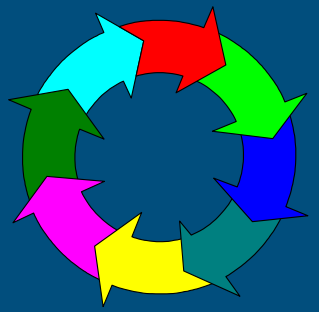
Preparation and Management of International Inspections



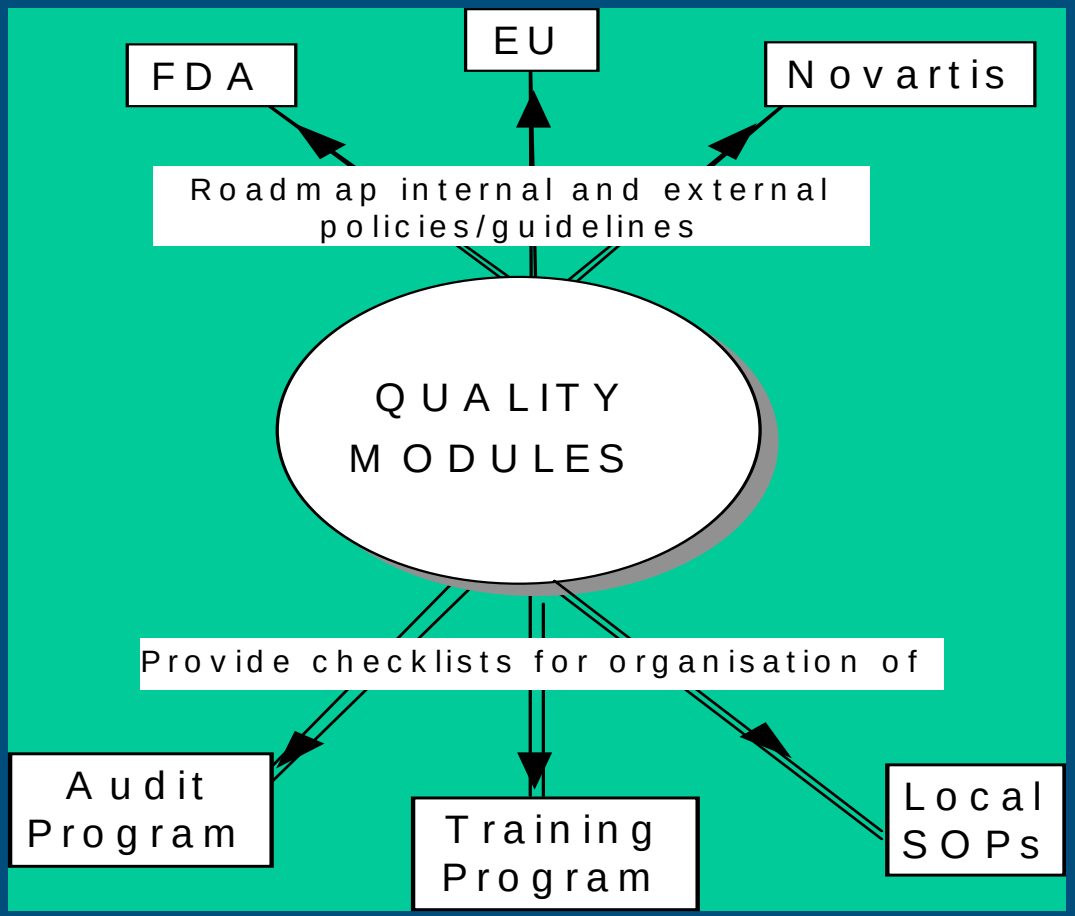
GMP Conference, 10.06.04, Istanbul

Dr. Andreas Brutsche, Novartis Pharma, Switzerland

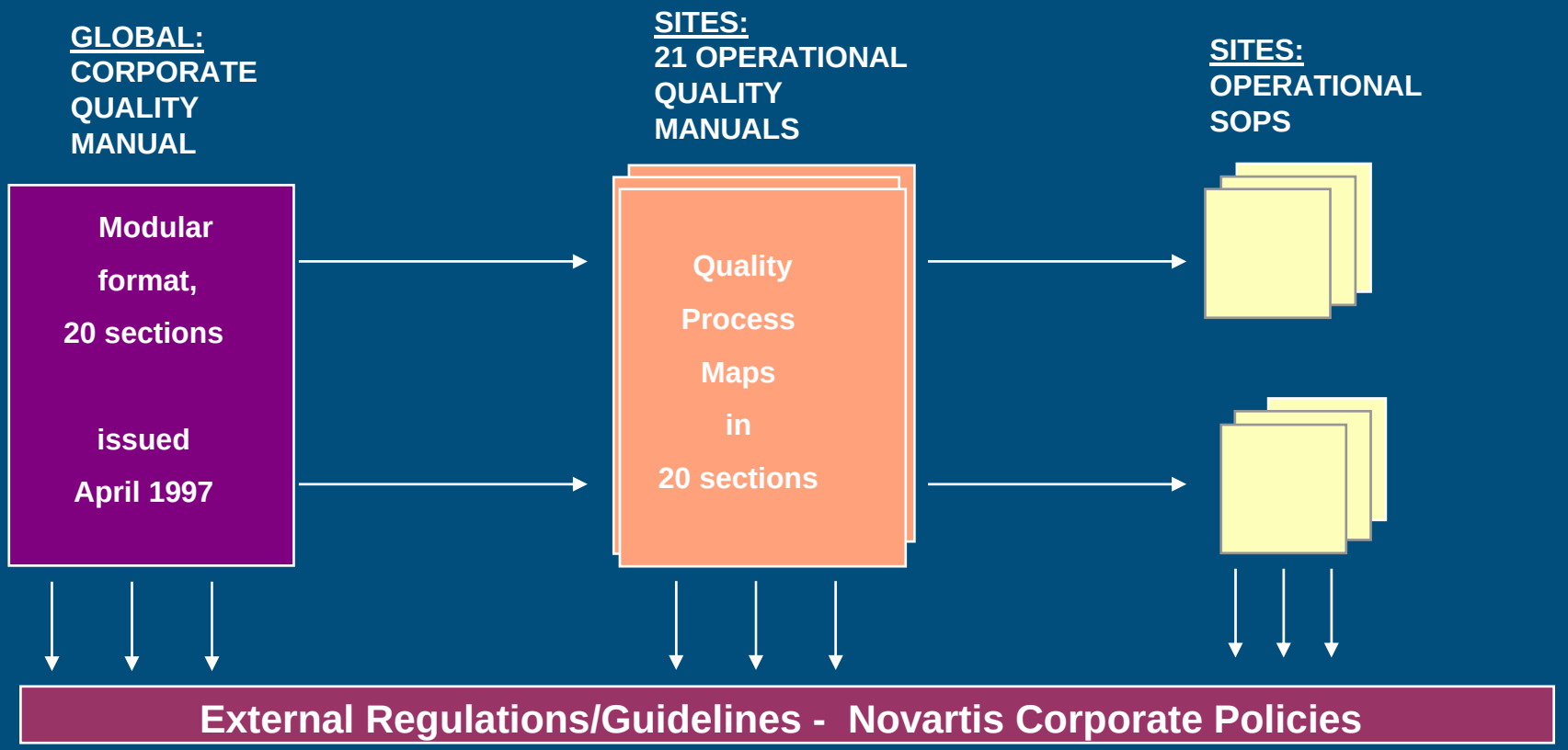
Overview

- Management of Inspections
- Audit Rating Systems
- Audit Techniques
- Risk Analysis applied to Auditing
- Regulatory Inspections - FDA and EU compared -
- Overview about International Inspection Findings

Different GMP understanding worldwide



A proper Quality System is key for each Inspection



Each site is required to produce an operational quality manual, based on the corporate manual, and including maps of key quality processes, with cross reference to operational SOPs.

This provides an overview of quality systems on site, and the basis for process re-engineering/SOP simplification (Corporate Project).

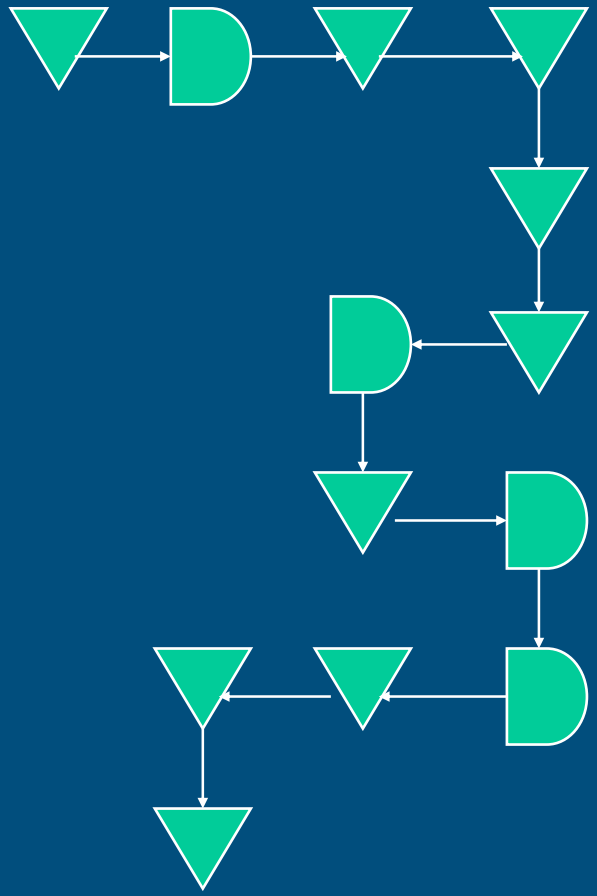
NOVARTIS

Reasons for Auditing :

- Audits can be used to ensure Compliance with regulations (Compliance audit)
- Audits can be used to build confidence in the Quality Assurance System (System audit, new FDA Approach)
- Audits can provide a basis for mutual trust, technical understanding, and good communication between authorities and companies
- Guarantee the high quality standard of pharmaceutical products (public pressure !!!!)

Use Process Mapping during Inspection preparation

Process Mapping to simplify / benchmark Processes



Actual Process

Process Reengineering

Improved Process

Goals :

1.) Improve GMP-Compliance

2.) Cost reduction

= Process steps

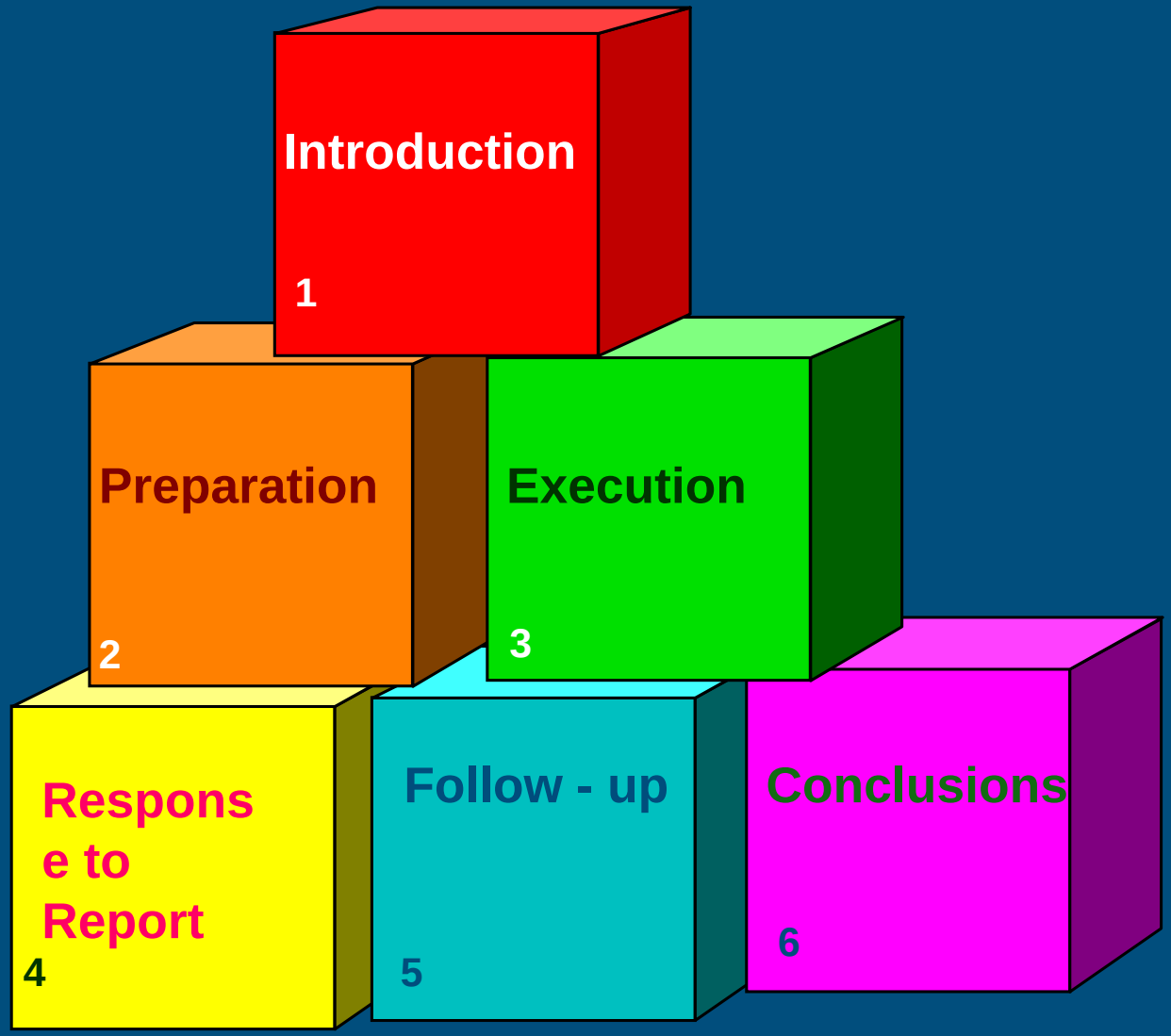
NOVARTIS

The Auditor (Regulatory Authority)

The success of an audit ultimately depends upon the abilities of the auditor. The ideal characteristics of an auditor can be summarised as follows :

- Appropriate technical / professional qualifications
- Wide experience in the development, design, formulation, processing, packaging and control of a variety of pharmaceutical dosage forms
- Well trained in auditing
- Possession of a wide range of personal skills
- Exposure to the inter-relationships of the various parts of a manufacturing organisation and appreciation of the overall business objectives of the company

Management of Audits



NOVARTIS

Introduction

- Site overview, location
- Organisation (top, down)
- Major site activities
- Product list
- FDA: List of products shipped to US
- Inspection history (timetable), Authorities
- Proposed Agenda

➡ Stay as long as possible in the driving position

Preparation

- Selection of the involved people, standard team
- Define role and responsibilities
- Information
  - **Involved areas / buildings / departments (e.g. don`t forget the development)**
  - **Product(s) in question - “quality” history (deviations, complaints)**
  - **Authorities / standard**
  - **previous audit findings, follow up presentation**
- Proposed Program
  - **List of areas to be audited**
  - **Program with timings (be flexible)**
  - **Briefing notes and allocation of tasks for involved people**
- Prepare Documents
  - **Trending Reports (Deviation, Complaints)**
  - **Examples for batch documents**
  - **Manufacturing and analytical procedure**
  - **Validation and Development Reports**
  - **Annual Product Reviews**

Execution

The execution of an audit should always follow a planned, agreed format, in control so time allowed to cover all areas required in a professional but amicable manner.

A suggested format is :

- Daily opening meeting
- Actual audit
- Daily review
- Preparation for the next day
- Summary session leading to report / follow-up

Execution

- **The audit itself**
  - Co-ordinated not confused
  - Keep control to ensure progress
  - Ensure right people are available (avoid misunderstandings)
  - Copies of documents and samples as required are available
  - Answers only to questions
  - Don`t talk too much
  - Clear separation: Audit-Coordinator, experts, writer

Execution

- **Daily review**
  - Summarise progress
  - Confirm outstanding items and program details
  - Ensure requests being progressed
  - Clarify open items
  - Discuss any misunderstanding / disagreement
- **Final summary**
  - Reply in facts not in opinions
  - Request priorities
  - Don`t commit too much

Make sure you are:

Courteous, diplomatic, calm and reasonable, in control, concise as possible

NOVARTIS

Response to the Report

Report Response :

- Don`t wait …… Write up as soon as possible, Keep deadlines, be friendly
- Follow a structure, e.g. Repeat finding – Commit Action
- Ensure accurate reflection of all findings
- Commit manageable timelines
- Don`t commit too much !!!!
- In case of critical findings – organise a meeting with authorities

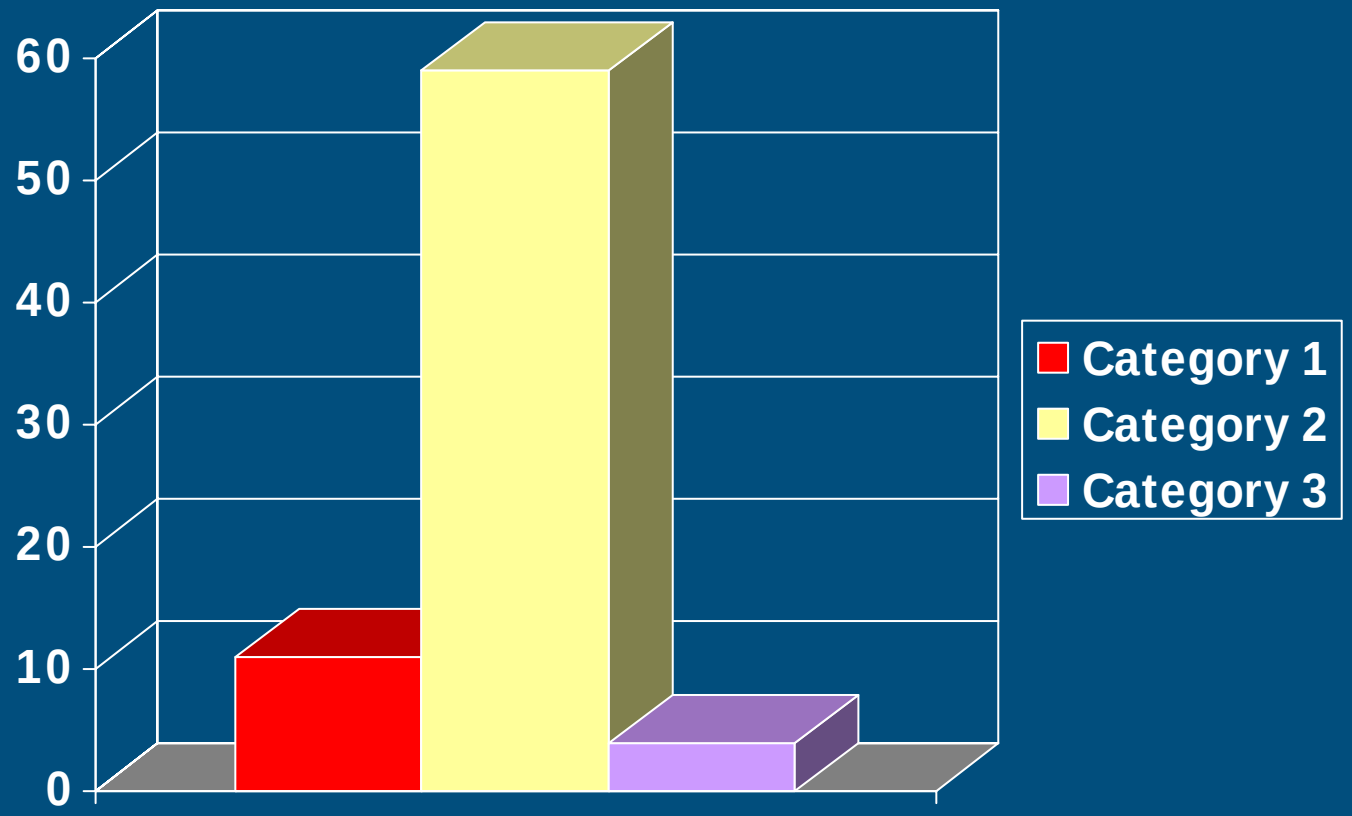
Follow - up

- This is often where audit and self-inspection programmes fall down - the audit is finished, the report received - then it is **filed** and **forgotten**.
- A plan is strongly recommended which clearly states :
  - **What is required**
  - **When it will be progressed - may be dependent on delivery dates, etc.**
  - **Who is responsible**
  - **Who will have the authority to state that a particular action has been successfully completed**
- The follow up may include : internal - audit (partial or in full)
- Defining GMP - upgrade Projects (if necessary, should be done in advance)

Conclusions

- Preparation is 90% of the success of an Audit
- You are the expert !!!! (Be proud of your site, processes)
- Ensure that enough resources are available
- Prevent the audit from drifting aimlessly by identifying and focusing attention on the matters to be considered
- Re-act quick on requests
- Don`t hide issues
- Ensure Management awareness !!!!!!

Audit Rating Systems



Categories:

1 Full compliance with Novartis Quality Standards - no regulatory issues

2 Partial compliance with Novartis Quality Standards - no critical regulatory concerns

3 Significant non-compliance with Novartis Quality Standards requiring immediate corrective action. Regulatory action could occur.

Note : Pharma numbers include Third Parties - other sectors not.

NOVARTIS

Audit Techniques

- **Trace Forward Audits**

  Conventional approach, which starts in the warehouse with goods inwards, and logically follows the process through dispensing, preparation, manufacturing, filling, packaging, labelling release and dispatch

- **Trace Back Audit**

  Essentially the reverse of 1 above

- **Random**

  Such an audit involves visiting all elements of the organisation in a random order

- **System Audit**

  See presentation on The Risk Based Approach: A new Initiative from the FDA

Audit Techniques

- **The Document Trail**

  A method, favoured by the American auditors, in which all documents relating to a given batch of product are examined and cross-referenced to each other. This will include not only primary batch records and testing results, but also all associated Standard Operating Procedures, log books, calibration records, transfer dockets etc., which may not be part of the batch protocol

- **Product Audit**

  This may be considered to be a specific case of the Trace Back Audit. The audit starts with a given product and batch number, and the objective is to explore backwards through the various activities

Risk analysis applied to auditing

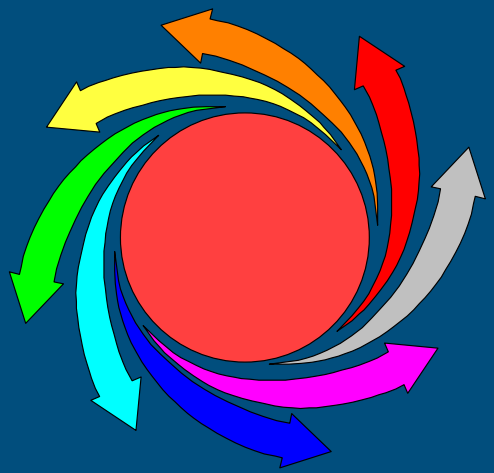
The use of risk assessment is a valuable tool in audit planning and helps in keeping a "sense of proportion"

Risk analysis in its widest sense covers the life cycle of medicines and can be divided into:

Product and process development

Market surveillance
- Complaint review
- Recall procedures

Scale-up and technology transfer



Quality Assurance System, Quality Control

Manufacture of the bulk active substance

Deviation handling Failure investigation

Procurement of external supplies

Manufacturing and packaging of the dosage form

NOVARTIS

Regulatory Inspections - FDA and EU compared

- **Legal Differences**

  In essence, the legal basis is rather similar from the inspection point of view. However, one major difference is the US Freedom of Information which allows public access to FDA inspection reports.

- **Philosophical Differences**

  US view is adamant - compliance and enforcement! EC, so far, tends to operate on the basis of trust and co-operation although some recent experiences may modify this approach.

Regulatory Inspections - FDA and EU compared

- **Operational Differences**

  FDA inspectors are much more likely to carry out unannounced inspections (not overseas) and will also put more emphasis on pre-approval inspections, whereas EC effort in this area has not really started in many member states.

- **Technical Differences**

  In general terms, there are few differences, although some specific aspects, such as bio-validation, are given more emphasis by FDA - as is the whole subject of validation.

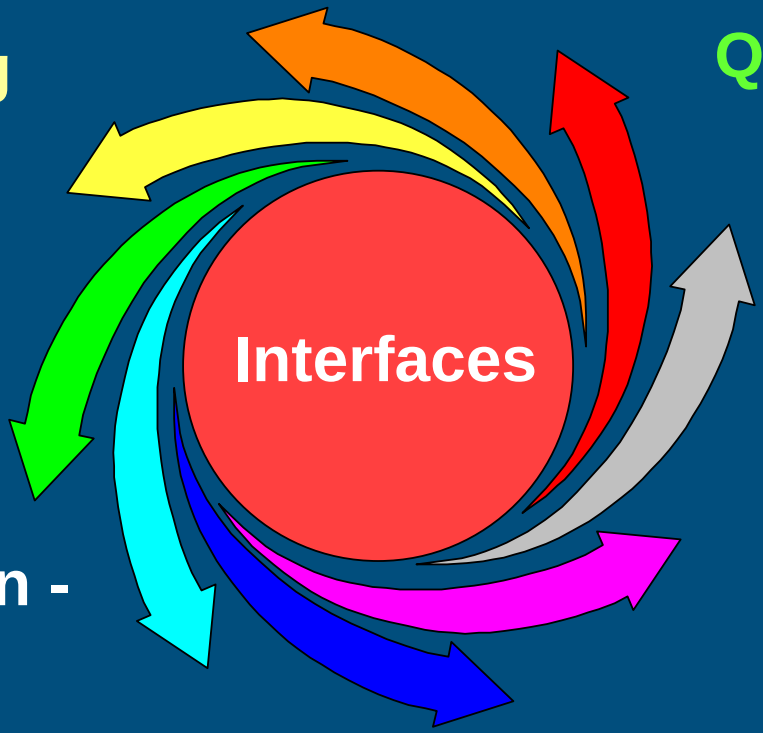
Critical Areas :
Interfaces

QA - QC

Production - Engineering

QA, QC - Production

QA, Production - EDP



QA, Production - Suppliers

QA, Production - Registration

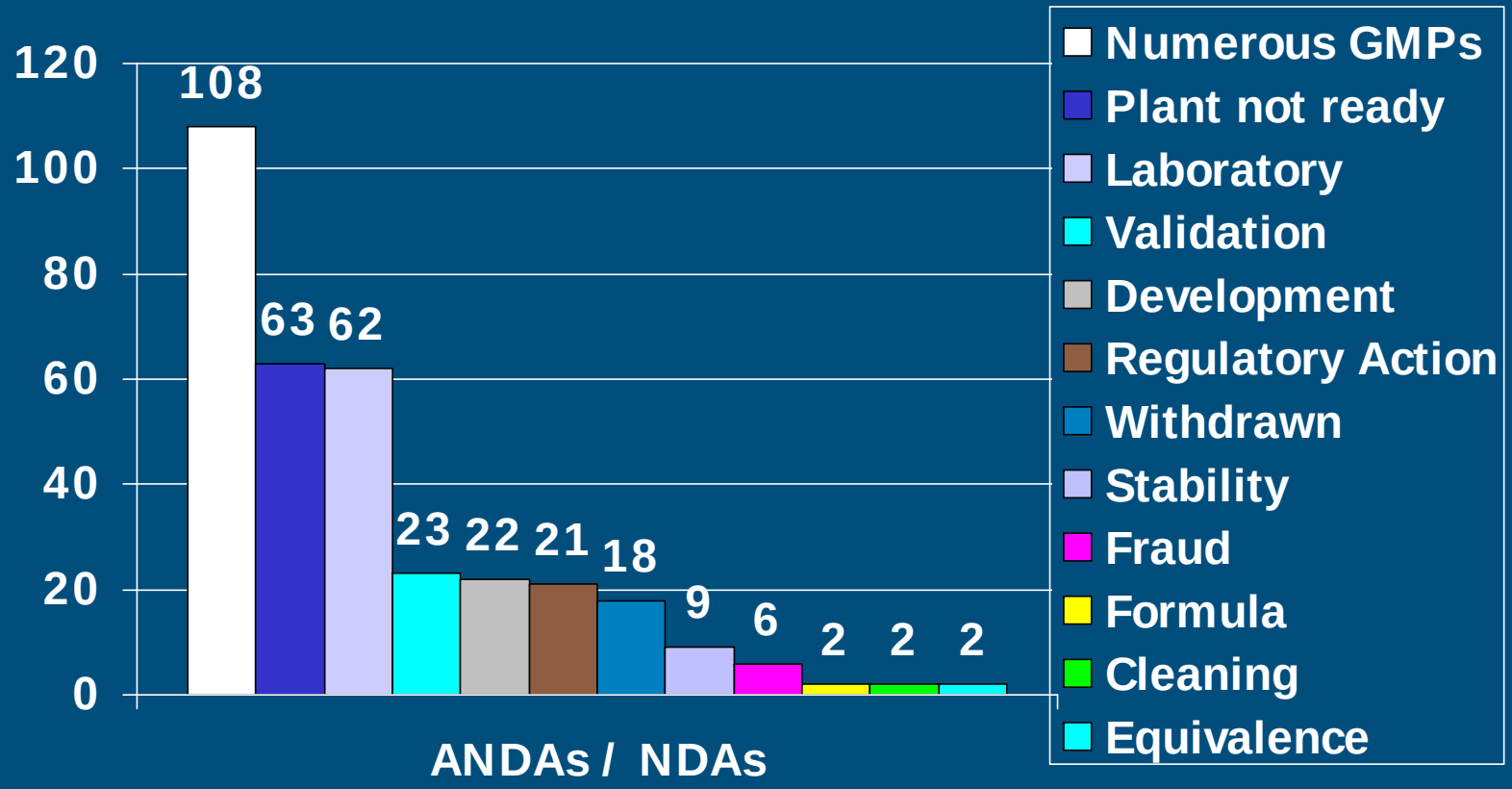
Engineering - Contractors

Development - QA, Production

NOVARTIS

Overview about International Inspection Findings

Evaluation of Recommendations to Withhold Approval of NDA/ANDAs by the FDA

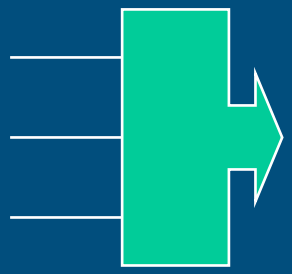


3/03 to 9/04

NOVARTIS

Major weakpoints found

- Comprehension and acceptance of GxP/quality standards at all operational levels
- Batch Documentation / Records
- Computer Validation
- Process Validation / Equipment Qualification
- Cleaning Validation
- Deviation / Failure Management
- Cleanliness Zoning
- Water Systems
- Development Data

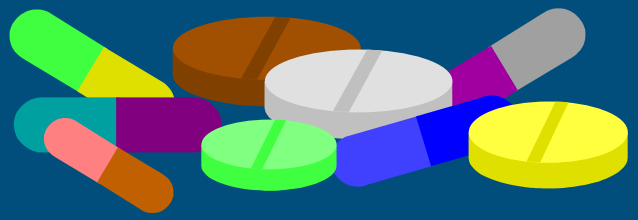


Validation

International Inspection Findings :

Validation

- **Ancillary or Support Systems not validated :**
  - Water and Steam Systems
  - Sterilizers
  - HVAC
  - Process Gases (e.g. N_2, CO_2)
  - Computer Systems



NOVARTIS

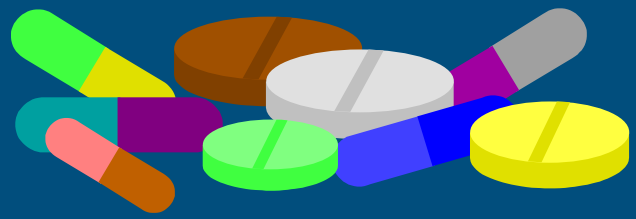
International Inspection Findings :

QC-Laboratories

- No inter-laboratory qualification
- Deficient methodology for related compounds
- Lack of preservative effectiveness testing
- Deficient stability testing
- Incorrect firm identified in application
- Incorrect analytical test listed in application

Active Pharmaceutical Ingredients

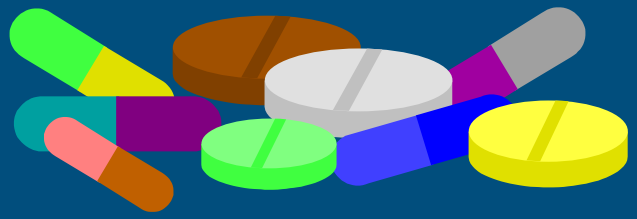
- Impurity Profiles
- Change to synthesis not validated
- Cleaning validation for multi-use equipment
  - **industrial chemicals and pharmaceuticals**
- Incorrect firm listed in application
- DMF not followed
- Stability program



International Inspection Findings :

Records / Reports

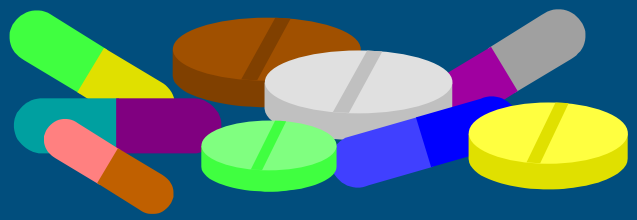
- Batch records incomplete or do not reflect actual operations
- Activities documented before actual completion
- Changes to process and equipment parameters in batch records are not addressed by change control system
- Product annual reviews not conducted or are inadequate



International Inspection Findings :

Process Controls

- Critical product attributes and critical process parameters not identified and monitored
- Out of specification API batches blended with batches that have passed specifications
- Inadequate in-process and end-product testing



International Inspection Findings :

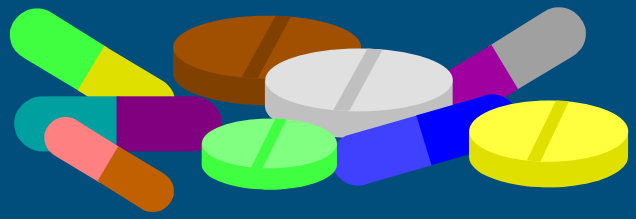
Water Systems

- Process water not shown to be suitable for its intended use
- Inadequate investigations and corrective actions following recurring microbiological test results
- Water used to produce sterile products not tested for endotoxins
- Reliance on point of use filters to clean up water while ignoring the production / distribution system

International Inspection Findings :

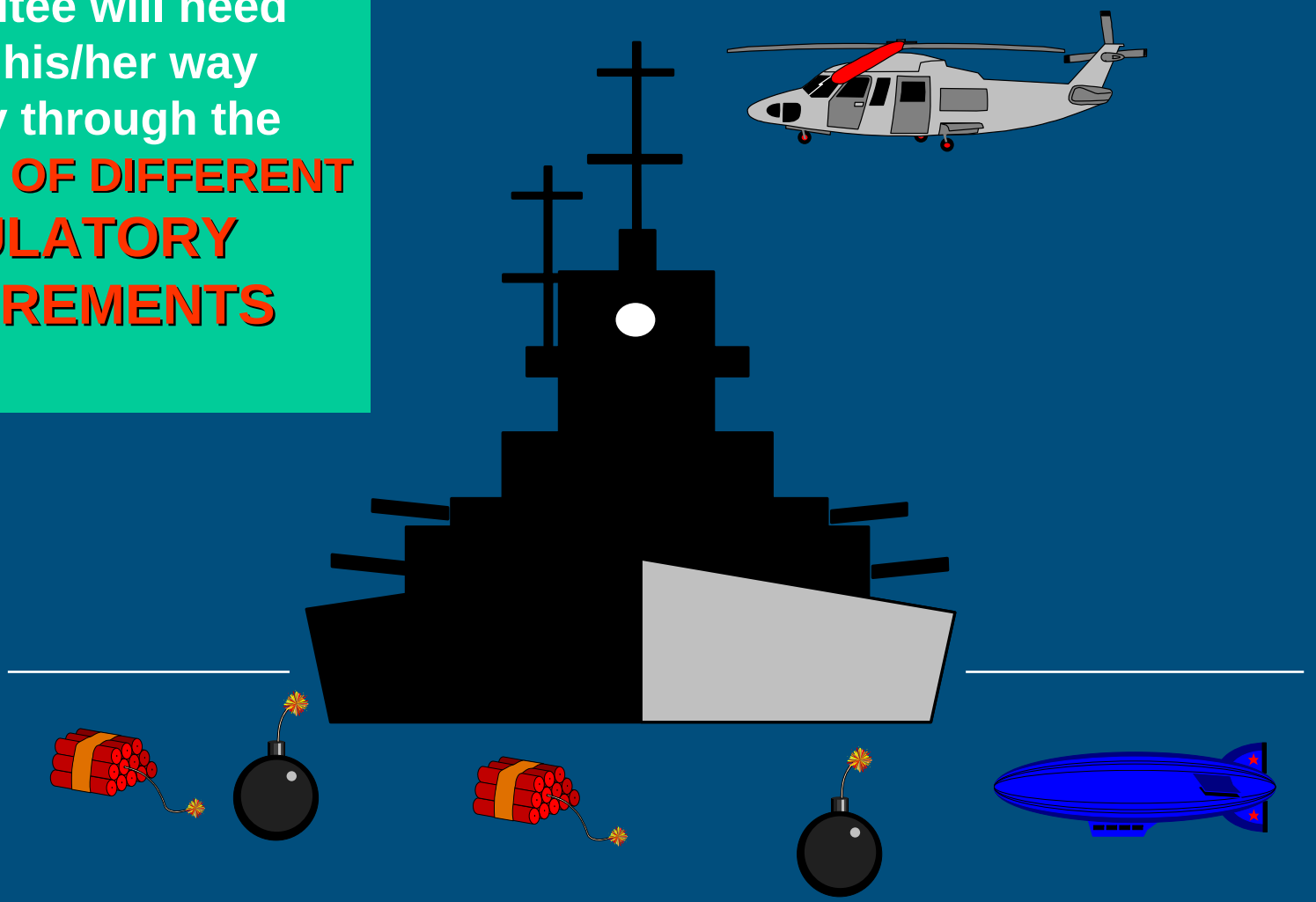
Buildings / Facilities

- Production facilities not adequately designed to minimize mix-ups and cross contamination
- Facilities not provided with air handling and dust control system to minimize product cross contamination
- Production areas not provided with adequate temperature and humidity controls



NOVARTIS

The Auditee will need to pick his/her way carefully through the **MINEFIELD OF DIFFERENT REGULATORY REQUIREMENTS**



At present we don`t have a common cGMP understanding

NOVARTIS