimizing the risk of transmitting animal TSE*)
- Materials are vectors or proteins produced by recombinant DNA technology
  - ✓ Traceability to the master cell bank/virus seed lot is required

GENERAL REQUIREMENT – 3/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

ORIGIN

- Materials of animal origin
  - ✓ these animals fulfil specific health requirement
  - ✓ should be fit for human consumption and reared under controlled condition
  - ✓ if the origin of the animals is not fully traceable, information of geographic locations at the time of sourcing should be considered
  - ✓ viral risk assessment is required (general chapter *5.1.7 Viral safety*)
  - ✓ to minimize the risk of TSE, suitable measures are taken (general chapter *5.2.8 Minimizing the risk of transmitting animal TSE*)

GENERAL REQUIREMENT – 4/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- all RMs are produced within a suitable QMS and production facility
- suitable in-process controls are in place to ensure that the production process is under control and consistently produce raw materials of defined quality
- quality attributes for raw materials include identity, purity and biological activity
  - quality attributes are to be demonstrated using appropriate, qualified control methods
  - relevant specifications in terms of identity, purity/impurity profile and assays are to be established

GENERAL REQUIREMENT – 5/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- production process is optimized to consistently minimize and/or remove adventitious agents and harmful impurities, whilst retaining the quality of the raw material
- can be achieved using one or a combination of the following measures:
  - ✓using validated inactivation/removal procedures such as gamma sterilization or low pH during chromatography, where possible
  - ✓demonstrating the ability of a production process to minimize, remove or inactivate adventitious agents or harmful impurities
  - ✓testing for adventitious agents or harmful impurities

GENERAL REQUIREMENT – 6/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- a RM is sterile and produced under aseptic conditions and/or subject to terminal sterilization, unless otherwise justified
- if the RM is not sterile, the level of microbial contamination must be known
- additives, such as stabilizers, may be added to the RM
  - ✓ in cases where antibiotics and stabilizers of biological origin are used in the production of the RM, their presence is justified and careful consideration is given to their selection, use, quality and concentration in the RM, as well as their impact on the actual RM itself

GENERAL REQUIREMENT – 7/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS

- RMs must meet pre-defined quality requirements
- to ensure the function of the RM, it is subject to testing using appropriately qualified methods for identity, purity and biological activity
  - ✓ identity test must reflect the uniqueness of the raw material and distinguish it from other related or similar substances
  - ✓ impurities include both process- and product-related substances:
    - -- process-related, e.g. recombinant proteins: host-cell-derived proteins (HCP), host-cell-derived DNA and vector-derived DNA (residual DNA), other biological or chemical substances)
    - -- product-related, e.g. aggregates and degradation products
- the content of a raw material may be expressed either in absolute or relative terms
  - ✓ the assay for determination of biological activity may be used to establish the content

GENERAL REQUIREMENT – 8/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS -- IDENTIFICATION

- identity tests are specific for the particular RM and address the molecular structure/composition or other relevant physicochemical, biological or immunochemical properties
- identification may be carried out by comparison with a defined reference material or a representative batch of the RM
- methods used in the determination of biological activity and purity may also serve to identify the RM

GENERAL REQUIREMENT – 9/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS -- TESTS

- tests that may be applicable to RMs include the following:

Test	Description
Appearance	Liquid or reconstituted freeze-dried raw materials comply with the limits defined for the particular raw material with regard to degree of opalescence *(2.2.1)* and degree of coloration *(2.2.2)*
Solubility	Freeze-dried raw materials dissolve completely in the prescribed volume of reconstituting liquid within a specified time, at a specified temperature, as defined for the particular raw material
Osmolality *(2.2.35)*	within the limits defined for the particular raw material
pH *(2.2.3)*	within the limits defined for the particular raw material

GENERAL REQUIREMENT – 10/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS -- TESTS

- tests that may be applicable to RMs include the following:

Test	Description
Elemental impurities	within the limits defined for the particular raw material
Total protein *(2.5.33)*	within the limits defined for the particular raw material
Related substances	The content of product-related substances is within the limits defined for the particular raw material
Microbiological control	Depending on the raw material concerned, it complies with the test for sterility *(2.6.1)* or the microbial contamination is determined *(2.6.12)*
Viral contaminants	Depending on the raw material concerned, relevant virus contamination is determined

GENERAL REQUIREMENT – 11/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS -- TESTS

- tests that may be applicable to RMs include the following:

Test	Description
Bacterial endotoxins *(2. 6.14)*	less than the limit defined for the particular raw material
Mycoplasmas *(2.6.7)*	Raw materials are free from mycoplasmas
Stabilizer	Where applicable, it complies with the limits defined for the particular raw material
Water *(2.5.12)*	Freeze-dried raw materials comply with the limits defined for the particular raw material

GENERAL REQUIREMENT – 12/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS -- ASSAYS

ASSAY	Description
Content	The content (e.g. protein content)/composition of the raw material is determined by an appropriate qualified method.
Biological Activity	Where relevant, the biological activity is determined by a suitable assay. Where relevant (e.g. for enzymes), the biological activity is expressed per milligram of total protein (specific activity).

GENERAL REQUIREMENT – 13/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

GENERAL QUALITY REQUIREMENTS – REFERENCE MATERIAL OR BATCH

- an appropriate reference material or a representative batch of the raw material is used to perform the above-mentioned identification, tests and assay
- where available, the use of established reference standards, such as European Pharmacopoeia reference standards or WHO International Standards, is recommended

GENERAL REQUIREMENT – 14/14

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

STORAGE

- the shelf life and storage conditions are defined

LABELLING

- the label states the expiry date, conditions for storage and use and any code that may be required for traceability including the biological origin of the raw material

SERA AND SERUM REPLACEMENTS – 1/6

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

DEFINITION

- including platelet lysates and other undefined growth additives, conditioned media, blood and other cellular components
- used as growth additives for cell culture, to promote cellular growth
- typically complex biological mixtures, whose exact composition is not always possible to define
- special attention is given to verifying the consistency and performance of every batch

SERA AND SERUM REPLACEMENTS – 2/6

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

DEFINITION

Item	Description
bovine serum	complies with the monograph Bovine Serum (*2262*)
human serum and platelet lysates	RMs for the production of ATMP, can originate from the recipient (autologous) or from another individual (allogeneic)
conditioned media	used to enhance cell proliferation due to various growth factors and cytokines secreted by the cells into the medium
growth additives with undefined composition	cell and/or tissue lysates may be used as growth additives
composite media	contain growth additives; principles described in this section apply to individual ingredients of biological origin and/or biologically active ingredients of the composite media

SERA AND SERUM REPLACEMENTS – 3/6

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- due to potential differences in quality between batches of these RMs, suitable measures are implemented to verify the consistency of each batch before using them for the production of ATMP
- because of the inherent risk of transmitting infectious agents from these RMs, consideration is given to limit the number of donations which are pooled, unless sufficient methods for inactivation/removal of viruses are applied during production
- for conditioned media,
  - ✓ a cell bank system is preferred
  - ✓ the removal of the cells from the media must be ensured
  - ✓ potential impurities originating from these cells determined

SERA AND SERUM REPLACEMENTS – 4/6

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

IDENTIFICATION

- exact qualitative composition of sera and serum replacements are difficult to determine; however, the approximate protein composition in both cases may be determined by, for example,
  - ✓ protein electrophoresis
  - ✓ tests for total protein content
  - ✓ tests for any chemical additives
- for human serum, an appropriate reference batch is used for identification
  - ✓ the electrophoretic pattern
  - ✓ comparison of albumin content
- for serum replacements
  - ✓ the electrophoretic pattern
  - ✓ markers secreted by cells/platelets
- human origin is determined by a suitable immunochemical method (*2.7.1*)

SERA AND SERUM REPLACEMENTS – 5/6

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

TESTS

Test	Description
Hemoglobin	within the limits defined for the particular raw material
Cell-derived impurities	within the limits defined for the particular raw material
Specific tests for viral contaminants	- for bovine serum, the tests for viral contaminants specified in the monograph Bovine serum (*2262*) - for human serum, the tests for viral safety specified in the monograph Human plasma for fractionation (*0853*)

SERA AND SERUM REPLACEMENTS – 6/6

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

ASSAYS

- must show cell growth promoting properties that are within the limits defined for the particular raw material
- more than one type of assay may be necessary to show suitability for the intended use

PROTEINS PRODUCED BY RECOMBINANT DNA TECHNOLOGY – 1/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

DEFINITION including growth factors, cytokines, hormones, enzymes and mAbs

Item	Description
growth factors, cytokines and hormones	used for stimulation or inactivation, growth promotion or differentiation of cells in cell culture systems
other proteins	- enzymes (e.g. collagenases), used for extraction of active substances from tissues and/or fluids - other proteins (e.g. fibronectin), used as culture supports or media components
monoclonal antibodies	- including immunoglobulins and fragments of an immunoglobulin with defined specificity - can either be conjugated (chemically modified) or non-conjugated; typical chemical modifications include fluorescent labelling and conjugation to magnetic beads - used for selection, activation/stimulation, isolation or purification of cells in cell culture

PROTEINS PRODUCED BY RECOMBINANT DNA TECHNOLOGY – 2/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- based on a well-characterized host-vector system, using a master cell bank and, if applicable, a working cell bank derived from the master cell bank
- the expressed protein is extracted and purified using a variety of techniques, such as extraction, precipitation, centrifugation, concentration, filtration and/or chromatography
- process-related impurities including residual host-cell or vector DNA and host-cell proteins must be reduced to acceptable levels during protein production
- particular attention must also be given to product-related impurities.

PROTEINS PRODUCED BY RECOMBINANT DNA TECHNOLOGY – 3/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

IDENTIFICATION

- identity is established by appropriate qualified methods:
  - ✓ electrophoresis (*2.2.31*)
  - ✓ peptide mapping (*2.2.55*)
  - ✓ isoelectric focusing (*2.2.54*)
  - ✓ liquid chromatography (*2.2.29*)
- identification of antibodies is based on immunoglobulin class, isotype and/or specificity
- in addition to the above-mentioned methods, immunochemical methods (*2.7.1*) and determination of activity are also considered suitable for identification

PROTEINS PRODUCED BY RECOMBINANT DNA TECHNOLOGY – 4/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

TESTS

- see previous section

Item	Test Description
host-cell-derived proteins and residual host-cell or vector DNA	- determined using a suitable method unless the production process has been qualified to demonstrate suitable clearance - the content is within the limits defined for the particular raw material
related proteins	- determined using liquid chromatography, electrophoretic or immunological methods for related proteins with undefined specificities, glycoforms, degradation and oxidation products, oligomers and aggregates - the content is within the limits defined for the particular raw material

PROTEINS PRODUCED BY RECOMBINANT DNA TECHNOLOGY – 5/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

ASSAYS

Item	Description
content	- determined by an appropriate qualified method, e.g. by liquid chromatography (*2.2.29*) or UV spectrophotometry (*2.2.25*)
biological activity	- determined by, e.g. cell proliferation, cell differentiation or an enzyme assay - several acceptable bioassays may exist for a particular protein, e.g. for antibodies: cell-based immunoassays and assays based on ligand-binding and affinity may be used - the biological activity is expressed per milligram of total protein (specific activity)

PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL – 1/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

DEFINITION

- including enzymes, e.g. porcine - derived trypsin and endonucleases), polyclonal antibodies, other proteins of biological origin (e.g. albumin and transferrin) and peptides of biological origin
- may be of human, animal, plant or microbiological origin
- used in a wide range of applications such as growth promotion, differentiation or purification of cultured cells and extraction of active substances from tissues and/or fluids

PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL – 2/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- extracted by mechanical and/or chemical techniques, followed by subjected to further purification processes using a variety of techniques, such as:
  - ✓ centrifugation
  - ✓ filtration
  - ✓ chromatography
  - ✓ concentration
- polyclonal antibodies are produced by immunization with a specific antigen, followed by purification, such as:
  - ✓ selective enrichment
  - ✓ specific isolation of antibodies from serum
    - physicochemical fractionation
    - class-specific affinity
    - antigen-specific affinity

PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL – 3/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

PRODUCTION

- process-related impurities, such as blood components, tissue fragments or contaminating proteins, must be reduced to acceptable levels
- particular attention is given to product-related impurities

PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL – 4/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

TESTS

➢ see previous section

Item	Test Description
process-related impurities	- determined using a suitable method unless the production process has been qualified to demonstrate suitable clearance - the content is within the limits defined for the particular raw material
related proteins	- determined using liquid chromatography, electrophoretic or immunological methods for related proteins with undefined specificities, glycoforms, degradation and oxidation products, oligomers and aggregates - the content is within the limits defined for the particular raw material

PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL – 5/5

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

ASSAYS

Item	Description
content	- determined by an appropriate qualified method, e.g. by liquid chromatography (*2.2.29*) or UV spectrophotometry (*2.2.25*)
biological activity	- determined by enzyme assays, immunoassays or assays based on cell proliferation/differentiation. - for trypsin, the assay may be performed as described in the monograph Trypsin (*0694*) - the biological activity is expressed per milligram of total protein (specific activity)

VECTORS – 1/1

5.2.12 RAW MATERIALS OF BIOLOGICAL ORIGIN FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

- used as raw materials in the production of ATMP including DNA vectors (e.g. plasmids, transposon vectors) as well as viral vectors and bacteria (e.g. modified Lactococcus species)
- vectors are usually considered as starting materials, thus not under the scope of this general chapter
- In cases where vectors are used as helper plasmids or helper viruses, the principles of this general chapter and the principles of production and quality control as outlined in general chapter *5.14 Gene transfer medicinal products for human use* are to be followed.

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- INTRODUCTION
- QUALIFICATION OF AM
  - Identification
  - Selection and Suitability for Use
  - Characterization
  - Vendor Qualification
  - Quality Control and Quality Assurance
- RISK CLASSIFICATION
  - Tier 1
  - Tier 2
  - Tier 3
  - Tier 4
- PERFORMANCE TESTING
- AM RESIDUAL LEVEL ASSESSMENT AND REMOVAL
- CONCLUSION
- APPENDIX

INTRODUCTION – 1/5

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Reagents and Materials are required for the manufacturing of cell, gene and tissue-engineered products, including plasma- or serum-derived products, biological extracts, antibiotics, cytokines, culture media, antibodies, polymeric matrices, separation devices, density gradient media, toxins, conditioned media supplied by "feeder cell layers", fine chemicals, enzymes, and processing buffers.
- To prevent the introduction of adventitious agents or toxic impurities, as well as to ensure the safety, effectiveness, and consistency of the final product, careful and detailed examination of the materials used in the manufacturing is necessary.

INTRODUCTION – 2/5

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Ancillary materials (AMs) are synonymous with the following terms.
  - ancillary products, ancillary reagents in US FDA Notice: "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products", FR 58(197), 1993, pp.53248-53251.
  - processing aids, process reagents and processing materials in 21 CFR Part 1271, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule" (FR 66(5), 2001, pp. 1508-1559).
  - in some cased, analogous to components and containers in the current good manufacturing practice (cGMP) regulation for finished pharmaceuticals in s21 CFR 211.80 through 211.94 and 211.101 (b) and (c).

INTRODUCTION – 3/5

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- AMs are used as processing and purification aids or agents to exert their effect on the therapeutic substance.
- AMs are not intended to be present in the final products.
- The defining property of AMs
  - are **NOT** intended to be present in the final products,
  - are used as processing and purification aids or agents to exert their effect on the therapeutic substance.
- Materials or components that are intended to be in the final product dosage form are not AMs.
  - genetic materials, biopolymeric supports, physiological buffers (No)
  - cell banks, virus banks (No)
  - helper viruses, helper plasmids (Yes or No?)

INTRODUCTION – 4/5

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- The quality of AMs can affect the stability, safety, potency, and purity of the final products.
  - ✓ the mechanism of how an AM exerts its effect may not be known;
  - ✓ the impact of normal variation of the AM on the quality and safety of the final product may not be understood;
  - ✓ AMs of human or animal origin may present an infectious disease transmission risk.
- If AMs are not adequately removed from the final products…
  - ✓ may cause an immune reaction;
  - ✓ may expose the patients to a toxic substance;
  - ✓ may impair the effectiveness of the therapeutic entity.

INTRODUCTION – 5/5

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- The REALITY is the limited ability to conduct extensive in-process and release tests
  - ✓ lack of in-process holding steps or limited shelf life
    => administer the final products before test results are available
  - ✓ the scarcity of donor or the complex logistics in the transport
    => Limit the amount of material available for testing
- To Minimize the RISK
  - ✓ implement rigorous material qualification
  - ✓ prudent application of manufacturing controls

QUALIFICATION OF AM – 1/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Qualification is the process of acquiring data and establish the source, identity, purity, biological safety, and overall suitability of a specific AM.
- The responsibility for AM qualification goes to the developer or manufacturer of the ATMP.
- A qualification program for AM should address the following:
  - ✓ Identification;
  - ✓ Selection and suitability for use;
  - ✓ Characterization;
  - ✓ Vendor qualification;
  - ✓ Quality assurance and control.

QUALIFICATION OF AM – 2/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

➢ Identification is the first step in qualification program.

	Item	Process Applied	Source*	Intended Use	Quantity/Conc. Needed	Alternate Sources
1	DMEM	amplify	Gibco BRL	cell growth	0.2 mL/cm^2	STEMCELL
2	serum	amplify	Life Biotech	cell growth	10% in medium	Biological Industries USA
3	insulin	amplify	novo nordisk	cell growth	0.005 U/mL	Norvartis
4	trypsin	passage	Sigma Aldrich	cell detachment	1 mL/cm^2 @0.25 U/mg	BIO-RAD
5						
6						

* source in this case indicates vendor and/or countries

QUALIFICATION OF AM – 3/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Selection and Suitability for Use

Developers of ATMP should establish and document the selection criteria for AMs and qualification criteria for each vendor EARLY in the design phase of product development.

➢ **Selection Criteria for AM**
- ✓ microbiological & chemical purity
- ✓ identity
- ✓ biological activity
- ✓ alternatives or replacements

➢ **Qualification Criteria for Vendor**
- ✓ can supply documentation for animal-derived AM, e.g., country of origin (TSE, tuberculosis), the chain of custody for processing sites;
- ✓ can supply documentation for human-derived AM regarding material traceability, e.g., licensed facilities that control donor pool;
- ✓ different grades of animal- or human-derived AMs.

QUALIFICATION OF AM – 4/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Selection and Suitability for Use

- **The complexity of risk assessment** can be reduced by employing one of a number of quantitative or semiquantitative approaches, such as
  - ✓ FMEA, failure mode effects analysis
  - ✓ QFD, quality function deployment
  - ✓ HACCP, hazard analysis and critical control point

AM / Points (1-5)	XX	XX'
Safety Profile	2	2
Used Amount	3	1
Stage of Use (USP/DSP)	2	4
Washable	1	3
Risk Points	12	24

QUALIFICATION OF AM – 5/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Characterization

- For each AM, specific QC tests need to be developed or adopted and implemented to assess a variety of quality attributes, including identity, purity, functionality, and freedom from microbial or viral contamination.
- Test specifications are developed to ensure consistency and performance of the manufacturing process.
- Acceptance criteria are established and justified on the basis of data obtained from lots, such as, preclinical to early clinical; manufacturing development and consistency demonstration; analytical method development and stability studies.
- AM of biological nature: functional or performance testing needed

QUALIFICATION OF AM – 6/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Vendor Qualification – at the earliest opportunity

- basic: an early audit of the vendor's manufacturing facility, e.g. GMP and AM testing program
- essential: a review of the processing procedures and documentation program
- additional: having robust quality systems in place, if certified through an ISO inspection program, or audited by other government agencies
- augmented: with reports of past audits of US suppliers obtained through the Freedom of Information(FOI) Act

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QUALIFICATION OF AM – 7/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Vendor Qualification – at the earliest opportunity

- IMPORTANT to develop a good relationship with a vendor: higher manufacturing standards, custom formulation service, replacement of substandard components upon request, with or without additional costs
- It's critical to ensure the vendor takes appropriate steps to prevent cross contamination between products.
- Vendor should be familiar with the principles of validation, esp. cleaning validation, as well as viral inactivation and sterilization validation.
- Vendor can supply written certification of processing or sourcing changes to customers, well prior to the implementation of the changes.

QUALIFICATION OF AM – 8/8

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Quality Control and Quality Assurance

- Typical QAU (quality assurance/quality control unit) activities include:
  - ✓ incoming receipt, segregation, inspection, and release of materials prior to use in manufacturing;
  - ✓ vendor auditing and certification;
  - ✓ certificate of analysis verification testing;
  - ✓ formal procedures and policies for OOS materials;
  - ✓ stability testing;
  - ✓ archival sample storage.

RISK CLASSIFICATION – 1/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

[Example 1] A manufacturer utilized human serum albumin as a supplement for cell cultivation medium of a marketed cell-based product for human administration => prudent areas of investigation are:

- The impact of inherent variability of AM on final product function should be emphasized, e.g. lot-to-lot variability on cell growth rate or maintenance of a differentiated cellular property
- Stability of this material at the concentration employed in processing or its potential for interaction with other processing components

RISK CLASSIFICATION – 2/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

[Example 2] FBS is used as a supplement to a tissue culture medium to expand a stem cell population from a specific tissue and eventually for patient administration => a qualification program for this AM would include:

- ✓ assurance that the serum was sourced from a country/region free of BSE
- ✓ assurance that the source herds are monitored and test negative for specific diseases relevant in agricultural settings, e.g. tuberculosis, foot and mouth disease
- ✓ testing of the serum for sterility, mycoplasma, endotoxin content, and adventitious bovine viruses

RISK CLASSIFICATION – 3/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

[Example 2] FBS is used as a supplement to a tissue culture medium to expand a stem cell population from a specific tissue and eventually for patient administration => a qualification program for this AM would include:

- ✓ review and archiving of the supplier's COA
- ✓ Lot-to-lot assessment of the ability of the serum to consistently expand a representative cell population using a standardized cell culture QC assay
- ✓ on-site audit the supplier to ensure the material is sourced and processed in a manner deemed acceptable by a responsible QAU

RISK CLASSIFICATION – 4/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Tiers of sample risk categories are presented in the following tables and provided as a guide.
- Risk is also dependent on the amount and the stage at which the AM is used. Tables 1-4 do not address the impact of quantity or stage of use.

RISK CLASSIFICATION – 5/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Tier 1

- ✓ These AMs are low-risk, highly qualified materials that are well-suited for use in manufacturing.
- ✓ The AM is either a licensed biologic, an approved drug, an approved or cleared medical device, or it is intended for use as an implantable biomaterial.
- ✓ Generally these components or materials are obtained as a sterile packaging system or dosage form intended for their label use, but are instead utilized "off label" in the manufacturing process for the cell, gene, or tissue-engineered product.

RISK CLASSIFICATION – 6/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Table 1. AM Risk Tier 1
Low-Risk, Highly Qualified Materials with Intended Use as Therapeutic Drug or Biologic, Medical Device, or Implantable Material

Example	Typical Use in Cell, Gene, or Tissue-Engineered Product Manufacturing	Qualification or Risk Reduction Activities
Recombinant insulin for injection	Cell culture medium additive	DMF cross reference (when possible or practical)
Organ preservation fluid	Process biological fluid employed in tissue transport or processing	Certificate of analysis
Human serum albumin for injection	Cell culture medium	Assess lot-to-lot effect on process performance
Sterile fluids for injection	Process biological fluid employed in tissue transport, cell processing, purification	Assess removal from final product
Implantable biomaterials (formed collagen, silicone, polyurethane constructs intended for surgical implantation)	Scaffolds, matrices for immobilized cellular cultivation	Stability assessment on AM as stored for use in manufacturing[2]
Recombinant deoxyribonuclease for inhalation or injection	Process enzyme employed in viral vector manufacturing, stem cell processing	
Antibiotics for injection[3]	Cell culture medium and biopsy transport fluid additive to reduce risk of bacterial contamination	
Injectable monoclonal antibodies	Immunologically targeting specific cell populations for selection or removal	
Injectable cytokines	Cell culture medium	
Vitamins for injection; defined nutrients, chemicals, or excipients intended for injection	Cell culture medium additive employed in cell expansion, controlled cellular differentiation/activation step, or manufacture of a viral vector	
IV bags, transfer sets and tubing, cryopreservation bags, syringes, needles	Storage vessels or container closure systems, closed aseptic transfer systems	

RISK CLASSIFICATION – 7/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Tier 2

- ✓ These AMs are low-risk, well-characterized material that are well-suited for use in manufacturing.
- ✓ Their intended use is for drug, biologic, or medical device manufacture, including cell, gene, and tissue-engineered products as AMs, and they are produced under relevant cGMPs.
- ✓ Most animal-derived materials are excluded from this category.

RISK CLASSIFICATION – 8/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Table 2. AM Risk Tier 2
Low-Risk, Well Characterized Materials with Intended Use as AMs, Produced in Compliance with GMPs

Example	Typical Use in Cell, Gene, or Tissue-Engineered Product Manufacturing	Qualification or Risk Reduction Activities
Recombinant growth factors, cytokines	Cell culture medium additive	DMF cross reference (when possible or practical)
Immunomagnetic beads	Immunomagnetic separation of cells	Certificate of analysis
Human AB serum	Cell culture medium additive	Assess lot-to-lot effect on process performance
Progesterone, estrogen, vitamins, purified chemicals (USP-grade)	Cell culture medium additives, induction agents, buffer components	Assess removal from final product
Sterile process buffers	Process biological fluid employed in tissue transport, cell processing, purification	Stability assessment on AM as stored for use in manufacturing
Biocompatible polymers, scaffolds, hydrogels	Scaffolds, matrices for immobilized cellular cultivation	When relevant, confirm certificate of analysis test results critical to product (could include functional assay)
Proteolytic enzymes	Process enzyme	Vendor audit
Tissue culture media	Cell culture medium additive	
Monoclonal antibodies	Immunologically targeting specific cell populations for selection or removal	
Density gradient media	Cell separation via centrifugation	

RISK CLASSIFICATION – 9/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Tier 3

- ✓ These AMs are a moderate risk material that will require a higher level of qualification than previous tier materials.
- ✓ These materials are frequently produced for in vitro diagnostic use and are not intended for use in the production of cell, gene, or tissue-engineered products.
- ✓ In some cases, upgrade of AM manufacturing processes may be necessary in order to employ the AM in manufacturing of these products (e.g., modification of the production process for a diagnostic grade monoclonal antibody to include robust viral removal steps in purification).

RISK CLASSIFICATION – 10/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Table 3. AM Risk Tier 3
Moderate-Risk Materials Not Intended for Use as AMs
(frequently produced for in vitro diagnostic use or reagent grade materials)

Example	Typical Use in Cell, Gene, or Tissue-Engineered Product Manufacturing	Qualification or Risk Reduction Activities
Recombinant growth factors, cytokines	Cell culture medium additive	DMF cross reference (when possible or practical) Certificate of analysis Assess lot-to-lot effect on process performance[1] Assess removal from final product Stability assessment on AM as stored for use in manufacturing[2] When relevant, confirm certificate of analysis test results critical to product (could include functional assay)
Tissue culture media	Cell culture medium additive	Vendor audit
Monoclonal antibodies (diagnostic-grade produced in cell culture)	Immunologically targeting specific cell populations for selection or removal	Upgrade manufacturing process for material to GMP
Process buffers	Process biological fluid employed in tissue transport, cell processing, purification	Develop stringent internal specifications
Novel polymers, scaffolds, hydrogels	Scaffolds, matrices for immobilized cellular cultivation	Determine if lot-to-lot biocompatibility, cytotoxicity, or adventitious agent testing are needed
Proteolytic enzymes	Process enzyme	
Purified chemicals (reagent-grade)	Culture medium additives, induction agents, buffer components	

RISK CLASSIFICATION – 11/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Tier 4

✓ These materials may require:

(a) an upgrade of AM manufacturing processes;

(b) treatment of AMs to inactivate or remove adventitious agents, disease-causing substances, or specific contaminants (e.g., animal viruses, prions);

(c) testing of each lot of material to ensure that it is free of adventitious agents, disease-causing substances, or specific contaminants;

(d) validation of the manufacturing process of the cell, gene, or tissue-engineered product to assess consistency of removal of a known toxic substance or lot-release testing to demonstrate reduction levels considered to be safe; or

(e) validation of the manufacturing process of the cell, gene, or tissue-engineered product to assess consistency of removal or inactivation of adventitious agents, disease-causing substances, or specific contaminants associated with the material.

RISK CLASSIFICATION – 12/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Tier 4

- ✓ This is the highest risk level for AMs for they are not produced in compliance with cGMPs. Extensive qualification is necessary prior to use in manufacturing.
- ✓ These AMs, including highly toxic substances with known biological MOA, and also most complex, animal-derived fluid materials not subjected to adventitious viral removal or inactivation procedures, are not intended for use in the production of cell, gene, or tissue-engineered products
- ✓ Developers in the early stages of development should evaluate the necessity of these materials and explore alternative substances or sources.

RISK CLASSIFICATION – 13/13

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Table 4. AM Risk Tier 4
High-Risk Materials

Example	Typical Use in Cell, Gene, or Tissue-Engineered Product	Qualification or Risk Reduction Activities
FBS	Cell culture medium additive	Same as in *Table 3*, plus Verify traceability to country of origin Assure country of origin is qualified as safe with respect to source-relevant animal diseases, including TSE
Animal-derived (including human) extracts	Cell culture medium additive	
Animal-derived polymers, scaffolds, hydrogels	Scaffolds, matrices for immobilized cellular cultivation	
Purified enzymes	Process enzyme	
Ascites-derived antibodies or proteins	Immunologically targeting specific cell populations for selection or removal	
Animal or human cells used as feeder layers	Cell culture substratum or source of medium components	
Chemical entities with known toxicities (i.e. methotrexate, cholera toxin, *Staphylococcus aureus* pore-forming hemolysin, *Staphylococcus* enterotoxins A and B, toxic shock syndrome toxin)	Selection agents used in cell culture to improve or maintain transgene expression, enhance cellular proliferation, improve cell survival upon cryopreservation, superantigens for the activation of T cells	Adventitious agent testing for animal source-relevant viruses

PERFORMANCE TESTING – 1/2

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Performance testing is an essential component of the overall qualification for AM used in ATMP manufacturing.
  - ✓ No simple identity test, nor can they be easily characterized by physical or chemical tests.
- Development of well-defined performance assays for complex AM not only ensure process reproducibility and final product quality, but also, in many cases, satisfy the identity testing criteria in accordance with 21 CFR 211.84(d).
  - ✓ initial qualification of an AM => investigate the effect of the amount of AM on the desired response, e.g. yield, purity, potency of the product
  - ✓ used amount of AM should be chosen to consistently yield the desired effect

PERFORMANCE TESTING – 2/2

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Performance testing assesses the important functional attributes expected of the AM in a scale-down or simulated manufacturing process

Item	Used to	Assay to demonstrate
AM	promote proliferation or the secretion of a therapeutic agent	each lot of AM produces the expected rate and amount of cell proliferation or level of secreted agent
mAb	purify a cell type	the new lot could be shown to purify the cells with expected recovery and purity
DNAse	degrade cellular DNA	the new lot could be tested for DNAse activity
Density gradient material	purify a vector or cell	the new lot could purify the vector or cell to an acceptable level
Plasmid or viral vector	produce a gene therapy vector	the new lot could produce the expected amount of gene therapy vector
Hallow fiber bioreactor	produce a cell therapeutic	the new lot could produce the anticipated amount of cell product

AM RESIDUAL LEVEL ASSESSMENT AND REMOVAL – 1/4

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- AMs are NOT intended to be present in the final dosage form of ATMP for their presence in the final product could
  - ✓ have a detrimental effect on product potency;
  - ✓ lead to undesired effects in the recipient, e.g. direct toxicity of AM or unwanted immunogenic response.
- Risks can be mitigated through the design of processes to include steps to adequately remove the AMs through dilution, separation, or inactivation, as well as the development of analytical detection assays to assess the AM levels during processing and in the final product.
- Assessment and removal strategy for residual AMs should be considered in the early phase of process development.

AM RESIDUAL LEVEL ASSESSMENT AND REMOVAL – 2/4

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

Two approaches for assessing residual AM levels in the final product:

1. Validation study to demonstrate the process is able to remove more of the AM than would be present in the worst-case scenario, should consider:
   - ✓ the assay is able to accurately quantitate the AM in each sample matrix;
   - ✓ the compatibility of the small scale process to the full scale process needs to be demonstrated;
   - ✓ the need to demonstrate that additional, higher level of AM has not affected the purification process.
2. The residual level of AM can be measured for each lot at an appropriate step during manufacturing.
   - ✓ The specification for the maximal amount of AM in the final product is based on the amount of the AM in the lots used in toxicological or clinical studies or known toxicological data.

AM RESIDUAL LEVEL ASSESSMENT AND REMOVAL – 3/4

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Development of sensitive and reproducible analytical assays for AM is important for risk reduction.
  - ✓ Two types of assays are used for assessing the levels of residual AM impurities: a limit test and a quantitative test
  - ✓ Assays for residual AM may be performed on the product before it's formulated, i.e. drug substance, to avoid interference from other components.
  - ✓ Spike-recovery controls are used to demonstrate the sample matrix does not inhibit detection.
  - ✓ Assays should be designed to detect all forms of AMs including aggregates, fragments, or conjugates.

AM RESIDUAL LEVEL ASSESSMENT AND REMOVAL – 4/4

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- other assays used to assess residual AM levels
  - ✓ Immunoassays such as ELISA are most commonly used;
  - ✓ ELISA for BSA has been used to assess residual FBS;
  - ✓ PCR technology has been employed to assess residual host DNA;
  - ✓ and etc.
- If "wash out" of AM is achieved by exhaustive dilution associated with further processing activities, it may be useful to calculate the dilution factor for the AM during the processing.
- Information regarding the safety and tolerability of the AM should be collected in preclinical TOX and later with clinical studies in order to determine the safe or nontoxic levels that must be achieved.

CONCLUSION – 1/1

<1043> ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS

- Good quality of AM should perform as intended in a consistent manner, batch-to-batch, if they are carefully selected and appropriately used.
- To ensure the safety and effectiveness of the final product, it is necessary to implement an AM qualification program.
  - ✓ the risk associated with AM
  - ✓ the stage of manufacture at which it is used
  - ✓ the amount of the AM used

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