主題

水系統監測與趨勢分析

2018年藥廠GMP研習營（衛生福利部食品藥物管理署主辦）

日期	執行單位
107／04／19 & 23	社團法人台灣藥物品質協會

1

講義錯誤地方更正

* 投影片 6 (講義第3頁)
  * 微生物指南在Water for Pharmaceutical Purpose <1231>中提供
    * 用戶應該建立內部規格，或
    * 調整不適合使用之高微生物含量的用水
    * 仍有建議值：PW為100 cfu/mL, WFI為10 cfu/100 mL

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- USP水系統Q&A
- 水系統之趨勢分析

分組討論

Q & A

製藥用水與分析用水*FAQs*

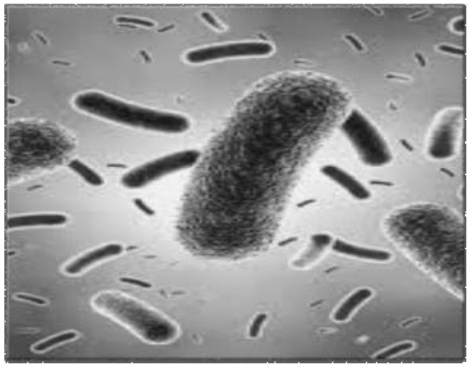
USP

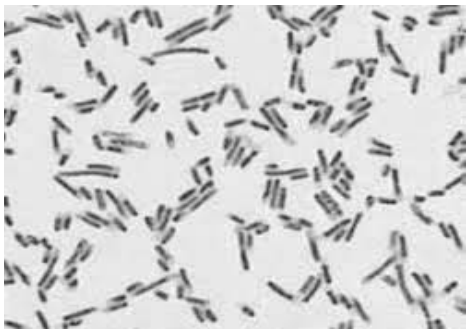
簡介

* USP這幾年修改了<1231>的內容
* 為了讓使用者更了解，USP提供了FAQs的服務
* FAQs整理了21個有關製藥用水及分析用水 (Water for Pharmaceutical and Analytical Purpose) 的問題，供使用者參考

微生物相關

問題01：
為何純水（Purified Water）與注射用水（Water for Injection）專論（Monograph）中，沒有微生物的要求？



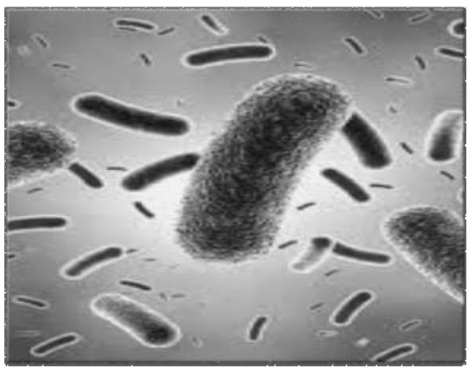


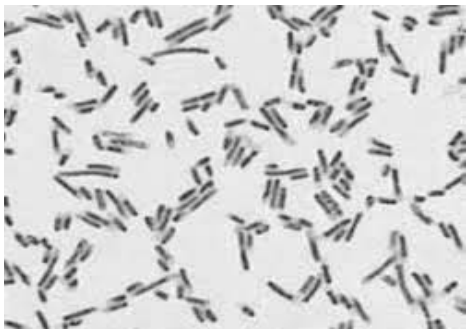
回答

* 因為藥廠的水會用於各種用途
* 放在專論 (Monograph) 中，會讓使用者造成不必要地負擔
  * 無意義的和/或無關緊要的或不適當的要求
  * 例如：用於許多實驗室分析的水
* 微生物指南在Water for Pharmaceutical Purpose <1231>中提供
  * 用戶應該建立內部規格，或
  * 調整不適合使用之高微生物含量的用水
  * 仍有建議值：PW為10 cfu/mL, WFI為10 cfu/100 mL

微生物相關

問題０２：
純水和注射用水中，訂定微生物警戒和行動標準的目的是什麼？





回答

* 警戒和行動標準是製程管制的術語，且應建立在可指示水系統於正常微生物控制範圍外的趨勢水準上
* 根據水系統的正常微生物性能趨勢，這些標準應建立在不高於，且最好低於USP <1231>製藥用水中所列出的標準
* 警戒和行動水平的目的是啟動額外的、不固定的，而不是例行性的微生物管制措施
* 根據水的使用狀況，這些額外的管制措施是用來防止存在於水中，令人不快之數量和類型的微生物

樣品相關

問題03：
針對USP <645>水導電度和<643>總有機碳的離線樣品檢驗，樣品可以在檢驗前儲存多久？

回答

* USP對這個問題的具體答案保持沉默。據了解，一些製造廠的分析由外部實驗室進行；這些分析可能需要幾天或更長的時間。因為這個原因，所以沒有限制時間
* 一般而言，樣品等待的時間，依據承擔的風險由自己決定。不過，還是建議盡快進行檢驗，原因如下：
  * 儲存時，水的純度會隨著時間的推移而降解。由於純化水，注射用水或無菌水的純度很高，因為週遭環境或容器因素，隨著時間的推移，可能降解樣品外，沒有任何幫助
  * 通常藥廠的用水不是批次生產，而是持續地生產與使用。在任何實驗室進行分析之前，水可能已直接的影響或接觸藥品。如果檢驗結果失敗，延遲檢驗只會增加潛在產品影響的風險

樣品相關

問題０４：
對於USP之<645>導電度和<643>總有機碳的離線檢驗樣品，我應該如何儲存樣品？

回答

* 對於實驗室分析，樣品應存放在不會影響檢驗結果的容器中。這是為了防止偽陽性發生，及不必要的調查
* 舉例來說，通常將水儲存於玻璃容器中幾小時是可以的，但儲存較長時間則會適度增加樣品之導電度。這是因矽酸鈉從玻璃中溶出，增加水的pH值和導電度，並可能導致不合格失敗的水導電度結果。一般來說，用於長期保存水導電度檢驗樣品，乾淨的塑膠容器是更好的選擇
* 對於總有機碳，也有類似的理由。許多種不脫落的塑膠或玻璃即足夠
* 一般而言，儲存於環境溫度或冷藏溫度，對這些化學檢驗是最好的。而用於微生物檢驗的樣品則建議冷藏儲存
* 任何容器的清潔度都是非常重要的。由於這些用水的純度非常高，必須避免指紋，肥皂和其他殘留物。可能會導致偽陽性的結果

樣品相關

問題 0 5 ：

我可以在線上進行<645>

水導電度和<643>總有

機碳的檢驗嗎 ？

回答

* USP <643>及<645>這兩章特別聲明這些檢驗可以離線或線上執行
* 每種方法皆有其優點和挑戰，且在這些章節和<1231>製藥用水中，對它們進行了更詳細的描述
* 一般而言，線上檢驗可避免人員，容器或環境對離線樣品造成污染的風險，並提供立即性的分析和及時控制、決策與介入的機會。例如，可以連續性地監測和接受化學屬性的水質。反過來說，可以及時防止因檢測失敗時，用水的分送
* 不過，對於具有多種用水和循環的設施，集中式的實驗室分析系統可能提供更經濟式的選擇
* 無論哪種情況，水的樣品須能代表製程中使用的水

TOC相關

問題06：

純水和注射用水的總有機碳限值是多少？

回答

* 目標限量為500 µg Carbon/L
* 真正的限量為：總有機碳測量系統對500 µg Carbon/L 的參考標準蔗糖配製溶液之對應值 (Rs) ，對試劑用水對應值 (Rw) 進行的校正值
* 這個限量等於Rs – Rw
* 實際的數量會根據您的參考標準溶液，您的設備，背景碳等而有所不同
* 所以，USP參考標準品是必需的

TOC相關

問題07：

在總有機碳一般章節<643>中，通常都多久執行系統適應性檢驗？

回答

* USP<643>故意沒有說系統適應性檢驗 (SST) 應該多長時間執行一次
* 推論是這個頻率取決於總有機碳 (TOC) 儀器的穩定性、以及與水質和風險相關的其他因素。
  * 如果水系統的TOC非常低，比如 < 20 ppb，那麼很多人會選擇降低檢驗頻率，因為風險較低。
  * 不同的TOC測量技術的穩定性可能會在很長一段時間內發生變化。
  * 經由儀器製造商或使用者的經驗分享，也有助於決定適當的頻率
* 另一個因素是不合格系統適用性檢驗結果的風險，因為本次計算中使用的Rs – Rw結果，是儀器的反應極限，它決定TOC檢測結果是否合格
  * 如果得到不合格的系統適用性檢驗，則表示自上次成功的系統適用性檢驗以來，所有TOC檢測結果是不準確的
  * 基於這個原因，許多使用者選擇比總有機碳儀器所建議的穩定性，更頻繁地執行系統適用性檢驗，只是為了減少可能得到樣品不合格結果的影響

回答

* 這也是低TOC水系統中，即便系統適應性檢驗失敗，其風險也很低的原因
  * 若系統適應性檢驗故障，則需要進行一些補救措施以重新調整儀器，更換燈泡或其他方法以進行儀器的改善
  * 但即使有50％的錯誤，對於過往的總有機碳數值亦無影響
    * 因為讀數，即使誤差，相對於限量也很低
* 在高的總有機碳水系統中，適用性檢驗的失敗可能更為重要。這取決於使用者願意承擔的風險，以及對儀器過往的穩定性和其他因素的了解
* 因此，總有機碳<643>沒有提到對執行系統適應性檢驗的頻率，因為這取決於使用者決定什麼是合適的

TOC相關

問題08：

請問用於總有機碳系統適應性，所配製的參考標準溶液可以重複使用及儲存多久？

回答

* 若USP對儲存條件和已準備的總有機碳 (TOC) 參考標準溶液的安定性保持沉默，則應該
  * 1) 準備新的溶液，或
  * 2) 在第三方供應商獲得的期限內使用，或
  * 3) 在經安定性研究得到的一定期限內使用
* 在所有情況下，USP的參考品都會被指定。
* 很多因素都會影響參考標準溶液的安定性。這些因素包括
  * 溫度
  * 照明
  * 氧氣
  * 微生物分解，和
  * 吸附於容器表面

回答

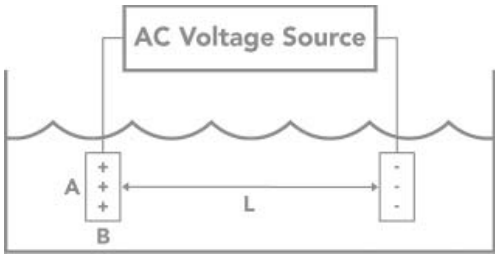
* 與新配製的溶液相比，濁度，額外的顏色或性能變化的發展都是不安定性的指標。
* 大部分溶液的供應商都會指定末效日期。
* 但實際的狀況是，在適當的保存溫度與容器，及避光 (pBQ) 下
  * 濃縮的參考標準蔗糖 (Sucrose) 溶液可放置3 – 6個月，
  * 類似的1, 4 Benzoquinone (pBQ)溶液，可以放置約 2 個月
* 建議放在冰箱，因為可以緩和溶液的降解，及降低微生物的生長，尤其是蔗糖溶液

電導度(Conductivity)相關

問題09：

在水的導電度檢驗中，

添加KCl的主因是什麼？



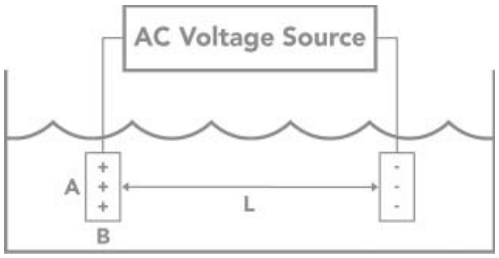
回答

* 在導電度檢測的第3階段中，加入中性電解質(KCl) 以增加離子強度，並準確測量溶液的pH值
* 如果溶液的離子強度沒有增加，那麼pH值的測量將高度不穩定且不準確。所以加入KCl，是為了有效地進行pH測量，以作為在<645>水導電度第3階段檢測的一部份。
* 離子強度的增加是需要的，才能使pH值的電極膜片/連接點的濃度梯度最小化。大的濃度梯度會導致不平衡和不安定的pH值

電導度(Conductivity)相關

問題１０：

試問，我可否從第2階段開始進行<645>水的導電度檢測，或者還是需要從第1階段開始？



英文-系統偵測

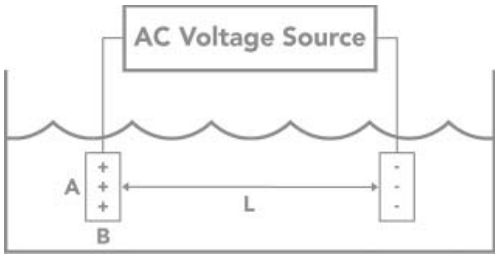
回答

* 不需按順序執行第1階段和第2階段
* 如果進行離線的檢測，可以直接進入第2階段，不必等第1階段失敗後再執行

電導度(Conductivity)相關

問題11：

導電度電極常數是否為標示值的±2%？



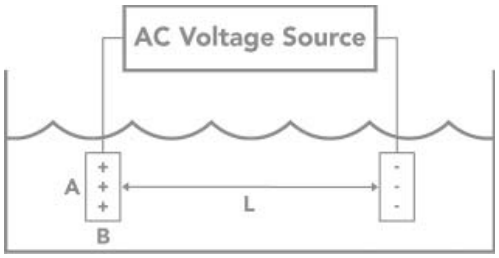
回答

* The cell constant accuracy must be ±2% of the certified value, not the nominal value
* 電極常數的準確性，必須是公認值的±2%，而不是標示值

電導度(Conductivity)相關

問題12：

對離線導電度的檢測而言，什麼是"合適的容器"？



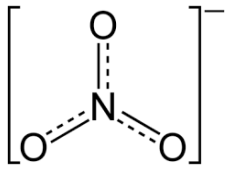
回答

* 一般而言，任何已知不會影響導電度的材質都是合適的
* 許多塑膠容器，包括PTFE，HDPE，LDPE和一些聚碳酸酯都是合適的
* 立即進行檢測時，玻璃容器也很適合
* 無論什麼材質，這些容器都必須被清潔且不含任何清潔劑，如肥皂。肥皂非常具有傳導性

其他化學檢驗相關

問題*13*：

沒有*pH*值、硝酸鹽或重金屬的檢驗，請問這是正確的嗎？

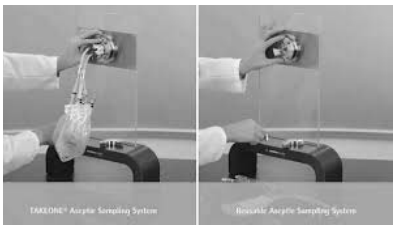


回答

* 是的，這是正確的
* 在USP中的水，從來沒有過硝酸鹽檢驗，USP在1996年取消了重金屬檢驗，1998年則取消pH值檢驗。
  * 註：pH值測量（不是檢驗）是水導電度<645>第三階段檢驗的一部分，但這仍是導電度限量檢驗
  * 請注意，如果水質通過了導電度的規格，pH值不能超出5.0 ~ 7.0的規格
  * 如果您通過了導電度，且水系統的原水也符合個論要求的飲用水（包含美國，歐盟，日本或世界衛生組織），重金屬檢驗或硝酸鹽檢驗也不能失敗
  * 在某些情況下，上述項目的檢驗，可能是其他藥典所要求的

取樣相關

問題14：
請問是否可以藉由執行水質取樣點的微生物檢驗，來放行使用嗎？

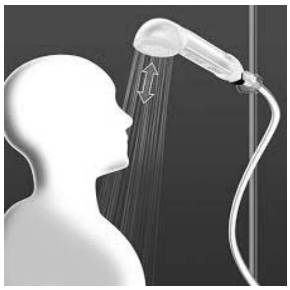


回答

* 在某些情況下，可以如此做。
* 水系統內的微生物品質，如同取樣點端口水質，可能比在製程使用期間運送至使用端 (POU) 的品質更好
  * 這是因為系統用水從出口移轉到POU時會發生微生物污染
  * 水質從系統運送到POU會影響藥品和其他用途的使用
  * 如果有良好的用水習慣，使得取樣點的微生物數量與製程使用規範中的POU相同，那麼取樣點的微生物數量和運送水質反應失敗的風險就會比較低
  * 一般來說，放行使用水應基於POU樣本反應製程的用水習慣，而不是取樣點的數據

取樣相關

問題15：
水系統的出水口，有時候被稱為使用的出口點可被視為使用點嗎？



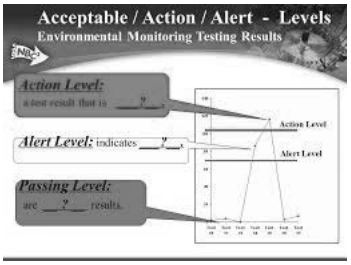
回答

* 不是
* 使用於藥品調配或清潔用水，或進入製造過程之處的點才是真正的使用點
* 應了解水系統中，所有真正使用點的水質；例如，藉由與製程用水過程相同的取樣過程，取得的水樣品進行檢驗。
* 真正使用點的水質是水必須在“適合使用”的地方，也就是通過水質規格

規格相關

問題16：

若沒有水中微生物的規格，只有警戒和行動標準，是否會被認為不適合使用？



回答

* 是的。
* 通常水中微生物超出USP <1231>中的行動標準 (純化水為100 cfu/mL，注射用水為10 cfu/100mL) ，即被認為不適合使用。
* 這就是為什麼如果超過這些行動標準就必須進行OOS調查。
* 因此，無論您是否聲明微生物規格，USP <1231>中的值，都被假設是藥典行動標準
* 為了避免超過水中微生物的規格，應使用基於趨勢的警報和行動標準來監測和控制水系統，以利於生產適合使用的水質

注射用水相關

問題17：
根據GMP的注射用水製程系統所遇到最常見的問題是什麼？我們應該尋找什麼？

回答 - 1

* 一個常見的問題是在主要的WFI加熱器系統外，哪裡有包括一個大型遮罩和管狀之熱交換器，以冷卻WHI的子迴路
* 當子循環進行熱水消毒時，並不允許冷卻熱交換器有足夠的接觸時間，以便其可徹底加熱和消毒
* 如果未完全消毒，在恢復冷卻使用後，存活的生物膜，將立即於冷卻子循環系統中再次植入，且繁殖到可檢測出的微生物數量

回答 – 2

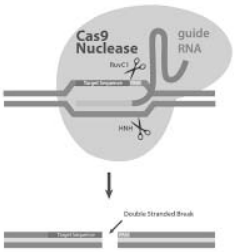
* 其他常見於冷卻注射用水系統中的問題是死角，有時是臨時性的，通過開放性的硬管連接到未使用且為排水的設備。
* 消毒過程中的熱水與死角中的積水並沒有混合的很好，所以永遠消毒不到死角。
* 如果在上次使用過程中，有任何污染進入該處，這些污染物會在未消毒的死角中，不斷增加，並持續污染循環用水

回答 – 3

* 另一個常見問題是，不堪負荷的蒸餾純化的過程，造成水中含高劑量的內毒素 (大於100 EU/mL)
* 這可能發生在
  * 預處理單位操作系統 (如活性碳床) 的缺乏維護，以及
  * 當原水中從氯胺切換成氯，而伴隨高內毒素含量長達一年的情況下

微生物相關

問題18：
核酸酶（*Nuclease*）是否從生物膜產出，並在消毒過程中釋放更多？



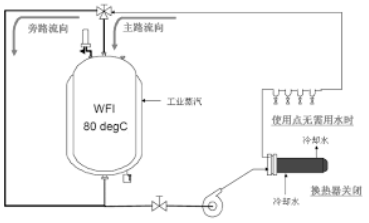
回答

* 如果在不常使用的化學消毒劑的系統中存在大量的生物膜，不需要感到驚奇
* 如果使用熱水進行消毒，會使核酸酶變性，因此，熱水消毒系統可能不會出現這種現象

消毒相關

問題19：

在新的USP <1231>中，熱水消毒的建議溫度從過去的80°C，到現在可允許的65°C～80°C；而現在高於80°C反而是不智的，這觀念是否正確？



回答

* 是的
* 80°C的溫度對於較冷的位置是非常「寬容的」，即使在10-15°C的溫度損失下，仍然可以進行消毒，因為它通過對流和傳導穿透整個系統，因此非常有效
* 較低的溫度（低至65°C）也可以使用，但，對於較冷的位置（例如主迴路外的出口閥）是「不可寬恕的」
* 因此，為了確保所有表面達到超過60°C的消毒溫度，必須使用稍涼的熱水沖洗較冷的位置
* 除非系統專門為此設計，否則高於80°C的溫度會影響系統材料（例如墊片和隔膜）的壽命
* 80°C的溫度足夠以熱殺死大部分在水系統中耐熱的生物膜生物體，因為其D值約5毫秒

取樣相關

問題２０：
什麼時候取樣口須接上製程軟管？這是要求還是建議？

回答 – 1

* 如果抽樣是用於製造用水的QC放行，那製造使用的出口必須以
  * 與製造使用時相同的方式進行取樣
  * 相同的出口消毒方式 (如果有的話)
  * 相同的製造軟管 (不管多麼骯髒或維護不善)
  * 相同的預沖刷 (如果有的話)
* 樣本數據的目的是複製製造過程中使用的相同質量的水，因此您必須在樣本收集中複製如何從系統中取水以供使用
* 這些使用水的程序在離開水系統時，會嚴重污染系統中的原始水質，而將"討厭"的水輸送到製造作業中
* 如果以不同於 (優於) 製造使用的方式的取樣，將得到更低 (更好) 的微生物計數，這些數值並不代表實際使用的水質
* FDA要求，用於品管放行之製造用水的取樣，須和製造使用時一致。如果不是，這可能會得到FDA 483的觀察或更糟糕的結果

回答 – 2

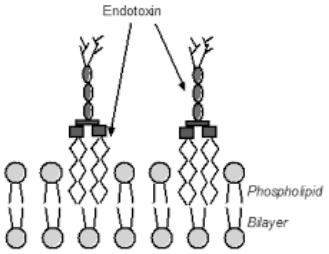
* 如果是為了水系統監測和微生物控制的目的，而進行製程管制的水取樣，則可以自非製造使用的取樣口取樣
* 因在出口處收集樣品，可能同時得到來自出口處的生物負荷 (Bioburden) ，所以，可以努力確保在出口處取得的樣品，在離開系統時不會增加水中的微生物含量
  * 極端出口處消毒
  * 強烈地徹底沖刷
  * 使用無菌軟管等
* 作為製程管制，我們會比較關心在取樣閥後的水質，且不希望在採樣口污染，而造成數據解釋時的偏差

回答 – 3

* 然而，從採樣口 (而不是生產用途出口) 收集的水，通常不能用於水的品管放行，因為它不是以實際使用的方式收集
* 製造業通常不在從採樣口擷取水樣品

內毒素相關

問題２１：
因不同消毒方法而造成
內毒數含量增加的風險
是什麼？



回答 – 1

* 內毒素水平通常只是WFI系統的一個問題
* 大多數WFI系統通過高溫消毒
  * 熱水比蒸汽更好
  * 因為熱水消毒不需要特殊工程
  * 並且非常充足
* 隨著歐洲藥典在WFI專論 (Monograh) 中，放寬注射用水的配製方法，非蒸餾純化技術變得更廣泛，未來幾年將會使用臭氧
* 通常因WFI系統用熱或臭氧消毒頻率不比每週低，所以沒有足夠的時間使生物膜 (及其內毒素) 在系統中發展，並通過定期消毒來釋放內毒素
* 如果系統消毒頻率低得多，那麼發展中的生物膜，有可能在定期消毒被殺死，而釋放可檢測出的內毒素

回答 – 2

* 如果使用臭氧以外的化學消毒劑 (這對於WFI系統或內毒素控制的純水系統來說，非常不典型) ，則必須將消毒劑沖刷掉，這也會沖掉任何已釋放的內毒素

水系統監測計畫

Testing Frequencies for Water System

Water	Testing Frequency
Drinking water/water that meets the requirements for drinking water	
Chemical	If certificates form the municipal works are available, additional testing is not required
Microbiological	If certificates from the municipal works are available, additional testing is not required
Purified Water	
Chemical	Weekly to once quarterly, depending on its use
Microbiological	Weekly to once quarterly, depending on its use

Testing Frequencies for Water System

Water	Testing Frequency
WFI for manufacture	
Chemical	Twice a month to once quarterly, depending on its use
Microbiological	Water at the start and end of production (batch-specific), however, at least monthly
WFI for final rinsing water	
Microbiological	Depending on its use, water at the start and at the end of rinsing, or on a weekly to monthly basis depending on the rinsing frequency
Water for autoclave cooling for cooling ampoules	
Chemical	Twice a month to once quarterly, depending on its use
Microbiological	Monthly

Measures required when deviations are discovered during water monitoring

* Actions to be taken:
  * Investigation of system endotoxin and water-chemical data
  * Investigation of bioburden data for other samples or locations in the system - valve contamination versus system contamination
  * Investigation of the efficiency of the sanitization approach and the sanitization intervals
  * Inspection of the maintenance reports for the system
  * Integrity check of the sampling and application process
  * Inspection of the system for dead legs, appropriate gradients, correct design and position of the sampling valves

GMP Manual

Measures required when deviations are discovered during water monitoring

* Following questions should also be asked:
  * Which and how many microorganisms were isolated at what location?
  * Who took the sample and which sampling containers were used?
  * How was the sample transported to the laboratory and how long did it take?

GMP Manual

水系統監測結果趨勢分析與調查

OOLS

Out of Trend v.s. Out of Limits

* Out of Trend
  * 和趨勢有關
  * 多用於
    * Stability Testing
    * Calibration
    * Maintenance
    * Qualification
    * Quality System
* Out of Limits
  * Alert Limit & Action Limit
  * 多應用於環境監測與水系統監測

SOP for Handling of OOL Results in EM & WSM

1. Purpose
   Describe procedure for handling OOL results of environmental monitoring (EM) and water system monitoring (WSM) results.
2. Scope
   This SOP is applicable to handling and conducting investigations when OOL (OOL) results are obtained in EM and WSM.
3. Responsibility
   - 3.1. QC Microbiology
     - 3.1.1. Microbiology Officer is responsible to notify Microbiology Head or his designee when and alert or action limit is obtained
     - 3.1.2. Head Microbiology or his designee is responsible to notify the QA and concerned departments and initiate investigation in the laboratory and concern department
     - 3.1.3. To implement any corrective action and preventive action

SOP for Handling of OOL Results in EM & WSM

3. Responsibility
   - 3.2. QA Department
     - 3.2.1. To participate in investigation
     - 3.2.2. To review and approve investigation reports
     - 3.2.3. To review action taken reports
   - 3.3. Production/Engineering Departments
     - 3.3.1. To participate in investigations
     - 3.3.2. To implement necessary corrective and preventive actions

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.1. Notification and allotment of number of OOL result

4.1.1. On obtaining an OOL result, the microbiologist shall notify the Microbiology In Charge or his designee and they shall notify the QA and concerned department.

4.1.2. The details of OOL results shall be entered in Logbook and a number shall be allotted as M-OOL-YYYYNNN, where

4.1.2.1. M-OOL: Microbiological Monitoring – OOL Result

4.1.2.2. YYYY: Represents digits of current year

4.1.2.3. NNN: Represents serial numbers starting with 001

4.1.2.4. Example: The first OOL reported in 2018: M-OOL-2018001

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.2. Handling and Investigation of OOL Results in Microbiological Monitoring of Cleanrooms
Note: This section is applicable for handling and investigation of OOL results in Passive Air Sampling (Settle Plate), Active Air Sampling and Surf Sampling.

4.2.1. Observe the plates under incubation (sampled after the date of sampling showing OOL results) of the sample location/room showing OOL and check of for any OOL results

4.2.2. Inform the observations to Head Microbiology or his designee.

4.2.3. Verify the negative control plate incubated along with test samples for any contamination

4.2.4. Inform the observation to Head Microbiology or his designee.

4.2.5. Process the OOL results for identification as follows:

4.2.5.1. In case of out of alert limit results, perform gram staining of morphologically similar colonies and identification of representative isolates based on Gram Staining Results as per SOP

4.2.5.2. In case of out of action limit results in Grade C and Grade D areas, perform gram staining of morphologically similar colonies and identification of representative isolates based on Gram Staining Results as per SOP.

4.2.5.3. In case of out of action limit results in Grade A and Grade B areas perform identification of all isolates as per SOP and also by DNA sequencing

SOP for Handling of OOL Results in EM & WSM

4. Procedure
   - 4.3. Investigation of Out of Alert Limit Results
     - 4.3.1. Review the data for the sample location/room in question for any previous instances of OOL results in last three months
     - 4.3.2. If review of data or plates under incubation shows occurrences of out of alert limit results for more than three consecutive days or occurs frequency, then the investigation should be elevated to out of action limits
     - 4.3.3. Laboratory Investigation
       - 4.3.3.1. Interview the microbiologist who performed sampling and verify whether the sampling was performed as per SOP and if any deviations observed during the sampling/testing/transportation and disinfection of plates
       - 4.3.3.2. Verify the instruments used (air sampler) were operated properly and accessories used (air sampler head or swab template) were sterilized
       - 4.3.3.3. Verify all the media used were within their shelf life and review their preparation records for results of pre-incubation and sterility checks
       - 4.3.3.4. Interview the media personnel for any deviation observed during preparation/pouring of plates
       - 4.3.3.5. Review the results of all EMP parameter of the particular days.(Active, Passive ,surface & personnel monitoring)
       - 4.3.3.6. If contamination in negative control plates is observed or laboratory investigation reveals fault in sampling, discrepancies in status of air sampler, air sampler head/swab templates or results of media pre-incubation and sterility check are not satisfactory, then the occurrence of OOL results could attributed to laboratory/sampling error

SOP for Handling of OOL Results in EM & WSM

4. Procedure
   - 4.3. Investigation of Out of Alert Limit Results
     - 4.3.4. Facility Investigation
       - 4.3.4.1. Review cleaning/disinfection logs, operational logs and other activities of subject area for any discrepancies
       - 4.3.4.2. If the sample location is in critical area, then review the entry exit logs for number of persons present in the area, their duration of stay in the area an their personal hygiene and training / qualification status
       - 4.3.4.3. Review of records of physical conditions like pressure differentials, temperature and relative humidity of the subject area on the day, days before and after occurrence
       - 4.3.4.4. Contact Engineering department for any discrepancies in the functioning of HVAC and other systems or any maintenance activities undertaken or du maintenance
       - 4.3.4.5. If any discrepancies observed during review, determine if it has any impact on the observed results.
       - 4.3.4.6. Record all the observations in the investigation report

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.4. Investigation of Out of Action Limit Results

4.4.1. Based on the criticality of operations performed in the area showing OOL results and observations of plates under incubation, decision sh be taken for use of the area for critical operations

4.4.2. If out of action limits are observed in Grade A and B of filling area then investigation to be trigged. B on the risk, the production shall be stopped till completion of investigation and after obtaining satisfactory results of three consecutive days, given the clearance to start the production by Head Q.A with the consultation of Head Engineering and Head Production

4.4.3. Quarantine the subject batches till investigation is complete, based upon the investigation & risk assessment if finding impact on product quality the concern batches shall be rejected and if finding no impact on product quality then concern batches shall be release

4.4.4. Review the data for the sample location/room in question for any previous instances of OOL results in last three months.

4.4.5. If the data indicates previous occurrences of OOLs, then review the previous investigation reports to determine any similarities

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.4. Investigation of Out of Action Limit Results

4.4.6. Laboratory Investigation

4.4.6.1. Interview the microbiologist who performed sampling and verify whether the sampling was performed as per SOP and if any deviations observed during the sampling/testing/transportation and disinfection of plates.

4.4.6.2. Verify the instruments used (air sampler) were operated properly and accessories used (air sampler head or swab template) were sterilized.

4.4.6.3. Verify all the media used were within their shelf life and review their preparation records for results of pre-incubation and sterility checks

4.4.6.4. Interview the media personnel for any deviation observed during preparation/ pouring of plates

4.4.6.5. Review the results of all EMP parameter of the particular days.(Active, Passive ,surface & personnel monitoring)

4.4.6.6. If contamination in negative control plates is observed or laboratory investigation reveals fault in sampling, discrepancies in status of air sampler, air sampler head/ swab templates or results of media pre-incubation and sterility check are not satisfactory, then the occurrence of OOL results could attributed to laboratory/ sampling error

SOP for Handling of OOL Results in EM & WSM

4. Procedure
   - 4.4. Investigation of Out of Action Limit Results
     - 4.4.7. Facility Investigation
       - 4.4.7.1. Review cleaning / disinfection logs, operational and other activities of subject area for any discrepancies.
       - 4.4.7.2. If the sample location is in critical area, then review the entry exit logs for number of persons present in the area, their duration of stay in the area an their personal hygiene and training / qualification status
       - 4.4.7.3. Interview the personnel's of particular day in which the OOL Observed for any deviation observed during gowning procedure and practices in area et • Review the material movement procedure and any other deviation /Change in procedure
       - 4.4.7.4. Review of records of physical conditions like pressure differentials, temperature and relative humidity of the subject area on the day, days before and after occurrence
       - 4.4.7.5. Review the preparation and sterilization records of materials used in the area for any deviations
       - 4.4.7.6. If the action limit has occurred during batch activity, review the executed batch record for any discrepancies or other helpful information
       - 4.4.7.7. Review the batches manufactured during occurrence of out of action limit results for microbiological parameters
       - 4.4.7.8. Contact Engineering department for any discrepancies in the functioning of HVAC (Velocity, air change & HEPA filter integrity) and other systems or maintenance activities undertaken or due for maintenance
       - 4.4.7.9. Review the nonviable particulate count results of the particular area performed on the day, days before and after occurrence
       - 4.4.7.10. Visit the subject area and verify the physical conditions, general cleanliness and any other abnormalities, which could have contributed for the occurring of out of action limit results
       - 4.4.7.11. If any discrepancies observed during, determine if it has any impact on the observed results

SOP for Handling of OOL Results in EM & WSM

4. Procedure
   - 4.4. Investigation of Out of Action Limit Results
     - 4.4.8. Based on the information gathered, determine if follow up monitoring is required or not as per investigation report and proceed accordingly
     - 4.4.9. If no assignable cause is identified or the follow up monitoring results are not satisfactory, in addition to above actions, appropriate additional measures can be initiated as follows:
       - 4.4.9.1. Increasing of cleaning/disinfection or change of disinfectants
       - 4.4.9.2. Increasing in monitoring frequencies or increase of sample points in subject area for monitoring
       - 4.4.9.3. Testing for nonviable particulate counts
       - 4.4.9.4. Testing of HEPA filters for integrity and air velocity
       - 4.4.9.5. Any other appropriate activity
     - 4.4.10. Review the identification results and verify if it is normal micro flora of the area. If isolate is different or objectionable, initiate necessary corrective actions

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.5. Handling and Investigation of OOLs Results in Non Viable Monitoring

4.5.1. On obtaining any OOL results during nonviable monitoring, immediately do the following:

4.5.1.1. Check the instrument is operating properly and any disturbance or changes in room conditions is observed

4.5.1.2. Check activities (specifically for particle or aerosol generating or disturbance to particle counter probe) performed around the sample location during the time of OOL result and evaluate if it has any effect on the reported result

4.5.1.3. Verify that the instrument used was within calibration and testing performed as per procedure. If appropriate perform the zero count of the particle counter

4.5.2. Resample the location after the conditions are restored and verify the results. Record the noted observation the report. If the results of resample conforming to limits, then no further action is required. If the results are still nonconforming proceed to 4.5.3

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.5. Handling and Investigation of OOLs Results in Non Viable Monitoring

4.5.3. Review the trend for the sample location / room in question and results of other sample locations performed on the day

4.5.4. Review department cleaning logs, room differential pressure records, number for personal in the room at the time of testing, number of equipment and their operation status and other activities for any discrepancies.

4.5.5. Contact Engineering / Maintenance department and review logs for any discrepancies in the functioning and maintenance of HVAC and other systems or any maintenance activities undertaken

4.5.6. Evaluate the information gathered and determine if it has an impact on the results observed

4.5.7. Based on the information gathered, evaluate the actions to be performed and perform resampling of the concerned location or room as per Investigation report and proceed accordingly

4.5.8. If the resample results conform to limits then no further action is required

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.5. Handling and Investigation of OOLs Results in Non Viable Monitoring

4.5.9. If the resample result does not conform to limits, then carry out further investigation for determining the root cause

4.5.10. Following activities can be performed to determine the root cause:

4.5.10.1. Extensive cleaning of area

4.5.10.2. Air Velocity verification of HEPA filters

4.5.10.3. HEPA filter integrity testing

4.5.10.4. Air flow studies

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.6. Handling and Investigation of OOL Results in Personnel Monitoring

4.6.1. Observe the plates under incubation (sampled after the date of sampling showing OOL results) of the sample same person(s) showing out limits and check of for any OOL results. Inform the observations to Head Microbiology or his designee

4.6.2. Verify the negative control plate incubated along with test samples for any contamination. Inform the observation to Head Microbiology or his designee

4.6.3. Observe the other plates of environmental monitoring performed on the day of OOL occurrence and compare the colonies with plates show OOL results

4.6.4. Process the OOL results for identification along with morphologically similar colonies from environmental monitoring plates if any as follows:

4.6.4.1. Perform gram staining of morphologically similar colonies and identification of representative isolates based on Gram Staining Results as per SOP

4.6.4.2. In case of OOL results in Grade A and Grade B areas perform identification of all isolates as per SOP and also by DNA sequencing

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.6. Handling and Investigation of OOL Results in Personnel Monitoring

4.6.5. Laboratory Investigation

4.6.5.1. Interview the microbiologist who performed sampling and verify whether the sampling was performed as per SOP and if any deviations observation during the sampling/testing.

4.6.5.2. Verify all the media used were within their shelf life and review their preparation records for results of pre-incubation and sterility checks

4.6.5.3. If contamination in negative control plates is observed or laboratory investigation reveals fault in sampling, discrepancies in results of media pr incubation and sterility check are not satisfactory, then the occurrence of OOL results could be attributed to laboratory/sampling error

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.6. Handling and Investigation of OOL Results in Personnel Monitoring

4.6.6. Facility Investigation

4.6.6.1. Review the previous data of concerned person for any OOL results

4.6.6.2. Verify the personal hygiene and health status of concerned person. Review the medical and training records of the concerned person

4.6.6.3. Review the environmental monitoring data of day and days before and after the day of occurrence for OOL results

4.6.6.4. Review cleaning / disinfection logs, entry exits logs and other activities of subject area for any discrepancies

4.6.6.5. Review of records of physical conditions like pressure differentials, temperature and relative humidity of the subject area on the day, days before and after occurrence

4.6.6.6. Review the garment preparation and sterilization records for any discrepancies

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.6. Handling and Investigation of OOL Results in Personnel Monitoring

4.6.7. Based on the information gathered, determine the actions to performed as per Investigation and Decision Flow Chart and proceed accordingly

4.6.8. Review the activities performed the concerned individual and if he has performed critical aseptic operations, critically review the microbiological results of the concerned batch

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.1. Observe the plates of same type of water sampled and analyzed on the same day and those under incubation (sampled after the date of sampling showing OOL results) of the sample location / sample type showing OOLs and check of for any OOL results

4.7.2. Inform the observations t Head Microbiology or his designee.

4.7.3. Verify the negative control plate incubated along with test samples for any contamination

4.7.4. Inform the observation to Head Microbiology or his designee

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.5. Process the OOL results for identification as follows:

4.7.5.1. In case of out of alert limit results, perform gram staining of morphologically similar colonies and identification of representative isolates based on Gram Staining Results as per SOP

4.7.5.2. In case of out of action limit results, perform gram staining and identification of all colonies for WFI and Pure Steam Condensate and morphologically similar colonies isolates based on Gram Staining Results for Purified Water and other water samples as per SOP

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.6. Investigation of Out of Alert Limit Results

4.7.6.1. Review the data for the sample location / system in question for any previous instances of OOL results in last three months

4.7.6.2. If the data indicates previous occurrences of OOLs, then review the previous investigation reports to determine any similarities

4.7.6.3. Laboratory Investigation

4.7.6.3.1. Interview the microbiologist who performed sampling and verify whether the sampling was performed as per SOP and if any deviations observed duri the sampling/testing

4.7.6.3.2. Verify the materials used for sampling and testing was properly sterilized and handled.

4.7.6.3.3. Verify all the media used were within their shelf life and review their preparation records for results of pre-incubation and sterility checks.

4.7.6.3.4. If contamination in negative control plates is observed or laboratory investigation reveals fault in sampling and testing results of media pre-incubation sterility check are not satisfactory, then the occurrence of OOL results could be attributed to laboratory/sampling error

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.6. Investigation of Out of Alert Limit Results

4.7.6.4. Water System / Facility Investigation

4.7.6.4.1. Contact Engineering and Production Department for any discrepancies in the functioning of water systems or any maintenance undertaken. Verify the operation and sanitization log books for concerned system / area

4.7.6.4.2. If the OOL result is observed in only one sample location and rest of the system is conforming to specifications, then verify the sample location any discrepancies in the sample/user point and the location

4.7.6.5. Based on the information gathered, determine the actions to be initiated as per Investigation report and proceed accordingly

4.7.6.6. Review the identification results and verify if it is normal micro flora of the water system or of human commensal or from environment. If isolate different or objectionable, initiate necessary corrective actions

4.7.6.7. If the results of follow up sampling are satisfactory after carrying out corrective actions (if any) conclude the investigation

4.7.6.8. If the results of follow up sampling are not satisfactory carry out further investigation take necessary actions accordingly

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.7. Investigation of Out of Action Limit Results

4.7.7.1. Review the data for the sample location / system in question for any previous instances of OOL results in last three months

4.7.7.2. If the data indicates previous occurrences of OOLs, then review the previous investigation reports to determine any similarities

4.7.7.3. If the subject sampling location is a daily monitoring sample location and results of subsequent days are also showing OOL results or the sample location is on sampling rotation, them immediately schedule for three consecutive day sampling

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.7. Investigation of Out of Action Limit Results

4.7.7.4. Laboratory Investigation

4.7.7.4.1. Interview the microbiologist who performed sampling and verify whether the sampling was performed as per SOP and if any deviations observed during the sampling/testing.

4.7.7.4.2. Verify the materials used for sampling and testing was properly sterilized and handled

4.7.7.4.3. Verify all the media used were within their shelf life and review their preparation records for results of pre-incubation and sterility checks

4.7.7.4.4. If contamination in negative control plates is observed or laboratory investigation reveals fault in sampling and testing results of media pre-incubation sterility check are not satisfactory, then the occurrence of OOL results could be attributed to laboratory/ sampling error

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water

4.7.7. Investigation of Out of Action Limit Results

4.7.7.5. Water System / Facility Investigation

4.7.7.5.1. Contact Engineering and Production Department for any discrepancies in the functioning of water systems or any maintenance undertaken

4.7.7.5.2. Verify the operation and sanitization log books for concerned system / area

4.7.7.5.3. If the OOL result is observed in only one sample location and rest of the system is conforming to specifications, then verify the sample location fo discrepancies in the sample/user point and the location.

4.7.7.5.4. If the water from the specific location was used for batch manufacturing, then verify the results in process and finished product samples of concerned batch(es)

4.7.7.5.4.1. Bioburden results of bulk sample before filtration

4.7.7.5.4.2. Microbiological tests results of Oral Solid Dosages

SOP for Handling of OOL Results in EM & WSM

4. Procedure
   - 4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water
     - 4.7.7. Investigation of Out of Action Limit Results
       - 4.7.7.6. Evaluate the information gathered and determine if it has any impact on the observed results
       - 4.7.7.7. Based on the information gathered, determine the actions to be initiated as per Investigation report and proceed accordingly
         - 4.7.7.7.1. Review the identification results and verify if it is normal micro flora. If isolate is different, then include it micro flora stock for use in different tests.
         - 4.7.7.7.2. If isolate identified is of objectionable, then investigate the possible source of contamination and take necessary corrective and preventive actions.
         - 4.7.7.7.3. If the results of follow up sampling are satisfactory after carrying out corrective actions (if any) conclude the investigation
         - 4.7.7.7.4. If the results of follow up sampling are not satisfactory carry out further investigation take necessary actions accordingly. Following activities can be performed to determine the root cause:
           - 4.7.7.7.4.1. Sampling and analysis at different stages of generation and distribution system to identify the contamination
           - 4.7.7.7.4.2. Sanitization of generation, storage, distribution and heat exchangers as applicable
           - 4.7.7.7.4.3. Verification of air vent filters
           - 4.7.7.7.4.4. Verification of gaskets, valves and other components.
         - 4.7.7.7.5. The system can be released for use after obtaining satisfactory results for consecutive three days

SOP for Handling of OOL Results in EM & WSM

4. Procedure
   - 4.7. Handling and Investigation of OOLs Results in Microbiological Analysis of Water
     - 4.7.8. Investigation of OOLs Results in Chemical Analysis, BET of Water
       - 4.7.8.1. On obtaining OOL results in any chemical analysis (except for TOC) and BET, inform to Head Microbiology. Do not discard the original left sample (if any)
       - 4.7.8.2. Verify the status (cleaning or depyrogenation) of the glassware used for sampling and testing.
       - 4.7.8.3. Verify the status of the chemicals, reagents and instruments used in the analysis
       - 4.7.8.4. Verify the test is performed properly as per procedure for any analyst error during testing
       - 4.7.8.5. If any discrepancy is observed in glassware used for sampling and testing, then take necessary corrective actions and arrange for resampling fr particular sample point from glassware conforming to requirements
       - 4.7.8.6. If the any discrepancy is observed in chemicals, reagents or instruments, then take necessary corrective actions and retest using original sample available or with fresh sample
       - 4.7.8.7. If the analyst error is observed, then second analyst shall perform the test

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.8. Investigation of OOLs Results in Chemical Analysis, BET of Water

4.8.1. If the results of the resample conform to specifications, then record the results and water may be released

4.8.2. If the no assignable cause is determined above or the test results show non-conformance on resampling and testing, then inform the concerned department and QA

4.8.3. Perform the investigation to determine the root cause and take necessary corrective actions. Following activities can be performed to determine root cause:

4.8.3.1. Testing of input water and at different stages in the treatment and generation system

4.8.3.2. Cleaning and sanitization of generation, storage and distribution system

4.8.4. The system can be released for use after obtaining satisfactory results for consecutive three days

4.8.5. For investigation of chemical analysis follow chart

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.9. Investigation of OOL Results in TOC

4.9.1. Investigation out of Alert Limit Results

4.9.1.1. If TOC results exceed the above Alert level then the following actions shall be initiated

4.9.1.2. Any samples exceeding the alert limits shall be immediately informed to the Head Microbiology & QA and do not discard the original left over sample (if any)

4.9.1.3. Review the data for the sample location /system in question for any previous instances of OOL results in last three months

4.9.1.4. If the last data indicates previous occurrences of OOLs, then review the previous investigation reports to determine any similarities

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.9. Investigation of OOL Results in TOC

4.9.2. Laboratory Investigation

4.9.2.1. Interview the microbiologist who performed sampling and verify whether the sampling was performed as per sop and if any deviation observed during the sampling/testing

4.9.2.2. Verify the glassware used for sampling was properly cleaned

4.9.2.3. Verify that sample was intact during transportation

4.9.2.4. Verify that the instrument used was within calibration and testing performed as per procedure

4.9.2.5. If laboratory investigation reveals fault in sampling/glassware used/ and transportation

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.9. Investigation of OOL Results in TOC

4.9.2. Laboratory Investigation

4.9.2.6. Then the occurrence of OOL results could be attributed to laboratory /sampling error

4.9.2.6.1. An immediate repeat test of the original sample together with an additional sample from the same location shall be performed

4.9.2.6.2. If the TOC resample show results over the alert limit then additional user points shall be immediately sampled and tested

4.9.2.6.3. If results suggest that only one point is affected and it is an isolated incident then the result will be recorded and used for trending analysis & investigation for corrective and preventive action

4.9.2.6.4. If the retest results from the additional user points are found out of Alert limit, the results shall be informed to Head QA, Production and Engineering department to carry out the detailed investigation and take immediate corrective and preventive actions

4.9.2.6.5. If results suggest that only one point is affected and it is an isolated incident

SOP for Handling of OOL Results in EM & WSM

4. Procedure

4.9. Investigation of OOL Results in TOC

4.9.2. Laboratory Investigation

4.9.2.6. Then the occurrence of OOL results could be attributed to laboratory / sampling error

4.9.2.6.6. Investigation shall be initiated to identify the root cause.

4.9.2.6.7. If the retest results from the additional user points are found out of Action limit, the results shall be informed to Head QA, Production and Engineering department to carry out the detailed investigation and take immediate corrective and preventive actions

4.9.2.6.8. Until and unless the investigation is complete, and immediate corrective actions is completed no further batches will be manufactured

4.9.2.6.9. The system can be released for use after investigation & obtaining the satisfactory results

4.9.2.6.10. A trend of OOL shall be prepared and review for repetitive nature & Effectiveness of CAPA on half yearly basis

SOP for Handling of OOL Results in EM & WSM

5. Abbreviations

5.1. SOP: Standard Operating Procedure

5.2. OOL: OOL

5.3. OOS: Out of Specification

5.4. EM: Environmental Monitoring

5.5. WSM: Water System Monitoring

5.6. TOC: Total Organic Carbon

5.7. BET: Bacterial Endotoxin Test

5.8. CAPA: Corrective and preventive action

参考資料

High Purity Water System (7/93)

GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does no confer any rights, privileges, benefits, or immunities for or on any person(s).

This guide discusses, primarily from a microbiological aspect, the review and evaluation of high purity water systems that are used for the manufacture of drug products and drug substances. It also includes a review of the design of the various types of systems and some of the problems that have been associated with these systems. As with other guides, it is not all-inclusive, but provides background and guidance for the review and evaluation of high purity water systems. The Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories (May, 1993) provides additional guidance.

I. SYSTEM DESIGN

One of the basic considerations in the design of a system is the type of product that is to be manufactured. For parenteral products where there is a concern for pyrogens, it is expected that Water for Injection will be used. This applies to the formulation of products, as well as to the final washing of components and equipment used in their manufacture. Distillation and Reverse Osmosis (RO) filtration are the only acceptable methods listed in the USP for producing Water for Injection. However, in the bulk Pharmaceutical and Biotechnology industries and some foreign companies, Ultra Filtration (UF) is employed to minimize endotoxins in those drug substances that are administered parenterally.

For some ophthalmic products, such as the ophthalmic irrigating solution, and some inhalation products, such as Sterile Water for Inhalation, where there are pyrogen specifications, it is expected that Water for Injection be used in their formulation. However, for most inhalation and ophthalmic products, purified water is used in their formulation. This also applies to topicals, cosmetics and oral products.

Another design consideration is the temperature of the system. It is recognized that hot (65 - 80oC) systems are self sanitizing. While the cost of other systems may be less expensive for a company, the cost of maintenance, testing and potential problems may be greater than the cost of energy saved. Whether a system is circulating or one-way is also an important design consideration. Obviously, water in constant motion is less liable to have high levels of contaminant. A one-way water system is basically a "dead-leg".

Finally, and possibly the most important consideration, is the risk assessment or level of quality that is desired. It should be recognized that different products require different quality waters. Parenterals require very pure water with no endotoxins. Topical and oral products require less pure water and do not have a requirement for endotoxins. Even with topical and oral products there are factors that dictate different qualities for water. For example, preservatives in antacids are marginally effective, so more stringent microbial limits have to be set. The quality control department should assess each product manufactured with the water from their system and determine the microbial action limits based on the most microbial sensitive product. In lieu of stringent water action limits in the system the manufacturer can add a microbial reduction step in the manufacturing process for the sensitive drug product(s).

II. SYSTEM VALIDATION

A basic reference used for the validation of high purity water systems is the Parenteral Drug Association Technical Report No. 4 titled, "Design Concepts for the Validation of a Water for Injection System."

The introduction provides guidance and states that, "Validation often involves the use of an appropriate challenge. In this situation, it would be undesirable to introduce microorganisms into an on-line system; therefore, reliance is placed on periodic testing for microbiological quality and on the installation of monitoring equipment at specific checkpoints to ensure that the total system is operating properly and continuously fulfilling its intended function."

In the review of a validation report, or in the validation of a high purity water system, there are several aspects that should be considered. Documentation should include a description of the system along with a print. The drawing needs to show all equipment in the system from the water feed to points of use. It should also show all sampling points and their designations. If a system has no print, it is usually considered an objectionable condition. The thinking is if there is no print, then how can the system be validated? How can a quality control manager or microbiologist know where to sample? In those facilities observed without updated prints, serious problems were identified in these systems. The print should be compared to the actual system annually to insure its accuracy, to detect unreported changes and confirm reported changes to the system.

After all the equipment and piping has been verified as installed correctly and working as specified, the initial phase of the water system validation can begin. During this phase the operational parameters and the cleaning/ sanitization procedures and frequencies will be developed. Sampling should be daily after each step in the purification process and at each point of use for two to four weeks. The sampling procedure for point of use sampling should reflect how the water is to be drawn e.g. if a hose is usually attached the sample should be taken at the end of the hose. If the SOP calls for the line to be flushed before use of the water from that point, then the sample is taken after the flush. At the end of the two to four week time period the firm should have developed its SOPs for operation of the water system.

The second phase of the system validation is to demonstrate that the system will consistently produce the desired water quality when operated in conformance with the SOPs. The sampling is performed as in the initial phase and for the same time period. At the end of this phase the data should demonstrate that the system will consistently produce the desired quality of water.

The third phase of validation is designed to demonstrate that when the water system is operated in accordance with the SOPs over a long period of time it will consistently produce water of the desired quality. Any variations in the quality of the feedwater that could affect the operation and ultimately the water quality will be picked up during this phase of the validation. Sampling is performed according to routine procedures and frequencies. For Water for Injection systems the samples should be taken daily from a minimum of one point of use, with all points of use tested weekly. The validation of the water system is completed when the firm has a full years worth of data.

While the above validation scheme is not the only way a system can be validated, it contains the necessary elements for validation of a water system. First, there must be data to support the SOPs. Second, there must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications. Finally, there must be data to demonstrate that seasonal variations in the feedwater do not adversely affect the operation of the system or the water quality.

The last part of the validation is the compilation of the data, with any conclusions into the final report. The final validation report must be signed by the appropriate people responsible for operation and quality assurance of the water system.

A typical problem that occurs is the failure of operating procedures to preclude contamination of the system with non-sterile air remaining in a pipe after drainage. In a system illustrated as in Figure 1, (below) a typical problem occurs when a washer or hose connection is flushed and then drained at the end of the operation. After draining, this valve (the second off of the system) is closed. If on the next day or start-up of the operation the primary valve off of the circulating system is opened, then the non-sterile air remaining in the pipe after drainage would contaminate the system. The solution is to pro-vide for operational procedures that provide for opening the secondary valve before the primary valve to flush the pipe prior to use.

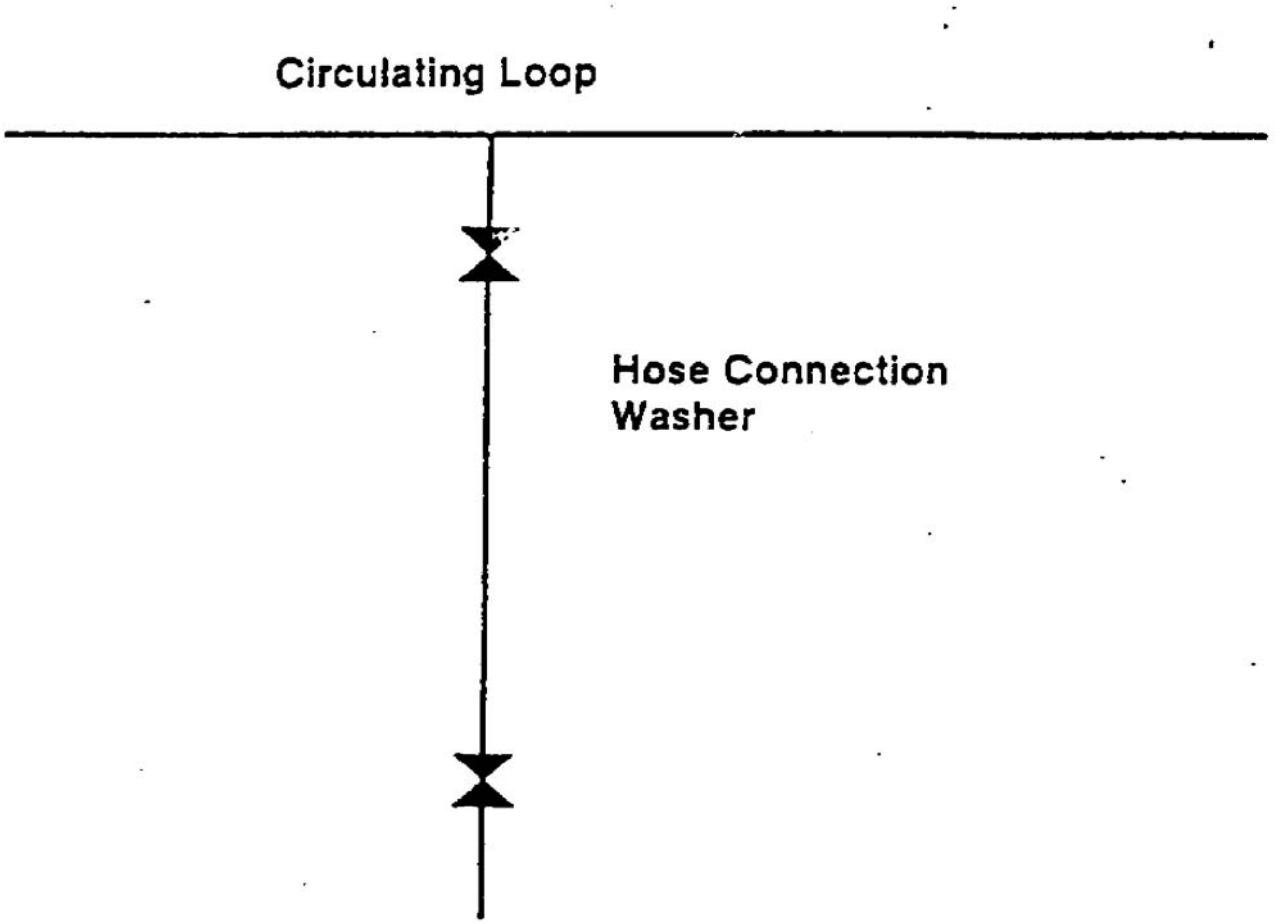


Figure 1

Another major consideration in the validation of high purity water systems is the acceptance criteria. Consistent results throughout the system over a period of time constitute the primary element.

III. MICROBIAL LIMITS

Water For Injection Systems

Regarding microbiological results, for Water For Injection, it is expected that they be essentially sterile. Since sampling frequently is performed in non-sterile areas and is not truly aseptic, occasional low level counts due to sampling errors may occur. Agency policy, is that less than 10 CFU/100ml is an acceptable action limit. None of the limits for water are pass/fail limits. All limits are action limits. When action limits are exceeded the firm must investigate the cause of the problem, take action to correct the problem and assess the impact of the microbial contamination on products manufactured with the water and document the results of their investigation.

With regard to sample size, 100 - 300 mL is preferred when sampling Water for Injection systems. Sample volumes less than 100 mL are unacceptable.

The real concern in WFI is endotoxins. Because WFI can pass the LAL endotoxin test and still fail the above microbial action limit, it is important to monitor WFI systems for both endotoxins and microorganisms.

Purified Water Systems

For purified water systems, microbiological specifications are not as clear. USP XXII specifications, that it complies with federal Environmental Protection Agency regulations for drinking water, are recognized as being minimal specifications. There have been attempts by some to establish meaningful microbiological specifications for purified water. The CFTA proposed a specification of not more than 500 organisms per ml. The USP XXII has an action guideline of not greater than 100 organisms per ml. Although microbiological specifications have been discussed, none (other than EPA standards) have been established. Agency policy is that any action limit over 100 CFU/mL for a purified water system is unacceptable.

The purpose of establishing any action limit or level is to assure that the water system is under control. Any action limit established will depend upon the overall purified water system and further processing of the finished product and its use. For example, purified water used to manufacture drug products by cold processing should be free of objectionable organisms. We have defined "objectionable organisms" as any organisms that can cause infections when the drug product is used as directed or any organism capable of growth in the drug product. As pointed out in the Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories, the specific contaminant, rather than the number is generally more significant.

Organisms exist in a water system either as free floating in the water or attached to the walls of the pipes and tanks. When they are attached to the walls they are known as biofilm, which continuously slough off organisms. Thus, contamination is not uniformly distributed in a system and the sample may not be representative of the type and level of contamination. A count of 10 CFU/mL in one sample and 100 or even 1000 CFU/mL in a subsequent sample would not be unrealistic.

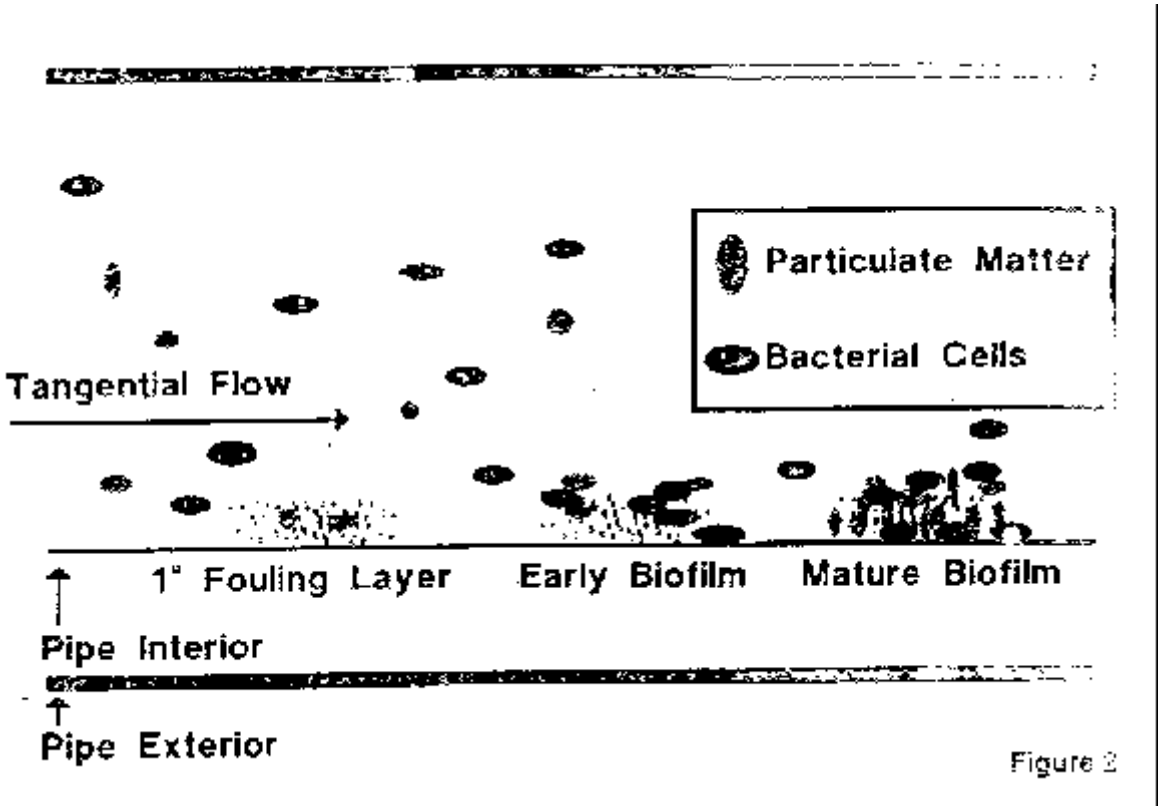


Figure 2

Thus, in establishing the level of contamination allowed in a high purity water system used in the manufacture of a non-sterile product requires an understanding of the use of the product, the formulation (preservative system) and manufacturing process. For example, antacids, which do not have an effective preservative system, require an action limit below the 100 CFU/mL maximum.

The USP gives some guidance in their monograph on Microbiological Attributes of Non-Sterile Products. It points out that, "The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential harm to the user." Thus, not just the indicator organisms listed in some of the specific monographs present problems. It is up to

each manufacturer to evaluate their product, the way it is manufactured, and establish am acceptable action level of contamination, not to exceed the maximum, for the water system, based on the highest risk product manufactured with the water.

IV. WATER FOR INJECTION SYSTEMS

In the review and evaluation of Water For Injection systems, there are several concerns.

Pretreatment of feedwater is recommended by most manufacturers of distillation equipment and is definitely required for RO units. The incoming feedwater quality may fluctuate during the life of the system depending upon seasonal variations and other external factors beyond the control of the pharmaceutical facility. For example, in the spring (at least in the N.E.), increases in gram negative organisms have been known. Also, new construction or fires can cause a depletion of water stores in old mains which can cause an influx of heavily contaminated water of a different flora.

A water system should be designed to operate within these anticipated extremes. Obviously, the only way to know the extremes is to periodically monitor feedwater. If the feedwater is from a municipal water system, reports from the municipality testing can be used in lieu of in-house testing.

V. STILL

Figures 3-5 represent a typical basic diagram of a WFI system. Most of the new systems now use multi-effect stills. In some of the facilities, there has been evidence of endotoxin contamination. In one system this occurred, due to malfunction of the feedwater valve and level control in the still which resulted in droplets of feedwater being carried over in the distillate.

Figure 3 (/ICECI/Inspections/InspectionGuides/ucm091052.htm)
Figure 4 (/ICECI/Inspections/InspectionGuides/ucm091054.htm)
Figure 5 (/ICECI/Inspections/InspectionGuides/ucm091055.htm)

In another system with endotoxin problems, it was noted that there was approximately 50 liters of WFI in the condenser at the start-up. Since this water could lie in the condenser for up to several days (i.e., over the weekend), it was believed that this was the reason for unacceptable levels of endotoxins.

More common, however, is the failure to adequately treat feedwater to reduce levels of endotoxins. Many of the still fabricators will only guarantee a 2.5 log to 3 log reduction in the endotoxin content. Therefore, it is not surprising that in systems where the feedwater occasionally spikes to 250 EU/ml, unacceptable levels of endotoxins may occasionally appear in the distillate (WFI). For example, recently three new stills, including two multi-effect, were found to be periodically yielding WFI with levels greater than .25 EU/ml. Pretreatment systems for the stills included only deionization systems with no UF, RO or distillation. Unless a firm has a satisfactory pretreatment system, it would be extremely difficult for them to demonstrate that the system is validated.

The above examples of problems with distillation units used to produce WFI, point to problems with maintenance of the equipment or improper operation of the system indicating that the system has not been properly validated or that the initial validation is no longer valid. If you see these types of problems you should look very closely at the system design, any changes that have been made to the system, the validation report and the routine test data to determine if the system is operating in a state of control.

Typically, conductivity meters are used on water systems to monitor chemical quality and have no meaning regarding microbiological quality.

Figures 3-5 also show petcocks or small sampling ports between each piece of equipment, such as after the still and before the holding tank. These are in the system to isolate major pieces of equipment. This is necessary for the qualification of the equipment and for the investigation of any problems which might occur.

VI. HEAT EXCHANGERS

One principal component of the still is the heat exchanger. Because of the similar ionic quality of distilled and deionized water, conductivity meters cannot be used to monitor microbiological quality. Positive pressure such as in vapor compression or double tubesheet design should be employed to prevent possible feedwater to distillate contamination in a leaky heat exchanger.

An FDA Inspectors Technical Guide with the subject of "Heat Exchangers to Avoid Contamination" discusses the design and potential problems associated with heat exchangers. The guide points out that there are two methods for preventing contamination by leakage. One is to provide gauges to constantly monitor pressure differentials to ensure that the higher pressure is always on the clean fluid side. The other is to utilize the double-tubesheet type of heat exchanger.

In some systems, heat exchangers are utilized to cool water at use points. For the most part, cooling water is not circulated through them when not in use. In a few situations, pinholes formed in the tubing after they were drained (on the cooling water side) and not in use. It was determined that a small amount of moisture remaining in the tubes when combined with air caused a corrosion of the stainless steel tubes on the cooling water side. Thus, it is recommended that when not in use, heat exchangers not be drained of the cooling water.

VII. HOLDING TANK

In hot systems, temperature is usually maintained by applying heat to a jacketed holding tank or by placing a heat exchanger in the line prior to an insulated holding tank.

The one component of the holding tank that generates the most discussion is the vent filter. It is expected that there be some program for integrity testing this filter to assure that it is intact. Typically, filters are now jacketed to prevent condensate or water from blocking the hydrophobic vent filter. If this occurs (the vent filter becomes blocked), possibly either the filter will rupture or the tank will collapse. There are methods for integrity testing of vent filters in place.

It is expected, therefore, that the vent filter be located in a position on the holding tank where it is readily accessible.

Just because a WFI system is relatively new and distillation is employed, it is not problem-free. In an inspection of a manufacturer of parenterals, a system fabricated in 1984 was observed. Refer to **Figure 6. (/ICECI/Inspections/InspectionGuides/ucm091056.htm)** While the system may appear somewhat complex on the initial review, it was found to be relatively simple. **Figure 7 (/ICECI/Inspections/InspectionGuides/ucm091057.htm)**is a schematic of the system. The observations at the conclusion of the inspection of this manufacturer included, "Operational procedures for the Water For Injection system failed to provide for periodic complete flushing or draining. The system was also open to the atmosphere and room environment. Compounding equipment consisted of non-sealed, open tanks with lids. The Water for Injection holding tank was also not sealed and was never sampled for endotoxins." Because of these and other comments, the firm recalled several products and discontinued operations.

VIII. PUMPS

Pumps burn out and parts wear. Also, if pumps are static and not continuously in operation, their reservoir can be a static area where water will lie. For example, in an inspection, it was noted that a firm had to install a drain from the low point in a pump housing. Pseudomonas sp. contamination was periodically found in their water system which was attributed in part to a pump which only periodically is operational.

IX. PIPING

Piping in WFI systems usually consist of a high polished stainless steel. In a few cases, manufacturers have begun to utilize PVDF (polyvinylidene fluoride) piping. It is purported that this piping can tolerate heat with no extractables being leached. A major problem with PVDF tubing is that it requires considerable support. When this tubing is heated, it tends to sag and may stress the weld (fusion) connection and result in leakage. Additionally, initially at least, fluoride levels are high. This piping is of benefit in product delivery systems where low level metal contamination may accelerate the degradation of drug product, such as in the Biotech industry.

One common problem with piping is that of "dead-legs". The proposed LVP Regulations defined dead-legs as not having an unused portion greater in length than six diameters of the unused pipe measured from the axis of the pipe in use. It should be pointed out that this was developed for hot 75 - 80o circulating systems. With colder systems (65 - 75oC), any drops or unused portion of any length of piping has the potential for the formation of a biofilm and should be eliminated if possible or have special sanitizing procedures. There should be n o threaded fittings in a pharmaceutical water system. All pipe joints must utilize sanitary fittings or be butt welded. Sanitary fittings will usually be used where the piping meets valves, tanks and other equipment that must be removed for maintenance or replacement. Therefore, the firm's procedures for sanitization, as well as the actual piping, should be reviewed and evaluated during the inspection.

X. REVERSE OSMOSIS

Another acceptable method for manufacturing Water for Injection is Reverse Osmosis (RO). However, because these systems are cold, and because RO filters are not absolute, microbiological contamination is not unusual. **Figure 8 (/ICECI/Inspections/InspectionGuides/ucm091059.htm)** shows a system that was in use several years ago. There are five RO units in this system which are in parallel. Since RO filters are not absolute, the filter manufacturers recommend that at least two be in series. The drawing also illustrates an Ultraviolet (UV) light in the system downstream from the RO units. The light was needed to control microbiological contamination.

Also in this system were ball valves. These valves are not considered sanitary valves since the center of the valve can have water in it when the valve is closed. This is a stagnant pool of water that can harbor microorganisms and provide a starting point for a biofilm.

As an additional comment on RO systems, with the recognition of microbiological problems, some manufacturers have installed heat exchangers immediately after the RO filters to heat the water to 75 - 80oC to minimize microbiological contamination.

With the development of biotechnology products, many small companies are utilizing RO and UF systems to produce high purity water. For example, **Figure 9 (/ICECI/Inspections/InspectionGuides/ucm091062.htm)** illustrates a wall mounted system that is fed by a single pass RO unit.

As illustrated, most of these systems employ PVC or some type of plastic tubing. Because the systems are typically cold, the many joints in the system are subject to contamination. Another potential problem with PVC tubing is extractables. Looking at the WFI from a system to assure that it meets USP requirements without some assurance that there are no extractables would not be acceptable.

The systems also contain 0.2 micron point of use filters which can mask the level of microbiological contamination in the system. While it is recognized that endotoxins are the primary concern in such a system, a filter will reduce microbiological contamination, but not necessarily endotoxin contamination. If filters are used in a water system there should be a stated purpose for the filter, i.e., particulate removal or microbial reduction, and an SOP stating the frequency with which the filter is to be changed which is based on data generated during the validation of the system.

As previously discussed, because of the volume of water actually tested (.1ml for endotoxins vs. 100ml for WFI), the microbiological test offers a good index of the level of contamination in a system. Therefore, unless the water is sampled prior to the final 0.2 micron filter, microbiological testing will have little meaning.

At a reinspection of this facility, it was noted that they corrected the deficient water system with a circulating stainless steel piping system that was fed by four RO units in series. Because this manufacturer did not have a need for a large amount of water (the total system capacity was about 30 gallons), they attempted to let the system sit for approximately one day. **Figure 9 (/ICECI/Inspections/InspectionGuides/ucm091062.htm)** shows that at zero time (at 9 AM on 3/10), there were no detectable levels of microorganisms and of endotoxins. After one day, this static non-circulating system was found to be contaminated. The four consecutive one hour samples also illustrate the variability among samples taken from a system. After the last sample at 12 PM was collected, the system was resanitized with 0.5% peroxide solution, flushed, recirculated and resampled. No levels of microbiological contamination were found on daily samples after the system was put back in operation. This is the reason the agency has recommended that non-recirculating water systems be drained daily and water not be allowed to sit in the system.

XI. PURIFIED WATER SYSTEMS

Many of the comments regarding equipment for WFI systems are applicable to Purified Water Systems. One type system that has been used to control microbiological contamination utilizes ozone. **Figure 10 (/ICECI/Inspections/InspectionGuides/ucm091064.htm)** illustrates a typical system. Although the system has purported to be relatively inexpensive, there are some problems associated with it. For optimum effectiveness, it is required that dissolved ozone residual remain in the system. This presents both employee safety problems and use problems when drugs are formulated.

Published data for Vicks Greensboro, NC facility showed that their system was recontaminated in two to three days after the ozone generator was turned off. In an inspection of another manufacturer, it was noted that a firm was experiencing a contamination problem with Pseudomonas sp. Because of potential problems with employee safety, ozone was removed from the water prior to placing it in their recirculating system. It has been reported that dissolved ozone at a level of 0.45 mg/liter will remain in a system for a maximum of five to six hours.

Another manufacturer, as part of their daily sanitization, removes all drops off of their ozonated water system and disinfects them in filter sterilized 70% isopropyl alcohol. This manufacturer has reported excellent microbiological results. However, sampling is only performed immediately after sanitization and not at the end of operations. Thus, the results are not that meaningful.

Figure 11 (/ICECI/Inspections/InspectionGuides/ucm091065.htm) and **Figure12 (/ICECI/Inspections/InspectionGuides/ucm091067.htm)** illustrate another purified water system which had some problems. Unlike most of the other systems discussed, this is a one-way and not recirculating system. A heat exchanger is used to heat the water on a weekly basis and sanitize the system. Actually, the entire system is a "dead-leg."

Figure 11 also shows a 0.2 micron in line filter used to sanitize the purified water on a daily basis. In addition to the filter housing providing a good environment for microbiological contamination, a typical problem is water hammer that can cause "ballooning" of the filter. If a valve downstream from the filter is shut too fast, the water pressure will reverse and can cause "ballooning". Pipe vibration is a typical visible sign of high back pressure while passage of upstream contaminants on the filter face is a real problem. This system also contains several vertical drops at use points. During sanitization, it is important to "crack" the terminal valves so that all of the elbows and bends in the piping are full of water and thus, get complete exposure to the sanitizing agent.

It should be pointed out that simply because this is a one-way system, it is not inadequate. With good Standard Operational Procedures, based on validation data, and routine hot flushings of this system, it could be acceptable. A very long system (over 200 yards) with over 50 outlets was found acceptable. This system employed a daily flushing of all outlets with 80oC water.

The last system to be discussed is a system that was found to be objectionable. Pseudomonas sp. found as a contaminant in the system (after FDA testing) was also found in a topical steroid product (after FDA testing). Product recall and issuance of a Warning Letter resulted. This system (**Figure 13) (/ICECI/Inspections/InspectionGuides/ucm091069.htm)** is also one-way that employs a UV light to control microbiological

contamination. The light is turned on only when water is needed. Thus, there are times when water is allowed to remain in the system. This system also contains a flexible hose which is very difficult to sanitize. UV lights must be properly maintained to work. The glass sleeves around the bulb(s) must be kept clean or their effectiveness will decrease. In multibulb units there must be a system to determine that each bulb is functioning. It must be remembered that at best UV light will only kill 90% of the organisms entering the unit.

XIII. PROCESS WATER

Currently, the USP, pg. 4, in the General Notices Section, allows drug substances to be manufactured from Potable Water. It comments that any dosage form must be manufactured from Purified Water, Water For Injection, or one of the forms of Sterile Water. There is some inconsistency in these two statements, since Purified Water has to be used for the granulation of tablets, yet Potable Water can be used for the final purification of the drug substance.

The FDA Guide to Inspection of Bulk Pharmaceutical Chemicals comments on the concern for the quality of the water used for the manufacture of drug substances, particularly those drug substances used in parenteral manufacture. Excessive levels of microbiological and/or endotoxin contamination have been found in drug substances, with the source of contamination being the water used in purification. At this time, Water For Injection does not have to be used in the finishing steps of synthesis/purification of drug substances for parenteral use. However, such water systems used in the final stages of processing of drug substances for parenteral use should be validated to assure minimal endotoxin/ microbiological contamination.

In the bulk drug substance industry, particularly for parenteral grade substances, it is common to see Ultrafiltration (UF) and Reverse Osmosis (RO) systems in use in water systems. While ultrafiltration may not be as efficient at reducing pyrogens, they will reduce the high molecular weight endotoxins that are a contaminant in water systems. As with RO, UF is not absolute, but it will reduce numbers. Additionally, as previously discussed with other cold systems, there is considerable maintenance required to maintain the system.

For the manufacture of drug substances that are not for parenteral use, there is still a microbiological concern, although not to the degree as for parenteral grade drug substances. In some areas of the world, Potable (chlorinated) water may not present a microbiological problem. However, there may be other issues. For example, chlorinated water will generally increase chloride levels. In some areas, process water may be obtained directly from neutral sources.

In one inspection, a manufacturer was obtaining process water from a river located in a farming region. At one point, they had a problem with high levels of pesticides which was a run-off from farms in the areas. The manufacturing process and analytical methodology was not designed to remove and identify trace pesticide contaminants. Therefore, it would seem that this process water when used in the purification of drug substances would be unacceptable.

XIV. INSPECTION STRATEGY

Manufacturers typically will have periodic printouts or tabulations of results for their purified water systems. These printouts or data summaries should be reviewed. Additionally, investigation reports, when values exceed limits, should be reviewed.

Since microbiological test results from a water system are not usually obtained until after the drug product is manufactured, results exceeding limits should be reviewed with regard to the drug product formulated from such water. Consideration with regard to the further processing or release of such a product will be dependent upon the specific contaminant, the process and the end use of the product. Such situations are usually evaluated on a case-by-case basis. It is a good practice for such situations to include an investigation report with the logic for release/rejection discussed in the firm's report. End product microbiological testing, while providing some information should not be relied upon as the sole justification for the release of the drug product. The limitations of microbiological sampling and testing should be recognized.

Manufacturers should also have maintenance records or logs for equipment, such as the still. These logs should also be reviewed so that problems with the system and equipment can be evaluated.

In addition to reviewing test results, summary data, investigation reports and other data, the print of the system should be reviewed when conducting the actual physical inspection. As pointed out, an accurate description and print of the system is needed in order to demonstrate that the system is validated.

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