AGING FACILITIES

IMPLICATIONS/TASK FORCE/APPROACHES

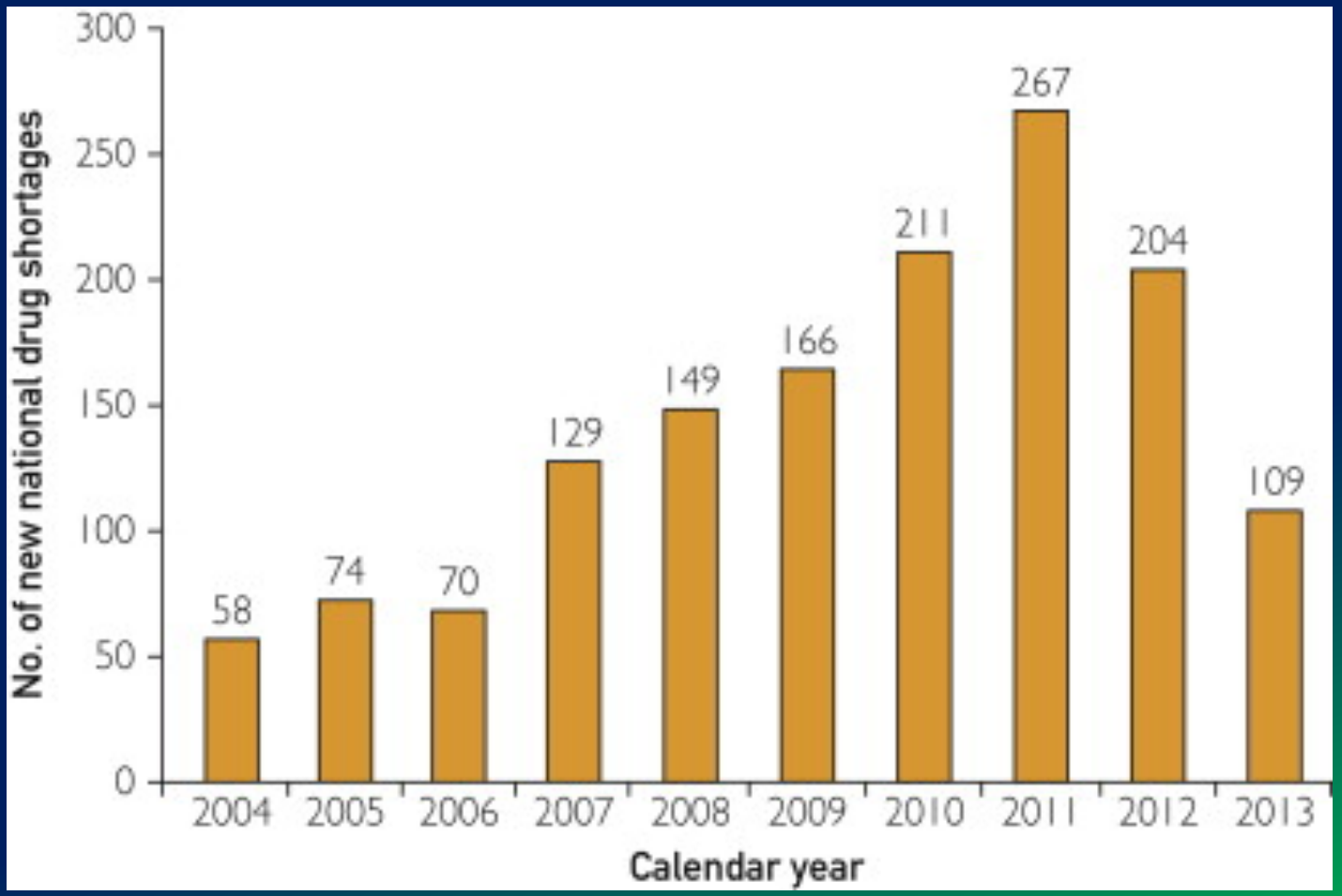
Maik Jornitz

CEO and President G-CON Manufacturing

AGENDA

- IMPLICATIONS
  - Drug Shortage
  - Why
  - Future Capacities
- TASK FORCE
  - Definition
  - Age Related Problems
  - The Task Force & Results
- APPROACHES
  - Corrective Possibilities
  - Hurdles
  - New Tasks

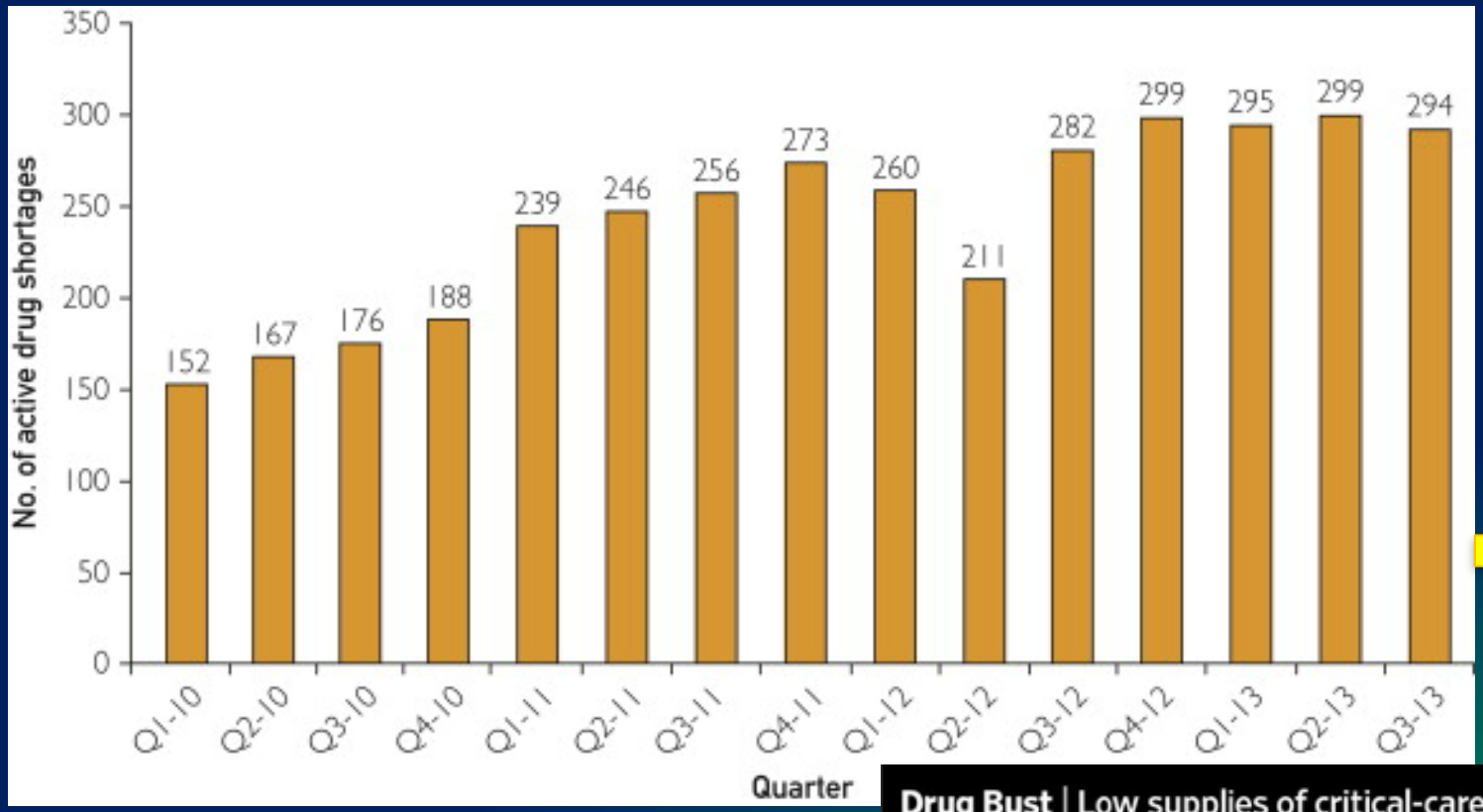
NUMBER OF NEW DRUG SHORTAGES



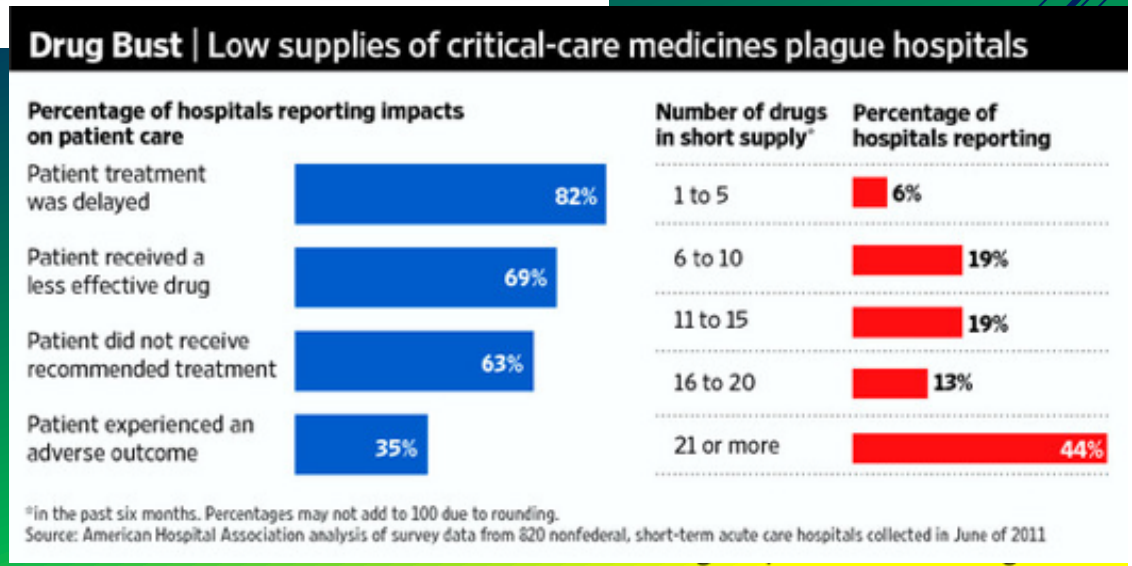
After a rise it seems the problem is under control

Source: IMS Institute for Healthcare Informatics

NUMBER OF ACTIVE DRUG SHORTAGE

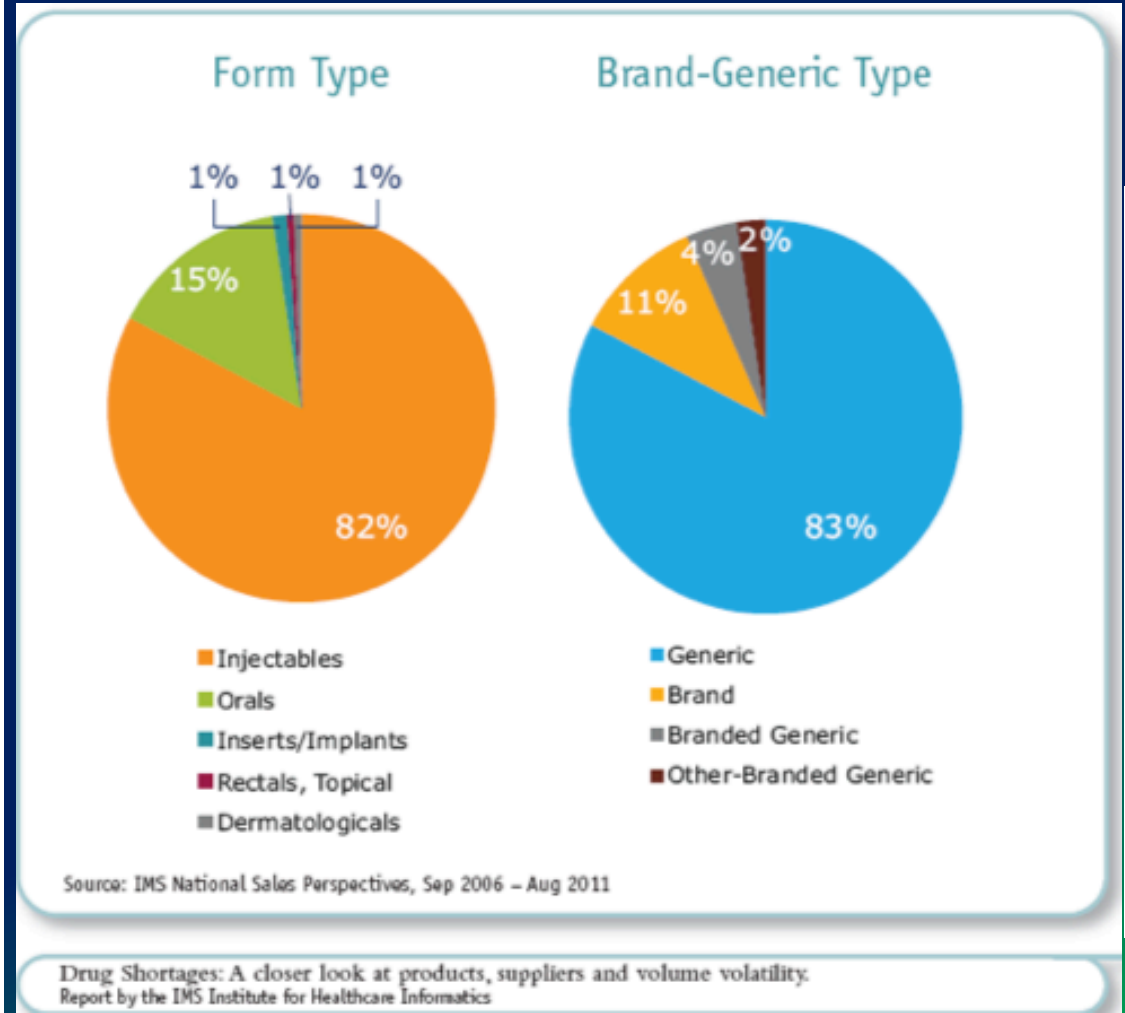


The carry-over from previous years still causes a major drug shortage problem



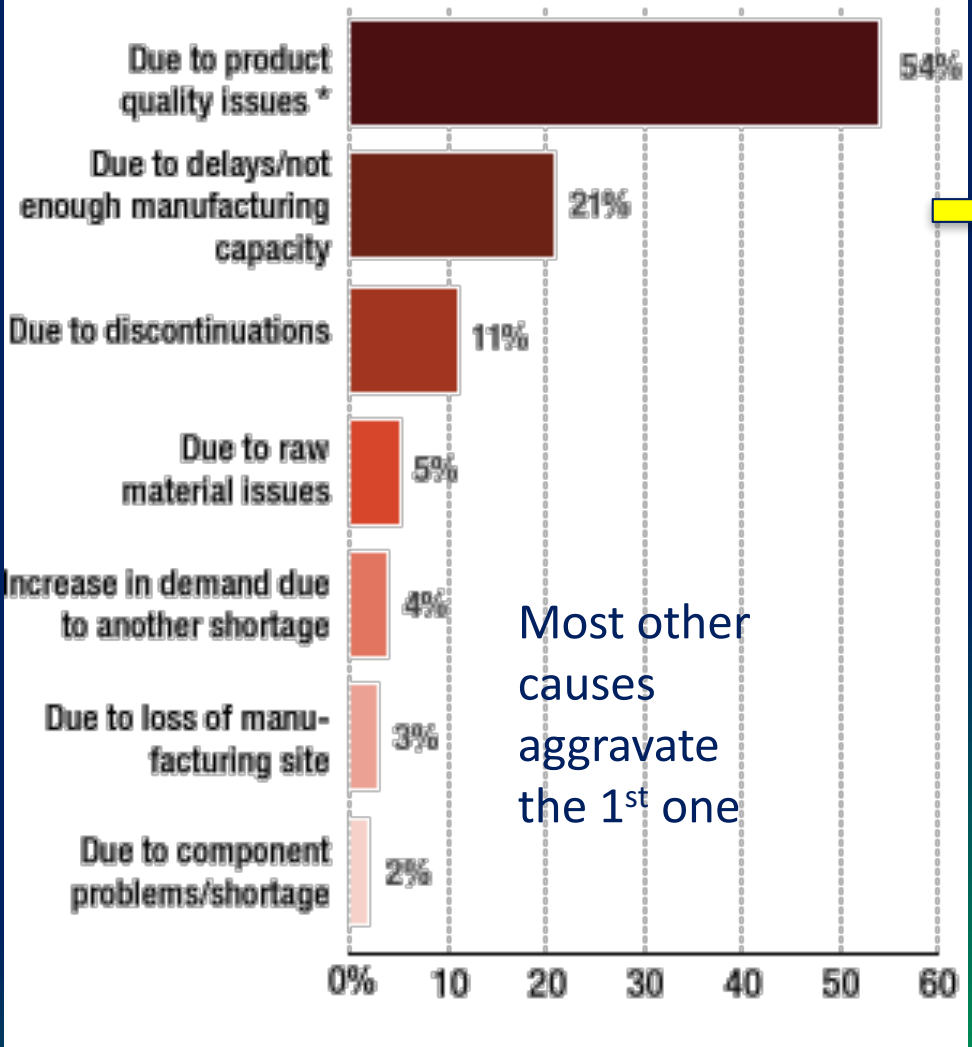
Source: IMS Institute for Healthcare Informatics

WHAT ARE THE MAJORITY OF DRUG PRODUCTS



Source: IMS Institute for Healthcare Informatics

WHAT ARE THE REASONS ?



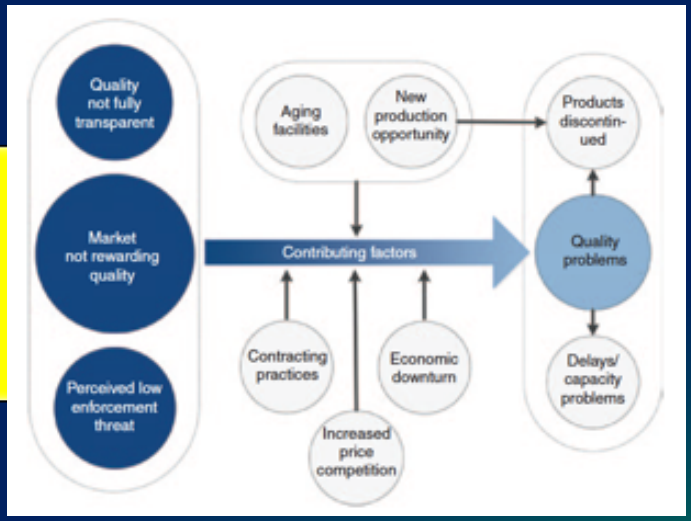
Most other causes aggravate the 1st one

- Foreign matter in filled product (particulates, fibers etc.)
- Microbial contaminations
- Glass breakage/container closure
- Mislabeling/incorrect product filling

Source: FDA

ECONOMIC DRIVERS CONTRIBUTE

Healthcare Cost Pressure
Generic Competition
Shareholder Satisfaction



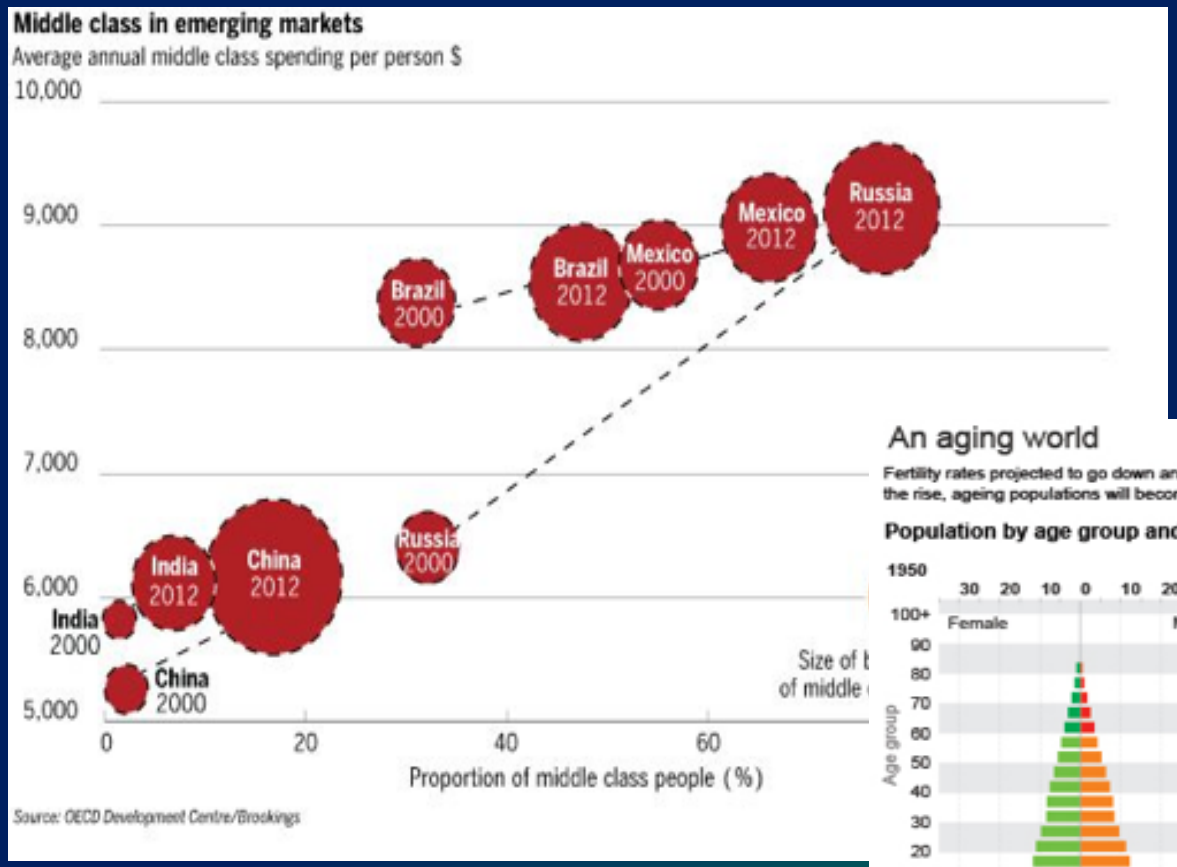
COGS Reduction

Single Site	High Throughput	Low Inventory	Reduced Maintenance	Reduced CAPEX	Lower Labor Costs

Drug Shortage

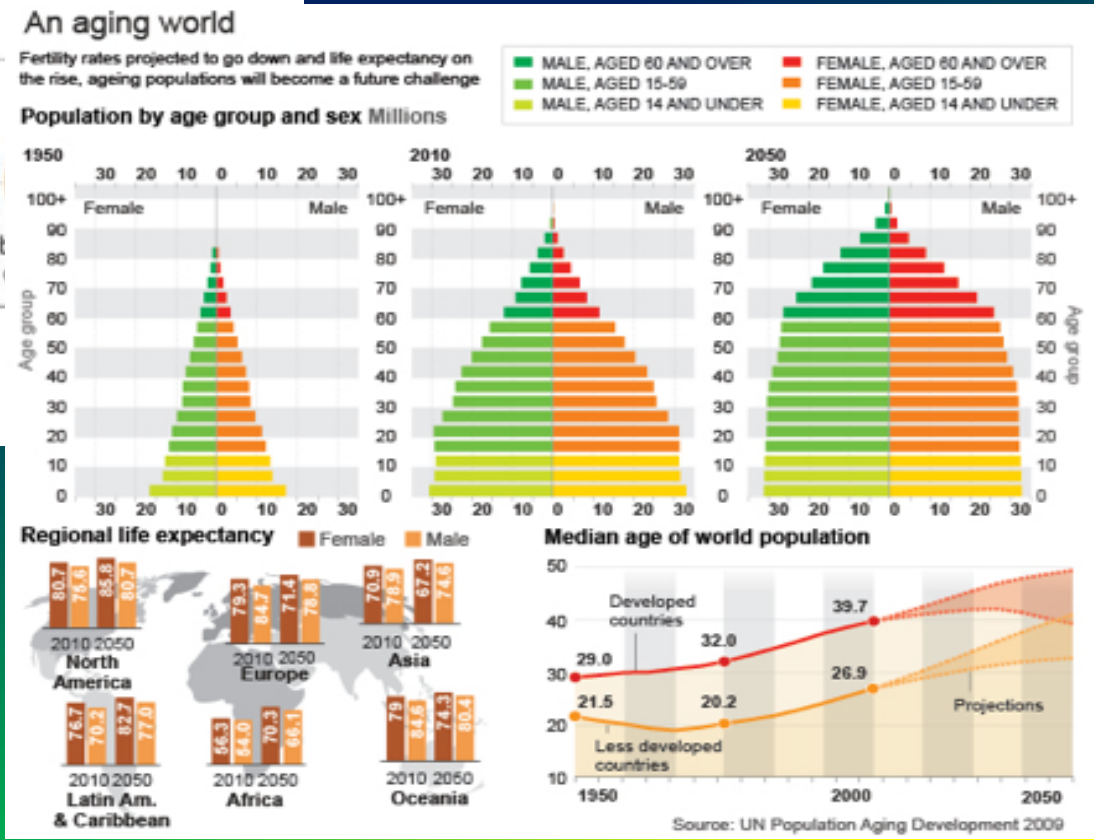
Source: Woodcock, Wosinska

FUTURE SUPPLY NEEDS



A rising middle class in the BRIC world

An aging population



Facility capacity increases are needed to fulfill the rapidly rising demand

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CURRENT SITUATION – AGING FACILITIES

- A rising scenario, a rising concern
- Can run smoothly, can be a ticking time bomb
- Rapidly aging, when COGS is sole focus
- Major contributor to drug shortage, when the facility is the sole supplier

CURRENT SITUATION – AGING FACILITIES

If processes are not automated, the precision of manual, human driven steps is crucial

Experience

Defined Tasks

Quality Conscious

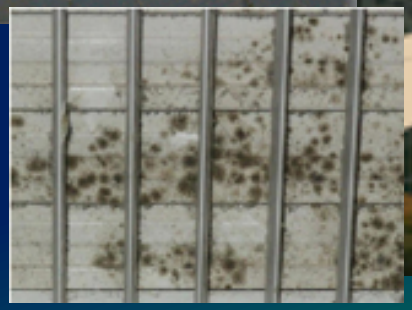
Dedication

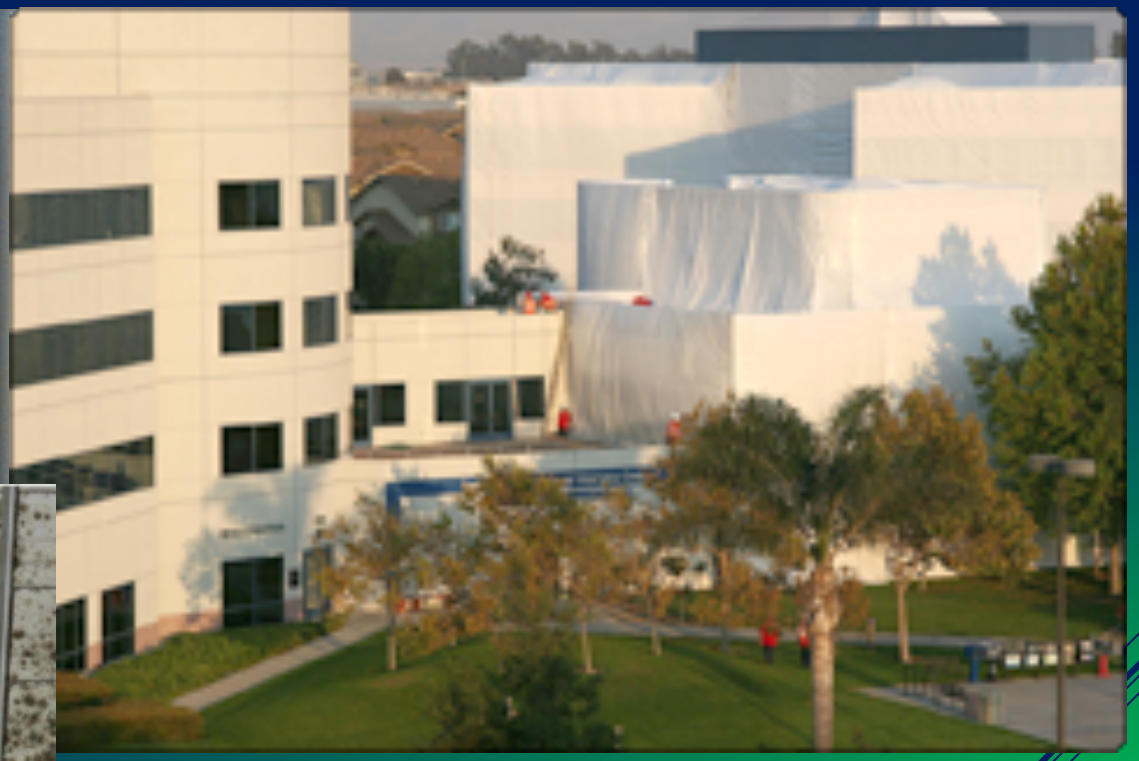
Pride

Long-term Employee

AGE CAN MEAN BREAKDOWN

Old wall panel material start to become contaminated





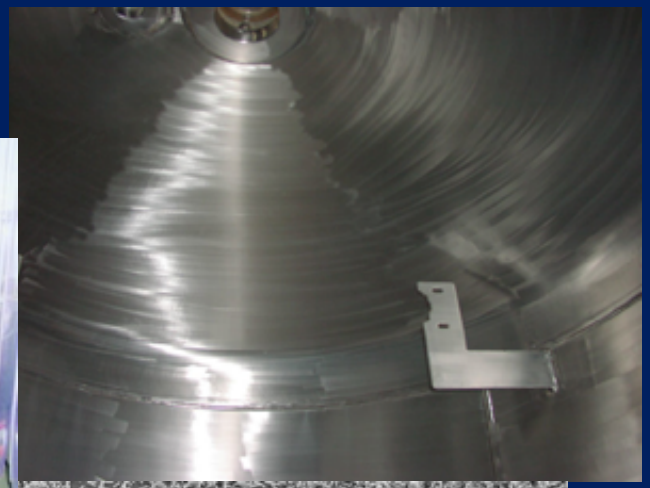
The need to decontaminate an entire site

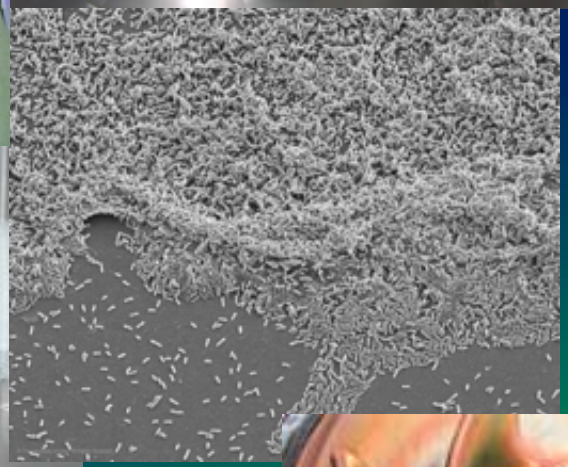
Risk:

- Quality issues
- Production shut-down
- High remediation costs

Sources: Sabre Companies

AGE CAN MEAN SUB-OPTIMAL PROCESSES



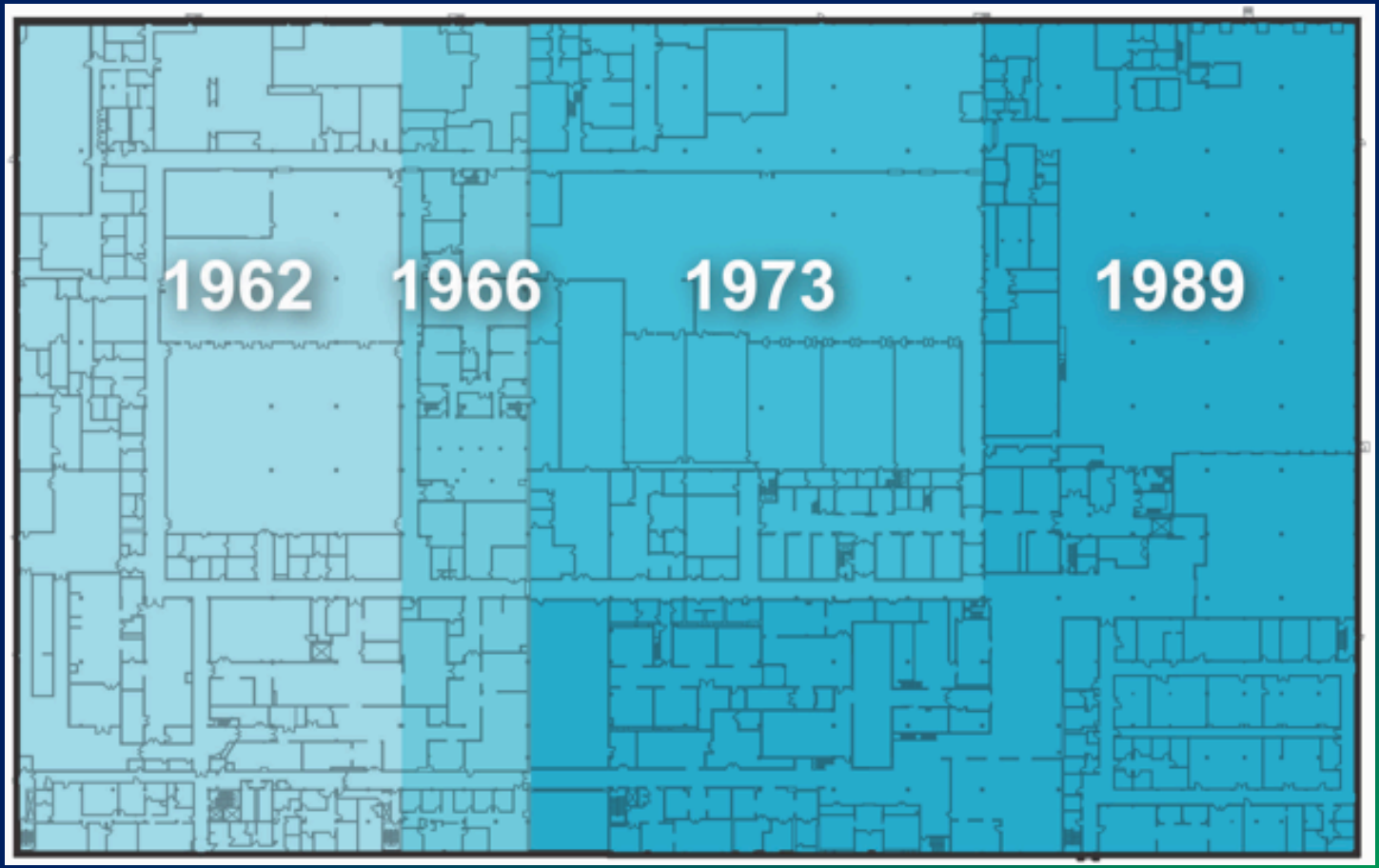


Risk:

- Quality issues
- Unit operation break-down
- Supply problems
- Yield losses

Sources: web

AGE CAN MEAN MULTIPLE EXPANSIONS



Risks:

Do we up-grade the quality standards ?

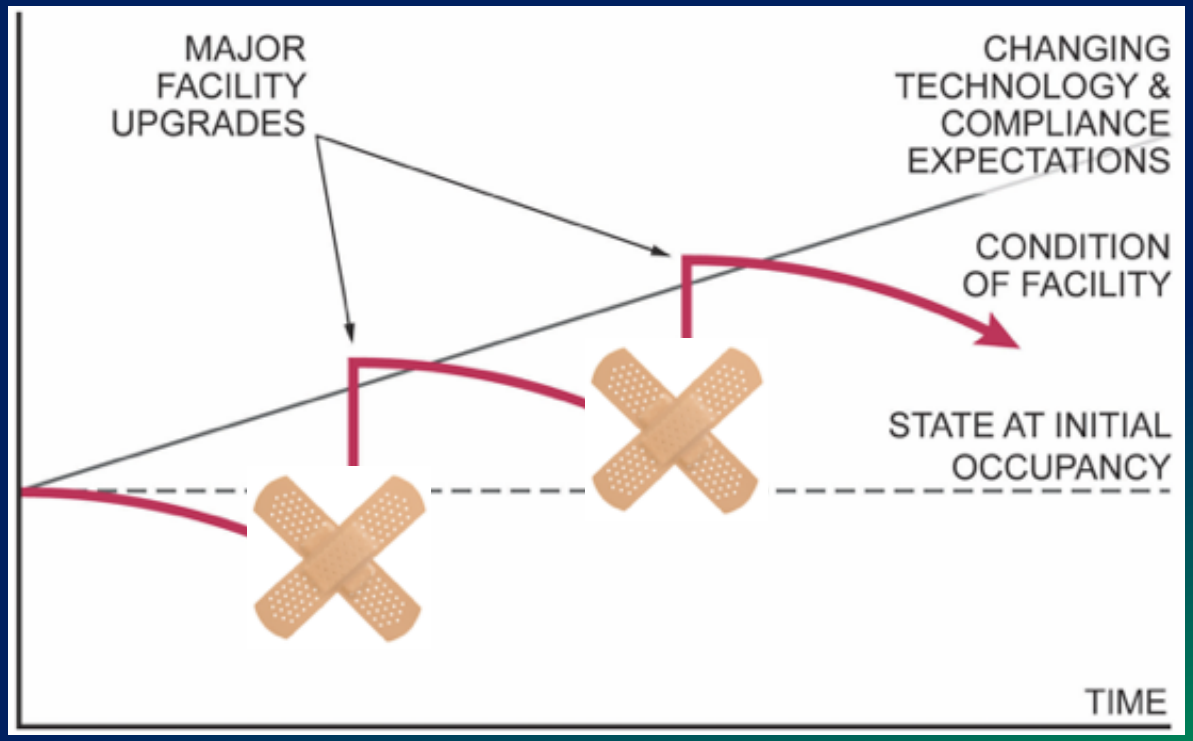
Do we have the right personnel/material/waste flow ?

Are the air handling systems or utilities up-to-par ?

Sources: blog ispe.org

HOW DO WE PERFORM UP-DATES

Continuous improvements or a seesaw approach; the later being probably motivated by regulators and not own initiatives



Risk:

- Quality issues
- Prolonged up-grade/shut down periods
- High remediation costs

Example:
We do not bring our car to the service when it broke down

Sources: blog ispe.org

A CASE OF AN AGING FACILITY – BVL

70 Years in service

2011

The FDA found 10 violations of good manufacturing practices during a late 2011 inspection and 48 violations in May 2011

Nov.'11

A recent internal review of documentation indicated that routine preventive maintenance and requalification of some manufacturing equipment did not occur at the specified time interval, and is overdue

>$300M investment in up-grades

SUN Pharma supplies generic

Oct.'12

Limited production has resumed

Jan.'13

announced that it has voluntarily entered into a consent decree with the U.S. Food and Drug Administration (FDA) that relates to current Good Manufacturing Practice requirements.

Jun.'13

will concentrate production in the company's newer, more commercially sustainable facilities. Ben Venue will cease production in one of the company's older manufacturing facilities and cease aseptic filling operations of drugs manufactured in the company's oldest manufacturing facility

Dec.'13

Company stops operations

SUN Pharma gets under FDA scrutiny

Jul.'14

Sold, the story to be continued…

Doxil Drug Shortage

Sources: Press releases, FDA files

Connecting People, Science and Regulation®

AGING FACILITY ACTIVITIES

Formation of Facility/Process/Analytics Subteams

PDA Aging Facility Workshop 2015

AGING FACILITIES DEFINITIONS

AGING FACILITY DEFINITIONS

- **Facility**: Structure and building wide systems that support manufacturing operations (e.g. wall/ceiling/floor composition and layout, water systems, compressed air systems, clean steam systems, automated facility control systems (including systems such as LIMS, SAP and others), HVAC systems, etc.). Personnel, material and waste flows, overall facility layouts including cleanroom classifications and pressure cascades.

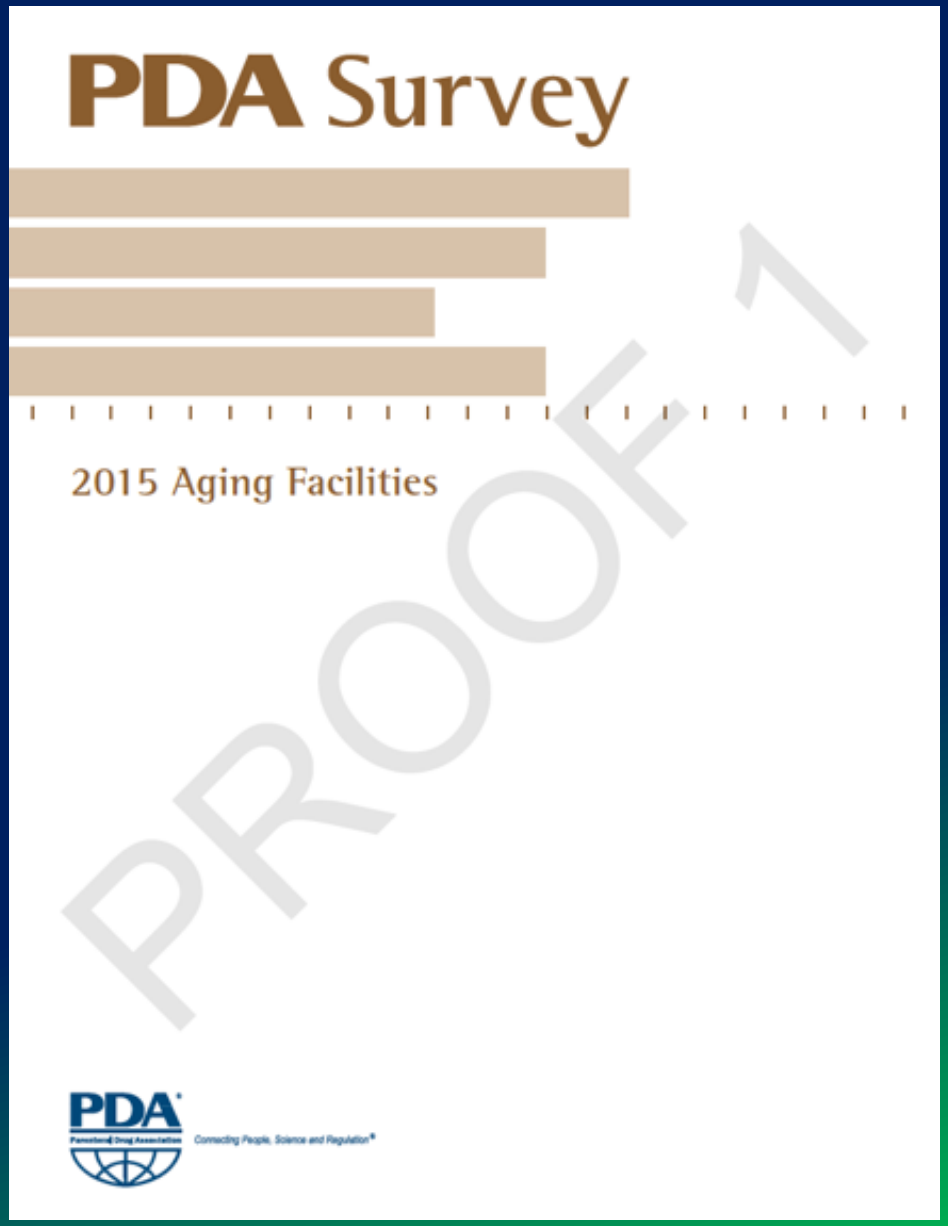
- **Process**: The manufacturing process (e.g. formulation, sterilization, filling, etc.) and related equipment specific to that process (e.g. bio reactors, process vessels, filling lines, lyophilyzers, CIP systems, etc.) Process flows, product transfers and flow of raw materials or components into the process unit operations.

- **Analytics**: In process tests performed during the manufacturing process (e.g. host cell proteins, biuret, conductivity, pH, potency, pre-filtration total microbial count, sterility, etc.) inline testing, process analytical technology tools, sensor technology, signal and test result capture via automation, the resulting statistics and potential corrections. Possible simulation tools, which can mimic specific quality, attribute shifts if changes are made. Sampling points, activities and testing.

AGING FACILITY ACTIVITIES

- Formation of Facility/Process/Analytics Subteams
- PDA Aging Facility Workshop 2015
- PDA Survey and Survey Report

SURVEY RESULT SUMMARY



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SURVEY RESULT SUMMARY

- Survey showed that most sites and products are older (>11 years = >80%)
- 73% of respondents say the facility runs good or excellent
- Aging is seen as dated technologies, frequent breakdowns, not meeting requirements
- Batch rejection rate is fairly high (>5% of 18% respondents)
- Very low portion of respondents perform in-process analytics or perform improvements
- Regulatory requirements encourage modernization and risk assessments are used extensively
- Improvements are mainly made to facilities, not to process and analytics
- Technology scouting is hardly ever done

AGING FACILITY ACTIVITIES

- Formation of Facility/Process/Analytics Subteams
- PDA Aging Facility Workshop 2015
- PDA Survey and Survey Report
- Assembly of questions by task force members
- Answers of questionnaire
- Points to Consider Document

Revised → Board ballot

AGING FACILITY QUESTIONS POSTED

Q1. How can enhanced maintenance programs (e.g., Total Productive Maintenance – TPM) be employed to retard the facility aging process and extend the life of current facilities?
Q2. Which building systems are most susceptible to performance deterioration due to age and what can be done to remediate these?
Q3. How can risk management methodology be used to evaluate and improve aging facility performance?
Q4. Older facilities may have architectural features (e.g., wall and floor finishes) that may be considered to be below modern standards (e.g., difficult to clean, possible cross-contamination hazard). What is the value-added proposition to remediate these?
Q5. How can enhanced process controls and/or analytical technology be employed to extend the life of aging process equipment?
Q6. How are existing facilities affected by revised international standards, such as ISO 14644?
Q7. How viable is the concept of re-purposing existing out-of-service facilities?
Q8. How would you recognize that your facility is aging, when you are living with it every day?
Q9.What do you suspect a regulator/Health Authority would be looking for to determine whether you have an aging facility?
Q10. Could a robust predictive maintenance program, as opposed to a compliant preventive maintenance program, keep a facility from aging?
Q11. Is a painted surface, as opposed to a non-painted non-corrosive washable surface, a sign of an aging facility?
Q12. How many times can a facility be piece-meal renovated before it is time to start with a blank piece of paper?
Q13. Is an upward trend in deviations involving equipment and processes a signal of an aging facility?
Q14. What is an aging facility?
Q15. How do you know that you facility is aging?
Q16. Is there a trigger point which determines that you are having an aging facility?
Q17. Which parameters to monitor for determine aging facility?
Q18. What do you need to take into consideration when modernizing a facility?
Q19. which risk model to use for evaluating whether my facility is aging?
Q20.Can you maintain the facility to ensure that it is not aging?
Q21. What are the major reasons for not modernizing the facility?
Q22. How do you know what is cGMP in relation to facilities?
Q23. What risk do you take when producing in an aging facility?
Q24. Why are we using aging facilities?
Q25. Does the level of recapitalization warrant a facility design evaluation?
Q26. As needs for modernization are identified are process flows (equipment/people/materials) acceptable for continued operation?
Q27. How do maintenance costs factor into analysis of recapitalization vs repair? (Are ongoing maintenance costs excessive when compared to re-capitalization?)
Q28. Do updated building codes warrant a new facility vs retro-fit?
Q29. Does the underlying infrastructure support process recapitalization (utility distribution piping, electrical distribution, water system, structural elements)?
Q30. How do changes in regulatory expectations impact facility recapitalization plans (Does the existing facility comply with intent and/or letter of regulatory expectations)?
Q31. Are hazardous/dangerous materials of construction within the facility and are remediation plans in place?
Q32. Have special considerations for soil exposure / adulteration of the clean space recovery been considered as part of recapitalization plan?
Q33. Has a Resource Assessment program been put in place and how does it impact facility modernization plans?
How do we reduce the fear of change?
Q34. Is a Brownfield project - installing new operations in an old building, considered an aging facility upgrade?
Q35. Is a Process Retrofit - installing new process equipmnent in an operating pharmaceutical facility, considered an aging facility upgrade?
Q36. What components should be included in the business case to justify/ demonstrate the need for a facility upgrade?
Q37. Is the risk of not changing greater than the risk of making a change?
Q.38 How do you document or prove that the need for modification if not admission that the past operation was inadequite?
Q.39 What is a strategy for grouping modifications to reduce downtime, regulatory, and validation efforts?
Q.40 What is the process to identify, justify, plan, review, and approve changes?

Task Force Team assembled 89 questions using the workshop, survey and other member input

Q.41 How are architectural modifications, affecting flow and gowning areas, handled within an existing pharmaceutical facility?
Q.42 How is HVAC equipment replacement handled for an existing line?
Q.43. How is Utility equipment replacement/ upgrades handled for an existing and operating facility?
Q44. What is an aging process?
Q45. What risk assessment tools should be used?
Q46. Can we learn from years of process data? Can we determine and document that the critical process variables are more or less critical than originally thought?
Q47. Is the process to implement an upgrade any easier, if there is a long history of the new equipment operating successfully and better in similar installations?
Q48. If a process appears to be "under control" based on the data gathered, is there a responsibility to learn from past data to improve the operation?
Q49. How is process equipment replacement handled for an existing line?
Q.50 How are instrument replacements handled?
Q51. How are control system replacements handled?
Q52. How shold years of past process data be maintained after upgrading a process control system?
Q53. How do you handle different regulatory authorities in different markets?
Q54. How can obtaining stability data be streamlined?
Q55. Can a Comparability Protocol be used to help validation of facility modifications?
Q56. Can an Operability Protocol be used to compare pre and post-change operation? Note (Not sure what Operability Protocol is Refereing to?)
Q57. Can a family approach be used to help validation of facility modifications?
Q58. Is it better to validate modifications that use an old technology previously validated in the facility, or modifications using a new technology that is the current industry standard?
Q59. If older processes don't have the design space defined to current standards, can it be defined prior to starting a new process validation?
Q60. How can statistical methods be upgraded/ optimized?
Q61. How can new analytical instruments be implemented?
Q62. Can rapid-micro be implemented?
Q63. How do you interpret old data?
Q64. How can data analytics be applied to reducing the risks associated with operating aging manufacturing facilities?
Q65. What are some best practices for managing the post-approval change process for an aging facility?
Q66. How can I construct a business case for modernizing an aging facility?
Q67. Are there some instructive warning letters that are directly related to the failure to modernize an aging facility?
Q68. What do I do when the Pharmacopeias revise a method/specification and it is not consistent with my registered specifications/test method?
Q69. What do I do when, after switching to a more modern methodology (i.e. HPLC to UPLC), a new unknown impurity peak is detected?
Q70. What do I do when I can no longer get an equivalent replacement piece of equipment for a method (i.e. Atomic Absorption)?
Q71. How do I determine a suitable replacement column for my HPLC when the manufacturerer of the original column discontinues making it.
Q72. How do I validate and integrate laboratory data systems into my operation? What do I do if the company no longer supports the product version I use?
Q73. When should a company begin considering modernizating a facility?
Q74. What approaches can be used to help inspectors understand my facility modernization plan?
Q75. What factors should be considered when planning the rate of facility modernization?
Q76. For facilities that manufactures product for global markets what are some of the regulatory filing factors that should be considered in a facility modernization plan??
Q.77. How to update, maintain and document cleaning procedures (CIP/SIP) in aging facilities?
Q78. How to convert aging facilities to closed operation?
Q79. How to convince the C-Suite to make necessary changes, what are the benefit propositions and how to bring them concisely forward ?
Q80. What is the most known "painfactor" to get rapidly motivated to change a facility or process ?
Q81. What facility and process materials and designs are considered modern or up to date ?
Q82. What facility layouts are required to accommodate new process technologies and designs and how can aged facilities be converted ?

Consolidated Question #1:
What components should be included when evaluating the need to modernize a facility or process and what factors often prevent companies from moving forward with modernization plans?

Touched on in the answer:

Q.08. How would you recognize that your facility is aging, when you are living with it every day?

Q.15. How do you know that you facility is aging?

Q.16. Is there a trigger point which determines that you are having an aging facility?

Q.21. What are the major reasons for not modernizing the facility?

Q.29. Does the underlying infrastructure support process recapitalization (utility distribution piping, electrical distribution, water system, structural elements)?

Q.35. How do we reduce the fear of change?

Q.38. What components should be included in the business case to justify/ demonstrate the need for a facility upgrade?

Q.39. Is the risk of not changing greater than the risk of making a change?

Q.71. How can I construct a business case for modernizing an aging facility?

Q.88. How to convince the C-Suite to make necessary changes, what are the benefit propositions and how to bring them concisely forward?

Q.80. When should a company begin considering modernizating a facility?

AGING FACILITY OUTCOME

PDA Points to Consider for Aging Facilities

Draft 23Jan2017

Points to Consider for Aging Facilities

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POSSIBILITIES – RETROFITTING PROCESSES

Needed conversion

POSSIBILITIES – RETROFITTING PROCESSES

From large scale stainless steel to medium volume single-use

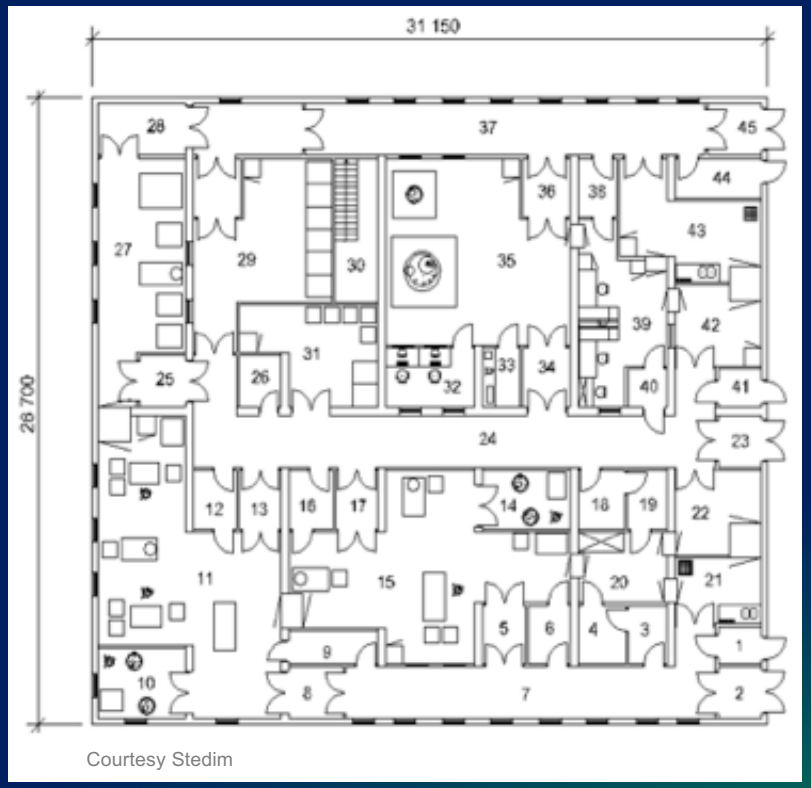
10kL

De-risking
Higher flexibility
Faster turn-around
Closed systems
Advanced PAT

2kL

THE GRAIN OF SALT…

Single-use technology processes create flexibility & speed, but…



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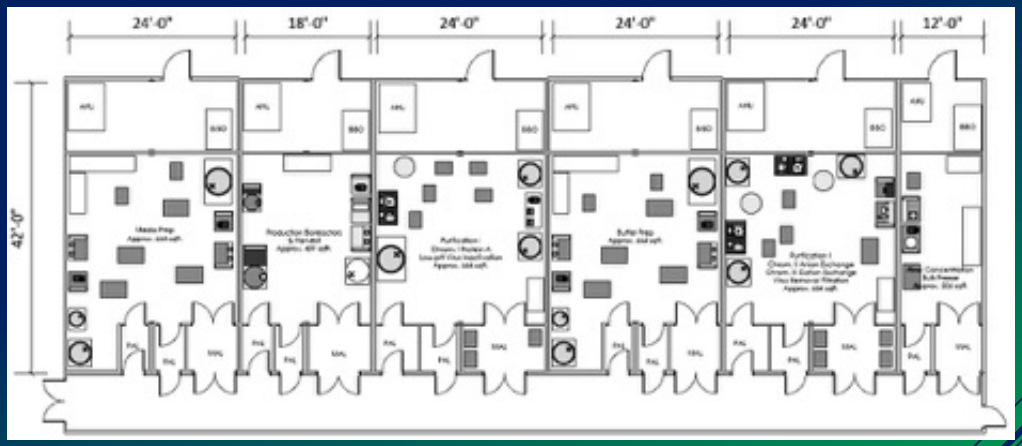
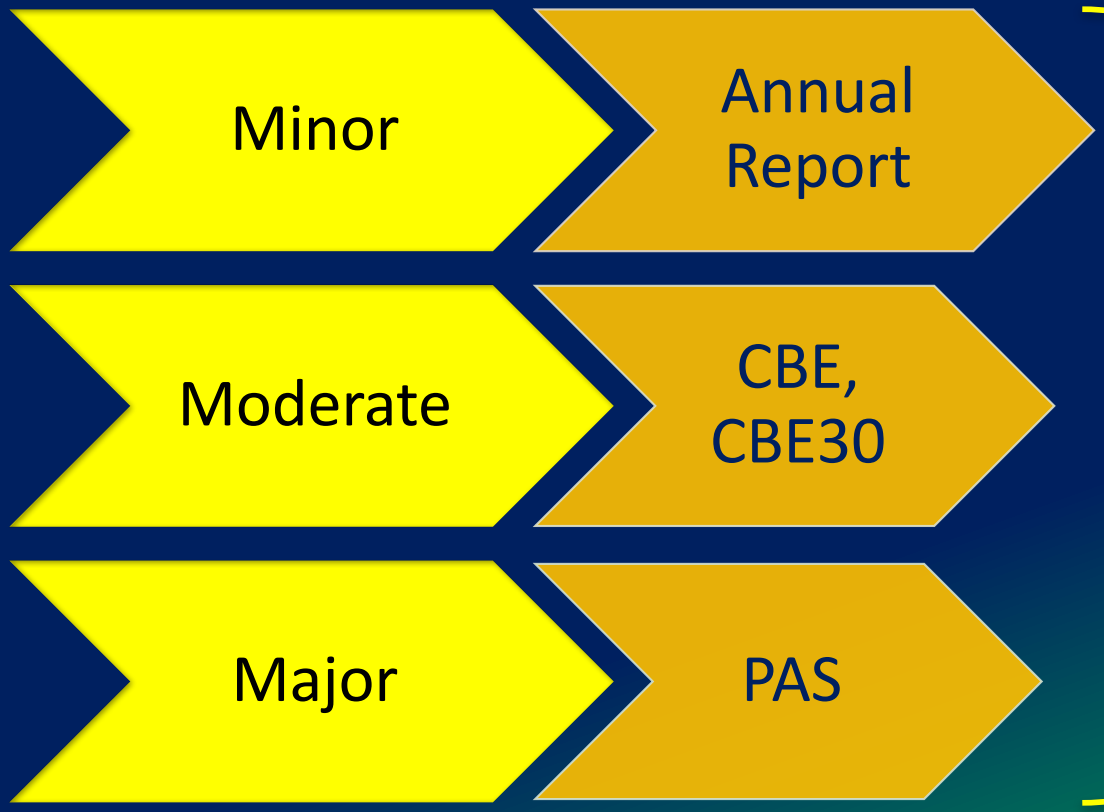


…is only as flexible as the surrounding infrastructure !

NEEDED – DEFINING & HARMONIZING



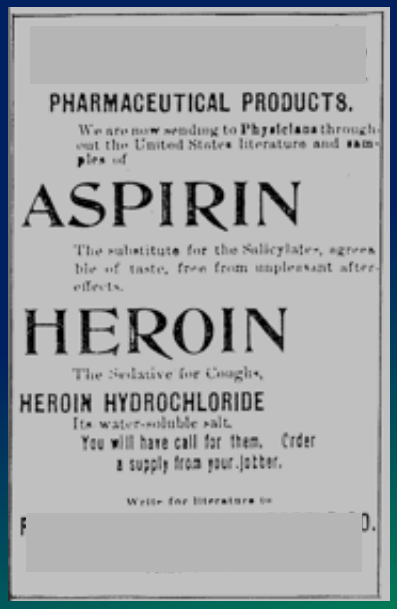
What is what, can mean:

- Substantial resources drain
- Lowering the motivation of change/ improvement
- Mothballing facilities

The PDA Task Force PAC IM needs to address change classifications and regulatory actions for example harmonization

NEEDED – NEW APPROACHES

….WE CAME A LONG WAY THOUGH !



THANK YOU !
ACKNOWLEDGEMENT

Ghada Haddad, Merck, Co-Chair

Maik Jornitz, G-CON Manufacturing Inc., Co-Chair

Glenn Wright, Eli Lilly and Company, Co-Chair

James Butler, Cimetrics

Jette Christensen, Novo Nordisk

Phil Desantis, DeSantis Consulting Associates

Robert Dream, HDR CO., LLC

John Lewis, DPS Consulting, Inc.

Anette Marcussen, Novo Nordisk

Morten Munk, NNE Pharmaplan

Shelley Preslar, Azzur Group

Sue Schniepp, Consultant

Chris Smalley, Merck

Matthew Taylor, Eli Lilly and Company

George Wiker, AES Clean Technology

mjornitz@gconbio.com