RCA (ROOT CAUSE ANALYSIS) of CHEMICAL PERITONITIS OUTBRAKE IN SAMEN PD FLUID

WINTER 1397

Sterile Peritonitis

- Sterile Peritonitis account for 12 to 30% of Peritonitis in different reports.
- The cause of it includes a list of different conditions .
- Among versatile causes “Chemical Peritonitis” could occur especially with Bio-incompatible PD solutions.

Differential Diagnosis of Sterile Peritonitis

Cellular causes

Increased neutrophils

- Atypical infection
  - Mycobacteria
  - Fungi
- Intraperitoneal disease
  - Cholecystitis
  - Appendicitis
  - Small bowel incarceration
  - Mesenteric ischemia
  - Sterile abscess rupture
  - Retroperitoneal disease
  - Pancreatitis
  - Splenic infarction
  - Abscess
  - Renal cell car cinoma
- Drugs
  - Amphotericin B
  - Vancomyvin
  - Contamination of PD fluid
  - Endotoxin
  - Acetaldehyde

Increased eosinophils

- Allergic reaction
  - Tubing
  - Bags
  - Intraperitoneal air
- Drugs
  - Vancomycin
  - Gentamicin
  - Streptokinase
  - Cephalosporins
- Following peritonitis Infection
  - Fungal
  - Parasitic
  - Retrograde menstruation

Increased monocytes

- Icodextrin related
- Mycobacteria
- In association with eosinophilia

Increased erythrocytes

- Any cause of hemoperitoneum
- Retrgrade menstruation
- Ovulation
- Ovarian/hepatic cyst rup ture
- Peritoneal adhesions
- Strenuous exercise
- Catheter-associated trauma

Increased malignant cells

- Lymphoma
- Peritoneal metastases
- Adenocarcinoma

Noncellular causes

Increased fibrin

- Post peritonitis
- Starting PD

Increased triglycerides

- Acute pancreatitis
- Neoplasms
- Catheter-associated trauma
- Superior vena cava syndrome
- Drugs
- Calcium channel blockers

How differentiate Chemical Peritonitis

- Negative effluent Culture
- Clustering of Peritonitis in multiple Center
- Clustering with some special Batches
- Disappearing of symptoms and signs with change of PD fluid batch.
- Relying on negative culture is not reliable. Epidemiologic point of view and notice to clustering in 1 or some batches and recovery with batch change are good clues.

Historical Examples of Chemical Peritonitis

Outbreak of sterile peritonitis among continuous cycling peritoneal dialysis patients

Hospital Infections Program, Centers for Disease Control and Prevention, Atlanta, Georgia, and University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, ***USA***

- **The largest reported outbreak of sterile peritonitis in the United States.**

The Largest outbreak of Chemical Peritonitis in USA, 260 pts . Investigation of case Revealed pre-sterilization colony count as causative factor.

Historical Examples of Chemical Peritonitis

EPIDEMIC OF ASEPTIC PERITONITIS CAUSED BY ENDOTOXIN DURING CHRONIC PERITONEAL DIALYSIS

From the Division of Nephrology and the Department of Bacteriology, Toronto Western Hospital, Toronto, ON, the Renal Unit, St. Joseph's Hospital, Hamilton, ON, Canada, and Baxter Laboratories, Morton Grove, IL, U.S.A. (address reprint requests to Dr. Oreopoulos at Rm. A44, Research Wing, Toronto Western Hospital, 399 Bathurst St., Toronto, ON M5T 2S8, Canada).

Epidemics of 48 episodes of peritonitis in 28 patients in a 4 week period.

Historical Examples of Chemical Peritonitis

Cytotoxic Glucose Degradation Products in Fluids for Peritoneal Dialysis

A Food and Drug Lab Research Center, Ministry of Health, Tehran, Iran. Adverse Drug Reaction Center, Food and Drug Deputy, Ministry of Health, Tehran, Iran.

224 ESRD patients experienced Peritonitis, investigation showed multiple times normal Acetaldehyde in PD Fluid (10x). Authors suggested use of multi-chamber bag or improve Heat sterilization process.

Table 1. Amount of acetaldehyde in three different Lots of peritoneal dialysis solutions,* n = 3.

	Before sterilization*	After sterilization*
Lot 1	1.76±1.1	19.9±1.5
Lot 2	1.69±1.5	19.7±1.3
Lot 3	1.78±1.8	20.5±1.7

Historical Examples of Chemical Peritonitis

Chemical peritonitis associated with high dialysate acetaldehyde concentrations

Akdeniz University Medical School, Department of Medicine, Division of Nephrology, Antalya, Turkey

21 cases of culture negative peritonitis observed, investigation showed Acetaldehyde as Causative factor in the range of 3-4X seen normally in PD fluids. The concentration in PD Fluid batches suspect was around 17 PPM (Normally less than 6 PPM)

Historical Examples of Chemical Peritonitis

Tintillier M, Pochet JM, Christophe JL, Scheiff JM, Goffin E. Transient sterile chemical peritonitis with icodextrin: clinical presentation, prevalence and literature review. *Perit Dial Int* 2002; 22:534–7.

Martis L, Patel M, Giertych J, Mongoven J, Taminne M, Perrier MA, *et al*. Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. *Lancet* 2005; 365:588–94.

A decline in the prevalence of Ico-Dextrin-induced sterile Peritonitis was observed After implementation of safety precaution , solution being checked for Peptidoglycan Levels.

Historical Examples of Chemical Peritonitis

Ico-Dextrin Associated Sterile Peritonitis, outbreak in Turkey, Ankara October 2010. 7 CAPD Patients using Ico-Dextrin admitted to hospital because of peritonitis signs and symptoms. Negative culture with same batch led to suspicion of Chemical Peritonitis. Investigation of Case revealed higher Endotoxin than permitted level (0.25 EU/ml) due to incomplete of Biofilm.

Historical Examples of Chemical Peritonitis

DESCRIPTION OF AN OUTBREAK OF ACUTE STERILE PERITONITIS IN IRAN

20 CAPD Patients showed signs of Peritonitis , negative culture and clustering with some Batches Of PD fluid. Patients show recovery with PD fluid batch change. The same had occurred in 2000 which caused many patients dropped from therapeutic regimen.

ROOT CAUSE ANALYSIS of Chemical Peritonitis

- As we are investigating the presence of some chemicals in PD fluid, it seems having a Process Oriented approach like Fish Bone or Swiss Cheese Analysis could be good choices.
- Strong adherence to norms and standards obligatory like USP, BP and EP are a must and strictly implemented.
- QA measures and QC measures are essential to assure a product (PD fluid is manufactured according to GMP guidelines).

ROOT CAUSE ANALYSIS of Chemical Peritonitis

- As International companies playing in field like Baxter and Fresenius has enormous experience, have been able to develop comprehensive in-depth standards and norms which seems more restrict than Pharmacopeias (Like Baxter Patents on Screening for Peptidoglycan).

US007118857B2

(12) **United States Patent**
Martis et al.

(10) **Patent No.: US 7,118,857 B2**
(45) **Date of Patent: Oct. 10, 2006**

(54) **METHODS AND COMPOSITIONS FOR DETECTION OF MICROBIAL CONTAMINANTS IN PERITONEAL DIALYSIS SOLUTIONS**

(75) Inventors: **Leo Martis**, Long Grove, IL (US); **Mehul Patel**, Sanderstown, RI (US); **Joseph A. Giertych**, Lake Forest, IL (US); **James W. Mongoven**, Long Grove, IL (US); **Jacqueline A. Kunzler**, Downers Grove, IL (US); **William F. Owen, Jr.**, Durham, NC (US)

(73) Assignees: **Baxter International Inc.**, Deerfield, IL (US); **Baxter Healthcare S.A.**, Zurich (CH)

6,077,836	A	6/2000	Milner	
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OTHER PUBLICATIONS

"The Prokaryotic Cell: Bacteria" http://www.cat.cc.md.us/courses/bio141/lecguide/unit1/prostruct/ew.html accessed Apr. 27, 2005.*

Mangram et al, "Outbreak of sterile peritonitis among continuous cycling peritoneal dialysis patients," Kidney Int, 1998, vol. 54, pp. 1367-1371.*

Goffin et al, Nephrol Dial Transplant, Nov 2003, vol. 18, pp. 2482-2485.*

Martin et al, Advances in Peritoneal Dialysis, Sep. 4, 2003, vol. 19, pp. 191-194.*

BP Regulations

- PH :5 to 6.5
- HMF: not more than 10 ug for 25mg Glucose.
- Bacterial Endotoxin: Less than 0.05 IU/ml
- (is it really Possible?) seems some debate exist as EP expresses :

Comments received during the public enquiry proposed to take into account solutions that cannot fulfill the bacterial endotoxin limit of 0.05 IU/mL, not because they are contaminated with bacterial endotoxins, but because they contain maltodextrin inducing a matrix effect that interferes with the validation of the LAL method. As a consequence, the validation of the LAL method cannot be done for a bacterial endotoxin limit lower than 0.14 IU/mL. To take this into account, 'unless otherwise justified and authorised' has been added to the requirement.

More Strict Regulations

- Researchers at Gambro Regulatory Affairs believe the normal ranges approved for 5 HMF may be need to be revised and are out of date.

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Regulatory Affairs and Preclinical Research, 1 Gambro Lundia AB, and Department of Nephrology, University Hospital of Lund,2 Sweden

glucose. Thus the results indicate that the quality standards for glucose fluids regarding the limits for 5-HMF might be out of date.

Strict Regulations-Corrective Action of 2009 Chemical Peritonitis in IRAN by MOH Reference Lab

<0.03	0.069	2.72	[illegible]	11
<0.03	-	-	97H08K268	12
0.03	0.185	4.53	97H08K214	13
<0.03	0.061	2.26	97H08K210	14
<0.03	0.059	2.05	97H08K241	15
<0.03	0.063	2.53	97H08K205	16
0.045	0.049	1.9	97H08K231	17
0.044	0.407	5.9	97H08K214	18
<0.03	0.093	2.809	97H08K214	19
0.03	0.076	2.145	97H08K214	20

production line. Following the revision in the heat sterilization acetaldehyde concentration in bags below 5 ppm, no further unusual patient complaints occurred during the use of locally produced PD-fluids in Iran. It is proved that the

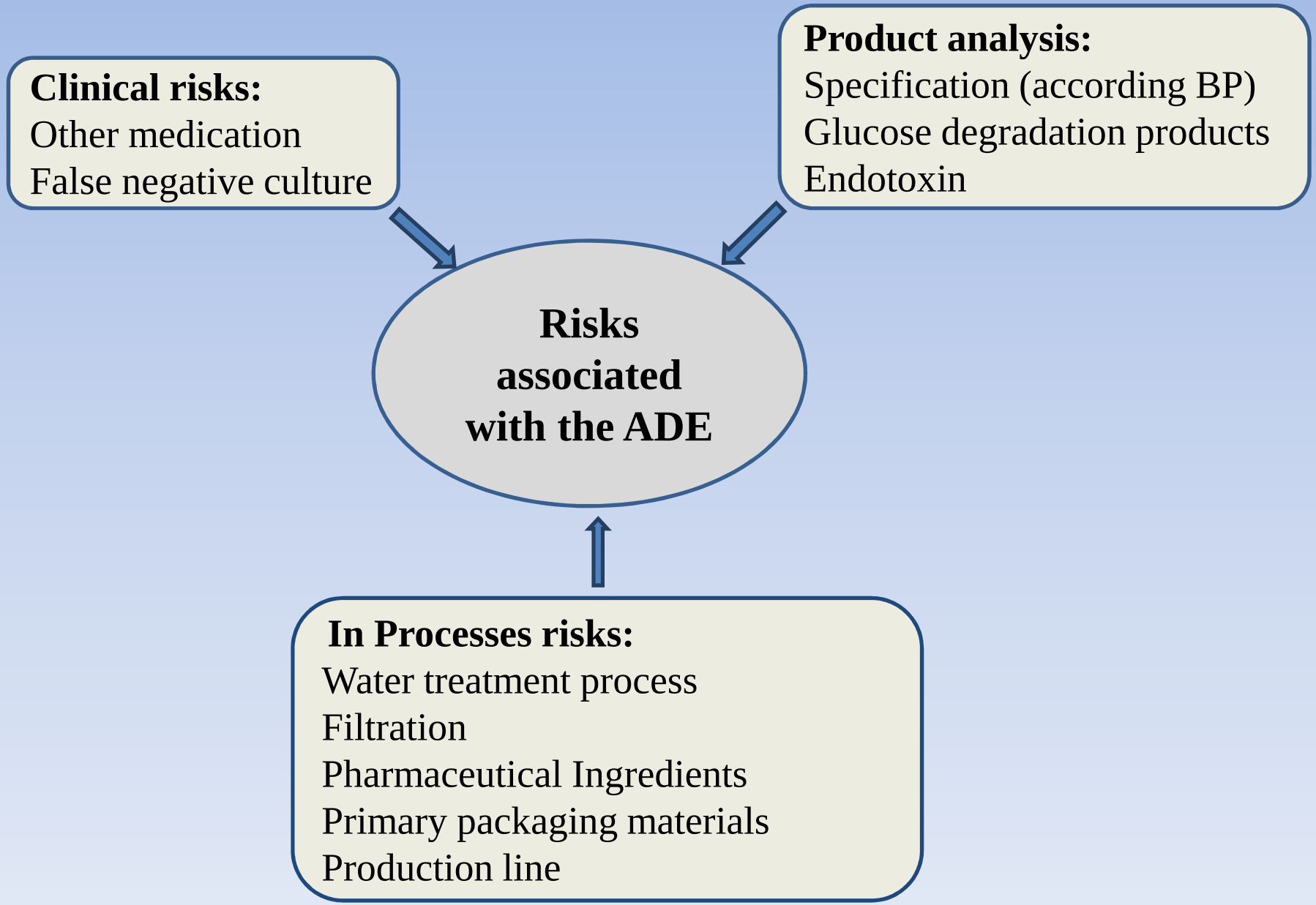
Product vs. Process Oriented Approach

- We can consider a product or the process of production of a product when see a defect or a NOT OK product.
- The Corrective Actions regarding a NOT OK product shall focus on finding the Probable Faults in Production lines . Then rank them and then correct them. So this is our Case.

A Process Look at NOT OK PD Fluid

- When we say NOT OK fluid there could be different criteria and standards in consideration, however the final user (Patient) can judge it in fact.
- If a patient is going happily with Tx modality then complains or drops this means something has happened ?
- What could be the result of this happening?

Sterile peritonitis Risk Assessment in CAPD patients



In-Depth Look

In Processes risks:

Water treatment process
Filtration
Pharmaceutical Ingredients
Primary packaging materials
Production line

How Water Treatment Could affect our line ? Deadlegs
How Pharmaceutical Ingredients could affect our line?
Impurities
Packaging Material ? Different Materials have different Properties , Oxygen Permeability could affect GDP formation.
Production Line ? Sterilization Process is one of the most critical Steps. It could affect GDP production.
Level of Technology could affect too. Single chamber vs Multi Chmaber .

In-Depth Look

Product Specifications:
Specification (according BP)
Glucose degradation products
Endotoxin

As mentioned earlier seems pioneers in this industry are keeping more strict Regulations and may we need to revise measures and implement more strict Regulations for product control and release.
GDPs are numerous and our goal is to reduce production in process as much As possible so more attention to Sterilization process (most GDPs are produced During sterilization) and most sophisticated online control of it is a must.
Let have a detailed look at sterilization and probable failure modes.

In-Depth Look (Sterilization)

Sterilization (Ph.Eur.6)

GMP-plan:

- „qualified person with appropriate training"
- „adequate premises" (place)
- „suitable production equipment, designed for easy cleaning and sterilization"
- „adequate precaution to minimize the bioburden prior to sterilization"
- „all critical production *steps*"
- „environmental monitoring"
- „in-process testing procedures"

- „The precaution necessary to minimize the pre-sterilization bioburden include the use of components with an acceptable low degree of microbial contamination."
- „For biological products of animal or human origin or in cases where such material has ben used in the production process, it is necessary during validation to demonstrate that the process is capable of the removal or inactivation of relevant viral contamination."
- „Where possible, a process in wich the product is sterilized in its final container (terminal sterilization)is chosen."

In-Depth Look (Sterilization)

Sterilization (Ph.Eur.6)

„When a fully validated terminal sterilization method:

by steam, dry heat or ionising radiation is used, parametric release, that is a release of a batch of sterilized items based on process data rather than on the basis of submitting a sample of the items to sterility testing, may be carried out, subject to the approval of the competent authority."

OR:

- „If thermal sterilisation is not possible, filtration trough a bacteria-retentative filter or aseptic processing is used; wherever possible, appropriate additional treatment of the product ... in its final container is applied."

„In all cases, the container and closure are required to maintain the sterility of product throughout its self-time."

In-Depth Look
(PD Solution Sterilization)

Steam sterilization (heating in an autoclave)

Ph.Hg.VII

Autoclave		
°C	atm	min
134 ±2	+2.1	10
121 ±3	+1.1	20

Ph.Eur. 6:

Under pressure.
Applicable, especially for aqueous preparations.(min: 15min, ≥125°C)

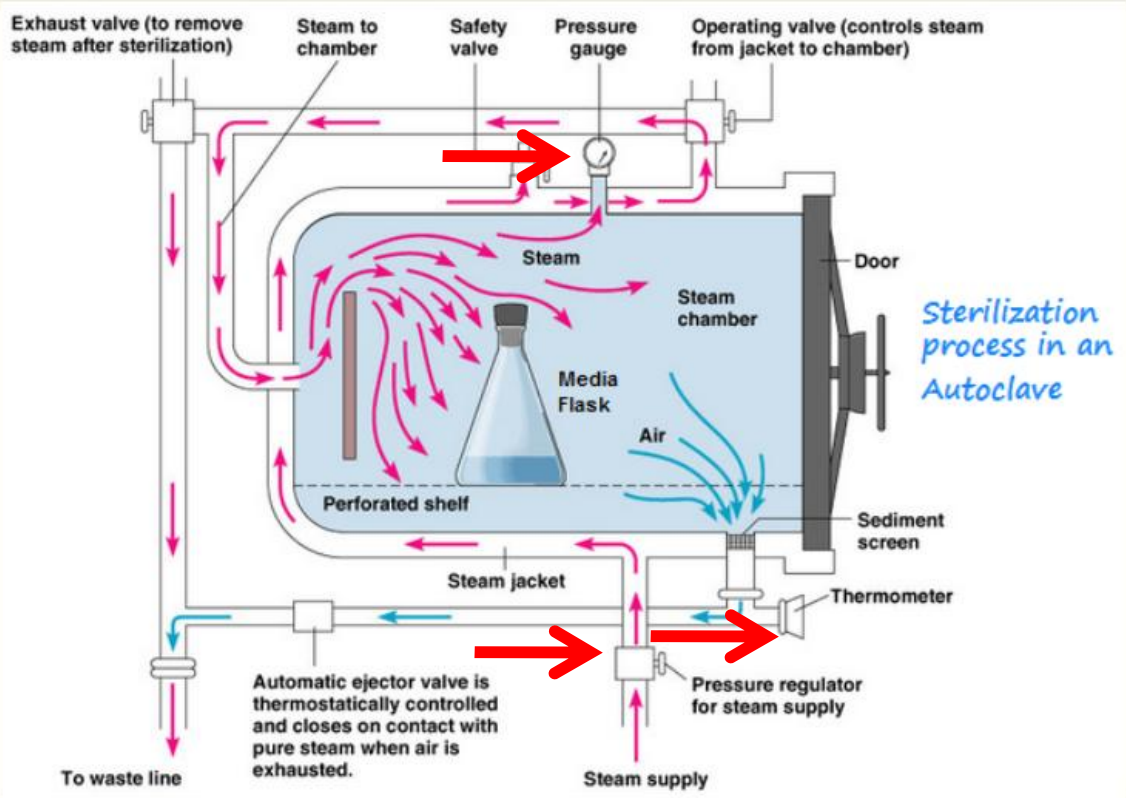
SAL 10^{-6} or better

Registration of temperature and pressure

Microbial indicators

In-Depth Look
(PD Solution Sterilization)

Steam sterilization (heating in an autoclave)



Sterilization process in an Autoclave

Sterilization
Critical Parameters of Process

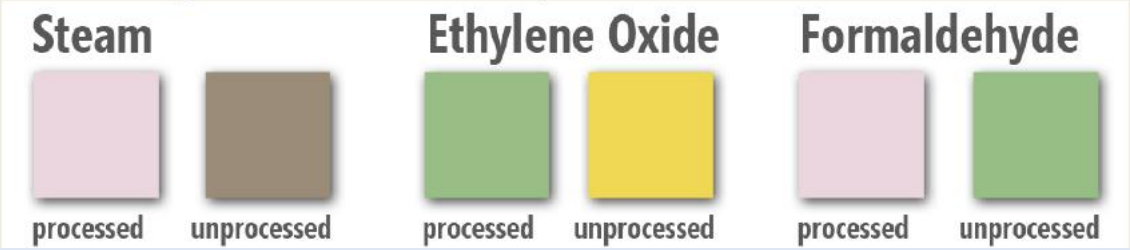
- Temp
- Pressure
- Timing
- Assuring Uniformity of Temp & Pressure in different locations of Chamber (If not uniform different batches could have different characteristics).
- Some indicator could be used to show what has gone with product.

Indicators
(Our eyes to understand process in Chamber)

Indicators: physico-chemical / biological

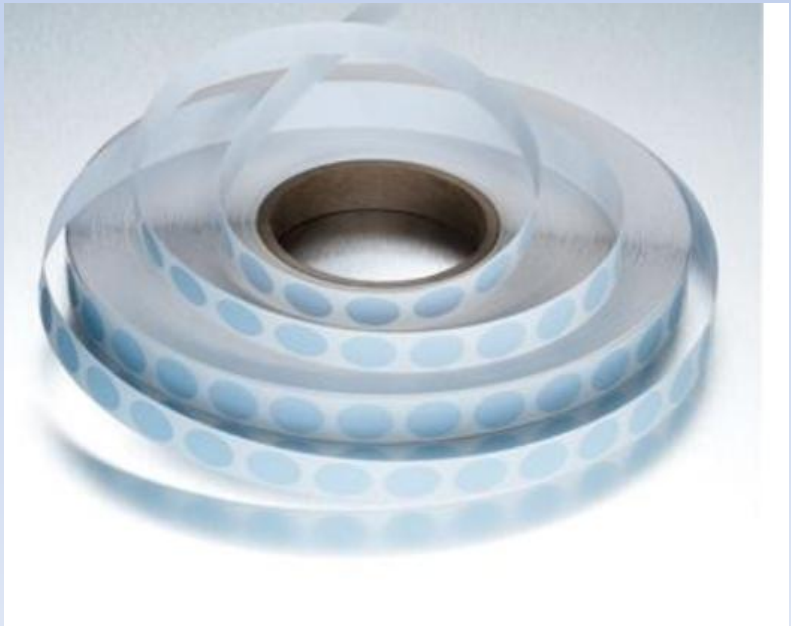
Indicators

- **Indicator tape**
- **Indicator strips**
  (non-uniform color = air in the workspace
  not colored spots – overheated steam*)*
- **Brown's indicator tube**
- **Bowie Dick indicator pack**
  (appearence of: ventilation, air infiltration, influx of non-condensable gases into the steam)

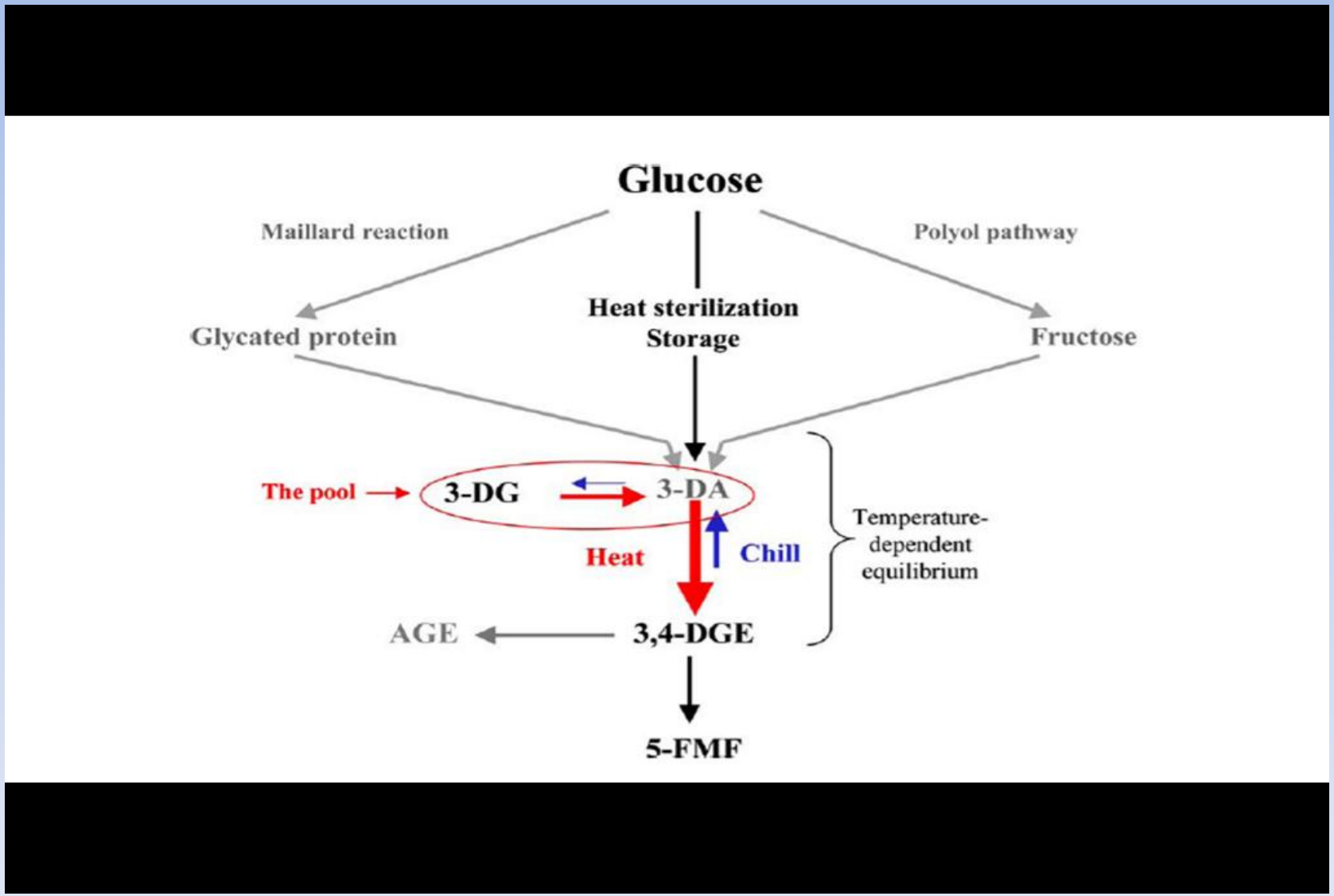


Indicators
(Process Monitoring Indicators)

Steam Chemical Process Indicators (CPIs) are manufactured to meet performance specifications described in ISO 11140-1 "Sterilization of health care products - Chemical indicators - Part 1: General requirements," for Class 1 Process Indicators. The blue-to-pink color transition is sensitive to time, temperature and the presence of saturated steam (see chart to right). Steam CPIs are not intended for use as sterility indicators, but rather as throughput process indicators used to monitor exposure to steam sterilization processes.



GDP Soup


Glucose
Maillard reaction
Polyol pathway
Heat sterilization
Storage
Glycated protein
Fructose
The pool
3-DG
3-DA
Heat
Chill
Temperature-
dependent
equilibrium
AGE
3,4-DGE
5-FMF

Serial Monitoring of a PD Fluid Batch

Peritoneal dialysis without dilution (week 0)

Batch No. of Peritoneal dialysis	Abs. in λ =228 nm (3,4-DGE)			Abs. in λ =284 nm (5-HMF)		
	0.536	0.536	0.536	0.091	0.091	0.091
	0.836	0.837	0.837	0.173	0.174	0.174

Week 1

Batch No. of Peritoneal dialysis	Abs. in λ =228 nm (3,4-DGE)			Abs. in λ =284 nm (5-HMF)		
	0.485	0.485	0.485	0.071	0.071	0.071
	0.763	0.742	0.742	0.204	0.204	0.204

Week 2

Batch No. of Peritoneal dialysis	Abs. in λ =228 nm (3,4-DGE)			Abs. in λ =284 nm (5-HMF)		
	0.429	0.430	0.430	0.066	0.066	0.066
	0.598	0.597	0.598	0.163	0.163	0.163

Week 3

Batch No. of Peritoneal dialysis	Abs. in λ =228 nm (3,4-DGE)			Abs. in λ =284 nm (5-HMF)		
	0.372	0.371	0.372	0.025	0.025	0.025
	0.498	0.500	0.500	0.112	0.112	0.112

Conclusion

- PD solutions are delivered to patients for their use. So they shall be monitored and controlled before exiting factory (QC measures like measurement of 5HMF , Acetaldehyde, Color, ….) and also patients shall be trained how to store them ? Where to store them and how to control visually and avoid NOT OK ones.

Conclusion

- Seems Samen Co. could exchange more information with Baxter and ask them about how to improve or up-regulate the control processes of production of PD fluids. This could help buy time .
- May upgrade to multi-chamber PD solutions could help to eliminate this complication.