Pharmaceutical cGMPs for the 21st Century
February 2004

Ludwig Huber
Compliance Fellow for
Life Sciences and Chemical Analysis

Chairperson: Rob Sample

Agilent Technologies

FDA GxP Regulations Along the Drug Life

← No GLP/GMP!!! → GLP GCP GMP

← 21 CFR Part 11 →

21 CFR:	GLP: Part 58	GCP Part 50	GMP 210/211

FDA Focus

Product Safety
+ Availability
+ Affordability

Pharmaceutical cGMPs for the 21st Century

- Announced August 21, 2002
- Two year program
- Merges science-based risk management with an integrated quality system approach
- Will not interfere with current enforcement - no deregulation!
- To be implemented in multiple steps
- First results in 2003

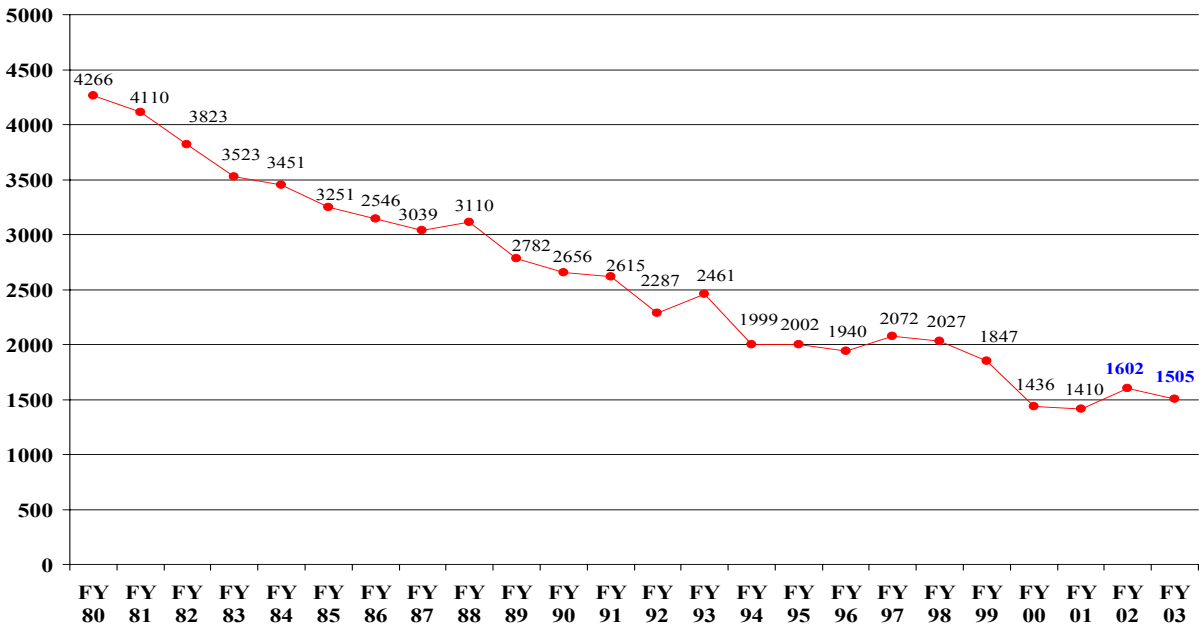
Risk based system inspections

Optimize FDA resources

Background: Significant Changes Occurred in the Last 25 Years

- **Increase #of pharmaceutical products and a greater role of medicine in health care**
- **Decreased frequency of FDA manufacturing inspections**

1981
4266



2002
1410

Source

Domestic non - medical gas GMP inspections

21st Century GMP Initiative - Three Goals

Goal #1

- Enhance focus of agency‘s cGMP requirements more on potential risks to public health. Focus on those aspects of manufacturing that pose **greatest potential risk**

Goal #2

- Help ensure that FDA‘s enforcement practices does **not slow down innovation and introduction of new manufacturing technologies** in the pharmaceutical industry

Goal #3

- Enhance **consistency and predictability** of FDA‘s approach for inspections

Use FDA resources more efficiently

Source

First Results

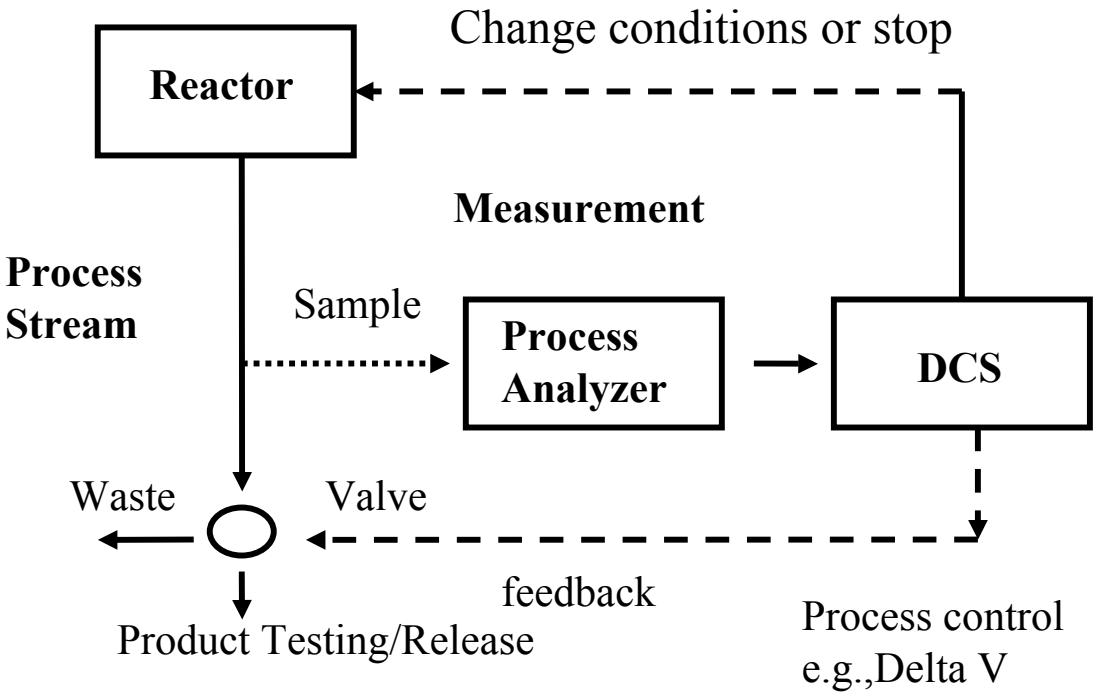
- Guidance on **Comparability protocols** for non-protein drugs and biological
  - allows certain manufacturing changes without submission of prior approval supplement

- Guidance on **Process Analytical Technology**
  - helps to modernize manufacturing

- **Electronic records/signatures (part11)** based on “justified and documented risk assessment” makes electronic records and signatures affordable and manageable

- Review of Warning Letters by Centers and guidance on dispute resolutions helps with **consistency and predictability of enforcement**

FDA Guide
Process Analysis Technology (PAT)



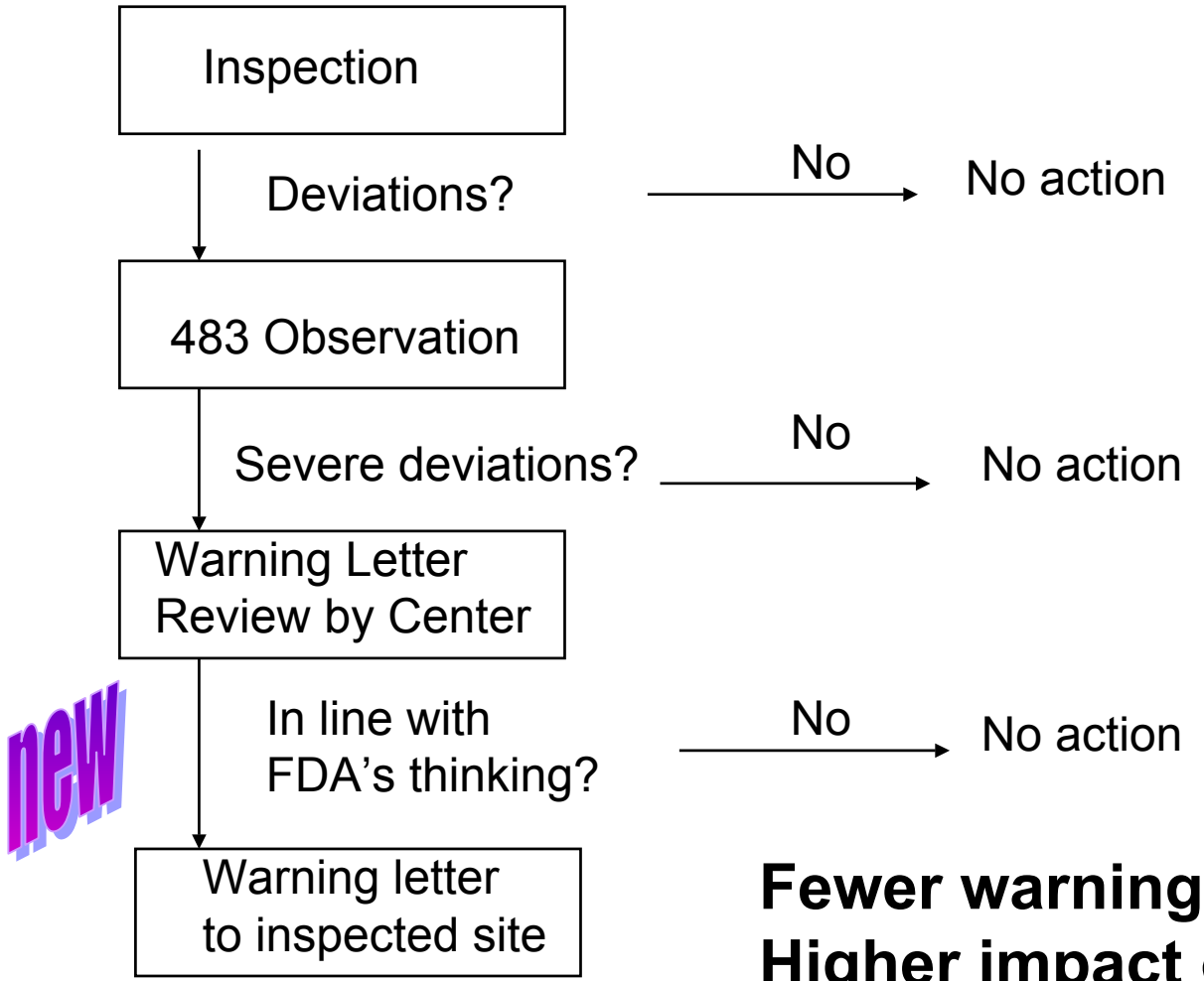
Advantages
- Less recalls
- Less waste

Previous problems
- Validation

FDA working with industry on how to optimize validation/compliance vs. risk

DCS = Distributed Control System

Review of Warning Letters



Fewer warning letters but
Higher impact on industry

Audit Trail and OOS

FDA Warning Letter

- Confirmed OOS results for … were **invalidated by Quality Assurance,** that concluded that the chromatographs were incorrectly integrated.
- The Chromatographs were **reprocessed with adjusted baseline parameters, yielding acceptable results**, and the lots were released for distribution.
- However, the laboratory investigation concluded that the results could not be invalidated and that no problems were observed during the chromatographic run.

October 2003

OOS

Recommendation:
keep all integration results, document changes

Ref.: www.fdawarningletter.com

Rationale Behind Systems Inspections Approach

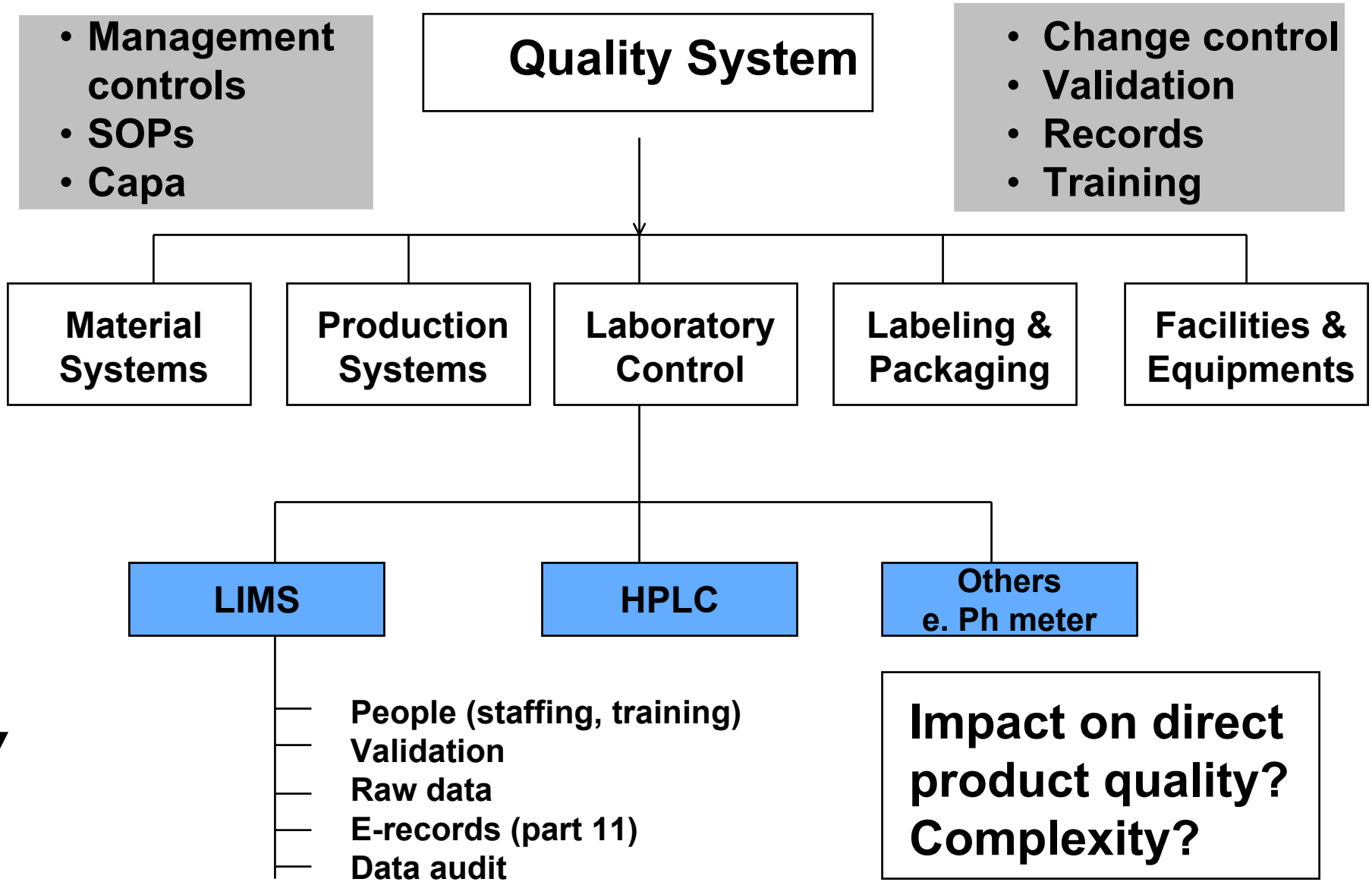
What does change?

- The way how inspections are done and evaluated
- Time for inspections may go down

Requirements do not change !!!

- If the quality system and one or more other systems are adequate all profiles covered by the system are adequate
- **If one site is not in compliance, other sites may not be in compliance!!!**

New Approach: System Inspection - Top Down



Recommendation for System Based FDA Inspections

Study FDA's Compliance Policy Guide 7356.002

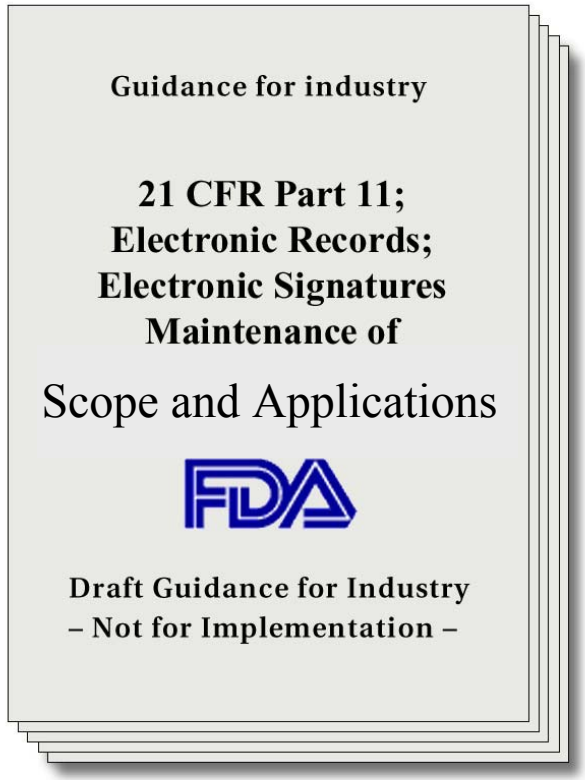
COMPLIANCE PROGRAM
GUIDANCE MANUAL PROGRAM

- Guidance for inspectors on how to conduct inspections
- Describes all six systems
- Includes checklist items for each system

Download from:
http://www.labcompliance.com/agilent/gmp

How Does this Impact Part 11?

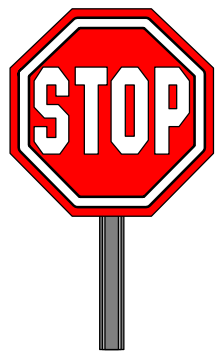
- The concept of risk based inspections will be applied to GMP AND part 11
- Ensure latest technology can be used
- Part 11 implementation based on documented risk mamagement
- Narrow the scope of part 11



First guidance Feb/Aug, '03

New Part 11 Approach

1. Determine Predicate Rule Requirements
2. Narrow Scope - Identify Electronic Records that Require Part 11 Compliance
3. Part 11 Records | Not Part 11 Records
4. Assess Risk - Evaluate Level of Controls Appropriate to Risk
5. Implement Appropriate Part 11 Controls



Ref: Famulare - Murray - McIntire

Risk Assessment

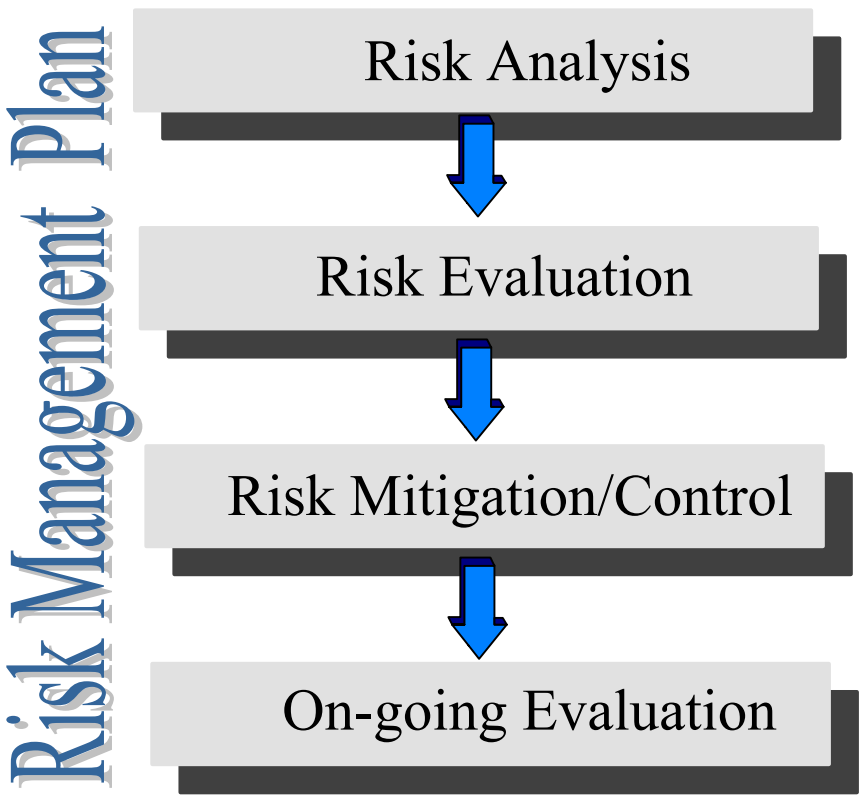
New part 11 guidance

We suggest that you base your decision on …
a justified and documented risk assessment

The magic word is 'risk'

- **Develop risk assessment strategies and SOP**
- **Identify, evaluate, and prioritize risks for Part 11**
- **Document risk assessment**
- **Define consequences for systems as defined high, medium or low risk**
- **For long term: develop and implement risk management**

Risk Management



- Identify the system
- Identify hazards and possible threats

- Estimate, justify and document risk level (probability/severity)

Risk assessment

- Estimate costs of mitigation vs. non-mitigation
- Define and take actions for mitigation

- Monitor for new threats
- Monitor risk levels
- Update plan and take actions

Documentation

Key criteria: product quality (public health), business continuity

Start With a Risk Management Master Plan

1. Approach
2. Steps for risk analysis/evaluation
3. Steps for risk mitigation/control
4. Inputs for risk assessment
5. Risk categories
6. Examples for risk levels
7. Appropriate controls for different risk levels
8. SOP with Templates

Risk descript.	Severity	Proba-bility	Risk factor

Risk Matrix

computer systems - networks - spreadsheets - legacy systems

Documenting Risk Assessment

For part11

Example

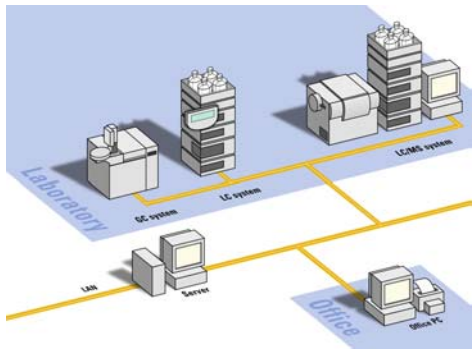
- Use tables with description of risks, severity, probability and the rationale behind
- Calculate overall risk factor
- Classify factors in high, medium and low

Risk descript.	Severity	Justification	Probability	Justification	Risk factor

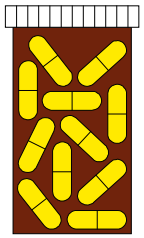
There are many other ways to do this

Example: QC Laboratory Data System

Sample
from plant



Release
Packaging
Labeling

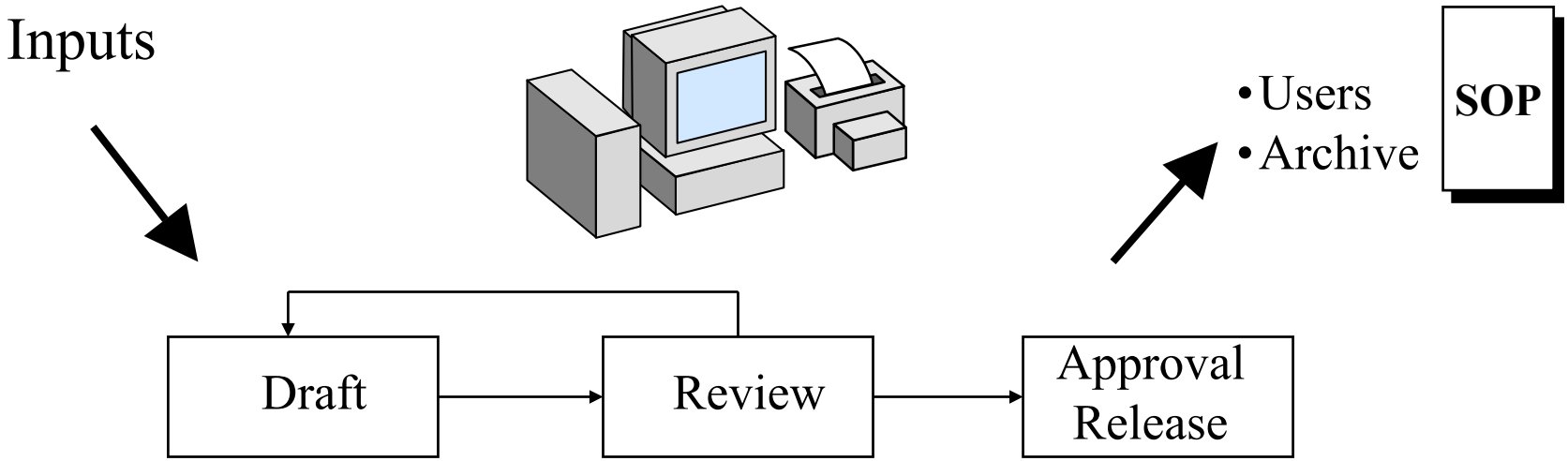


Sample receipt and log in → Sample analysis → Review and approval

High Risk

Direct impact on product quality
Computer performs regulated action

Example: Word Processing System for SOPs



Low Risk

No direct impact on product quality
Computer = type writer

What's Next?

Part 11 Re-examination and new rule making

- First public hearing in 2004
- Final release not expected before 2006

Announced

Quality system guide

- FDA develops Quality System Guide
- Agency wide concept
- Encourages industry to use quality system principles
- Release expected in late 2004
- Risk management expected to be a key element

www.agilent.com/chem/eseminars-compliance

updates

Recommendations

- **Start risk management/risk assessment process**
  - master plan - SOPs - ranking criteria -
  - assessment for Part 11

- **Monitor warning letters**

- **Start implementing quality system principles**
  - quality by design
  - ongoing process monitoring and improvement

Further Information

To attend the Agilent e-seminar series, please visit our WEBSITE:

http://www.agilent.com/chem/eseminars-compliance

For further information on our products and services please contact your local Agilent Office.