

**APR RIGHT FIRST TIME**

**DFSS: Next Process is the Customer**

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This presentation reflects the author's work and views only and does not necessarily reflect the company's view.

# Agenda

Story-board: How we started- How we got there

- Project Overview
- Assumptions
- Deliverables
- Tool Demonstration

## Where we started

An Annual Product Review (APR) is an annual compilation and review of the data and documentation related to the manufacture of a drug product or active pharmaceutical ingredients (API), intended to assess the need for changes in product specifications or manufacturing or control procedures.

A need was identified to define a robust process which supports an accurate and complete APR, to define 'RFT' for the APRs wrt 'Voice of Customer' to define CTQs to be able to reduce the errors defined.

## Abbreviations used

- RFT: RIGHT FIRST TIME
- VOC: VOICE OF THE CUSTOMER
  - The "voice of the customer" is a process used to capture the requirements/feedback from the customer (internal or external) to provide the customers with the best in class service/product quality. This process is all about being proactive and constantly innovative to capture the changing requirements of the customers with time.
- CTQ: CRITICAL TO QUALITY
  - CTQs (Critical to Quality) are the key measurable characteristics of a product or process whose performance standards or specification limits must be met in order to satisfy the customer. They align improvement or design efforts with customer requirements.
  - A CTQ usually must be interpreted from a qualitative customer statement to an actionable, quantitative business specification.

## Abbreviations used (Contd)

- QFD: QUALITY FUNCTION DEPLOYMENT
  - Quality Function Deployment (QFD) is a structured approach to defining customer needs or requirements and translating them into specific plans to produce products to meet those needs. It is used to translate higher level "whats" or needs into lower level "hows" – product requirements or technical characteristics to satisfy these needs. (CTQs)
- CMO: Contract Manufacturers
  - Roche's contracted manufacturers that make Roche Products and supply the Annual Product Review for their part to the team
- CQA: Critical Quality Attributes
  - Here, Critical Quality Attributes for the CMO RFT metrics are defined as the CTQs identified by the Executive Committee and the APR Team.

## Project Scope and Objective

### Scope

Contractor and Nutley Annual Product Reviews. The focus will be on the review and approval process.

Note: Root/driving causes of the RFT issue may lie in the earlier process steps of APR development. (i.e. who supplies/reviews what, RFT definition, roles and responsibilities)

## Objective & Project end-goals

- Develop project activity plans and assign resources
- Define 'Customer' to collect VOC and develop Critical-To-Quality parameters
- Define 'Error' and 'Right First Time' for the process. Establish RFT metrics
- Determine and prioritize the factors that affect the RFT metric

## Objective & Project end-goals

- Define roles and responsibilities at all levels (e.g.. Technical Review Members and Executive Review Members, APR Reviewer, Data Collector, Data Analyst)
- Design and develop a tool to capture all customer roles RFT levels.
- Establish an internal change control system
- Standardize APR format and Review and approve APR templates
- Update affected SOPs.

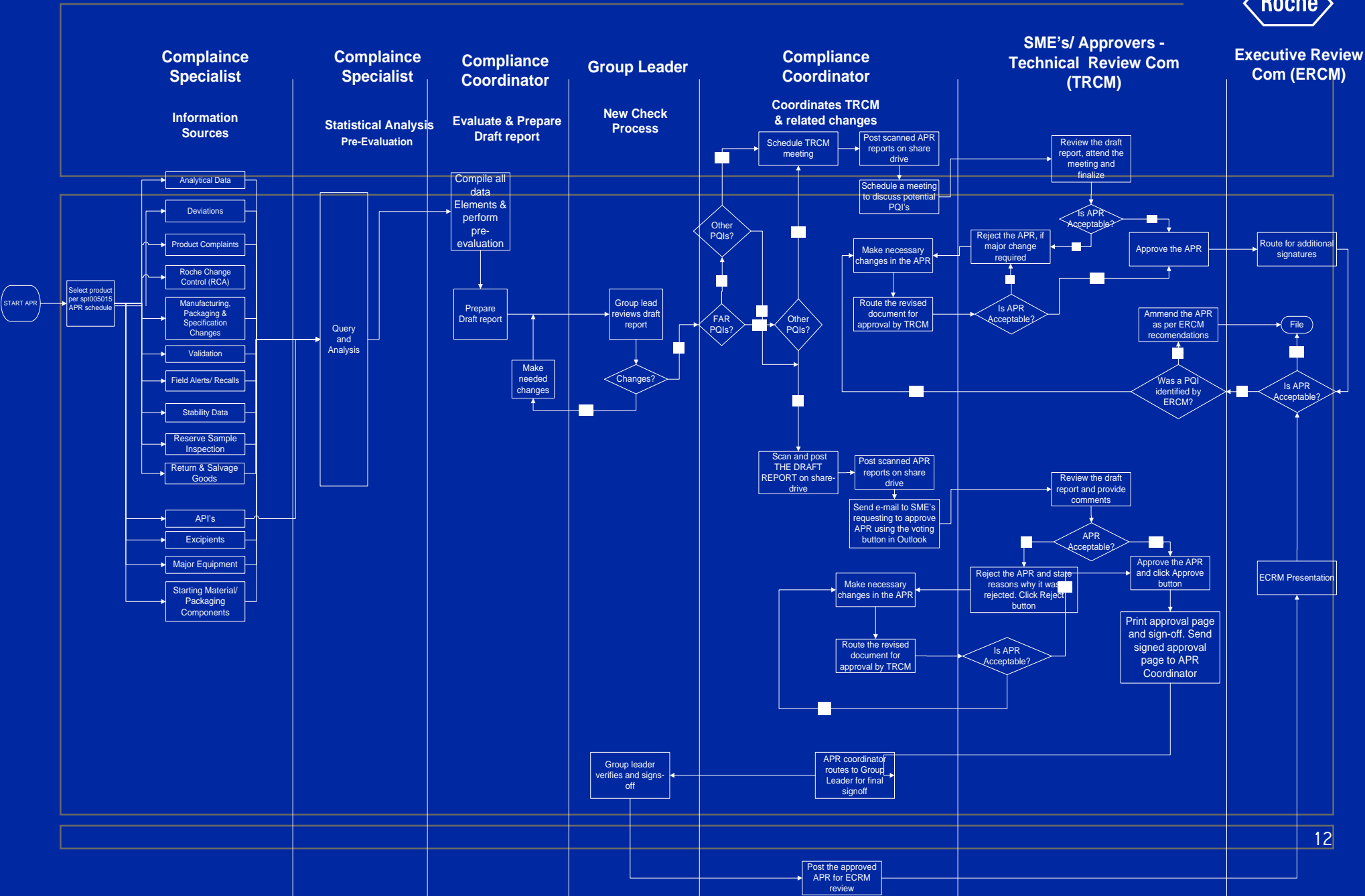
## Project Benefits

- Business Impact
  - Avoidance of delay in release of product to market
  - Elimination of retrospective trending of CMO data
  - Opportunity for continuous process improvement
  - Strengthened relationship with CMOs
  - Allows proactive, preventive, and corrective actions for potential failures/issues
  
- Regulatory Impact
  - Enhance regulatory compliance posture

## Key Assumptions

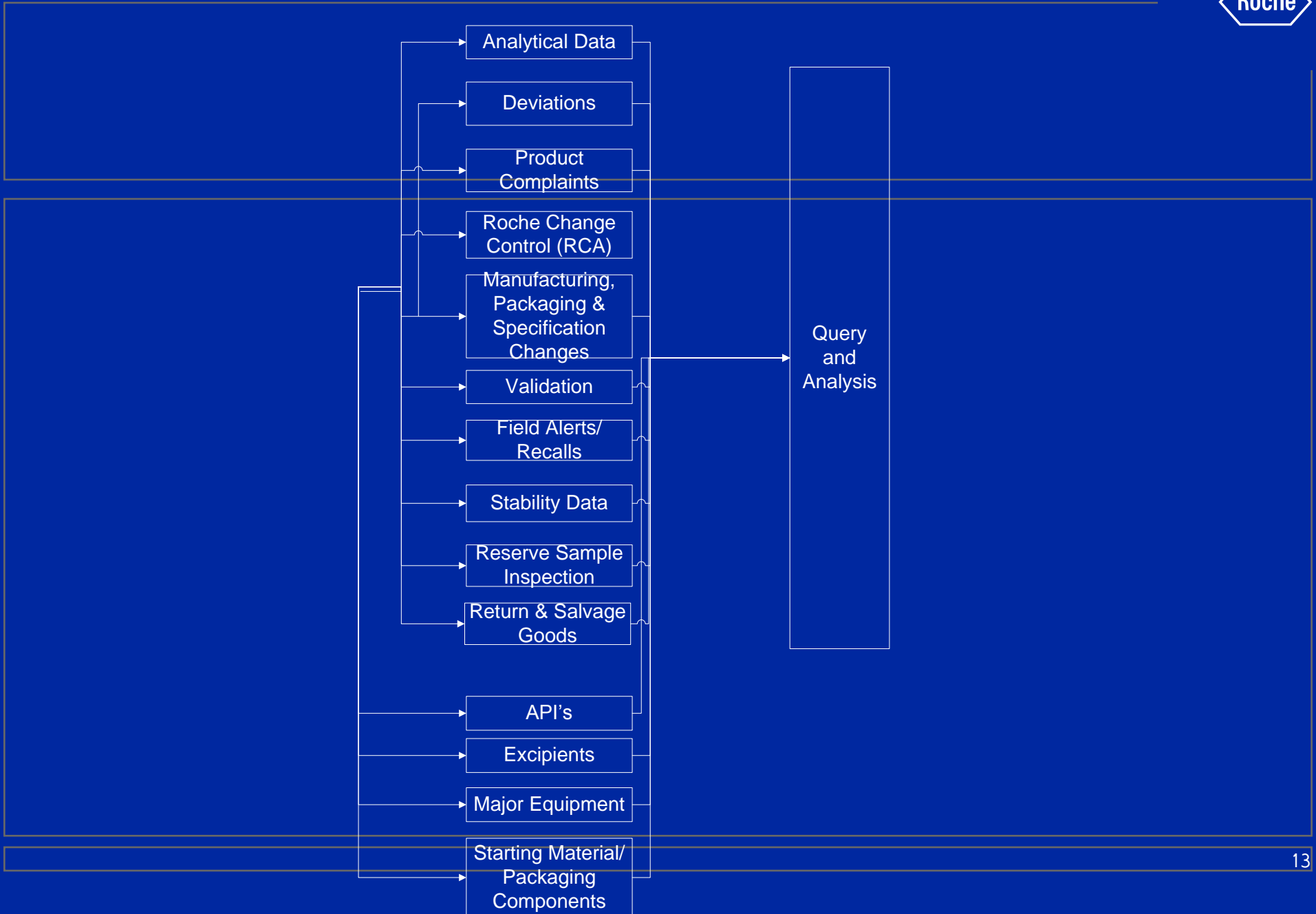
- APR Team has no control over data going in the System or data provided by the SMEs
- Errors occurring in any supplied or retrieved data is allocated to its source.
- Contract Manufacturers (CMO)s are responsible for the accuracy, completeness and timeliness of their APRs.
- Any error within the CMO report affects the 'RFT' metric for the CMO
- APR team is responsible for the accuracy of the conclusions and any evident errors in the CMO APR report.

# Annual Product Review Process-Re-design



Information Sources

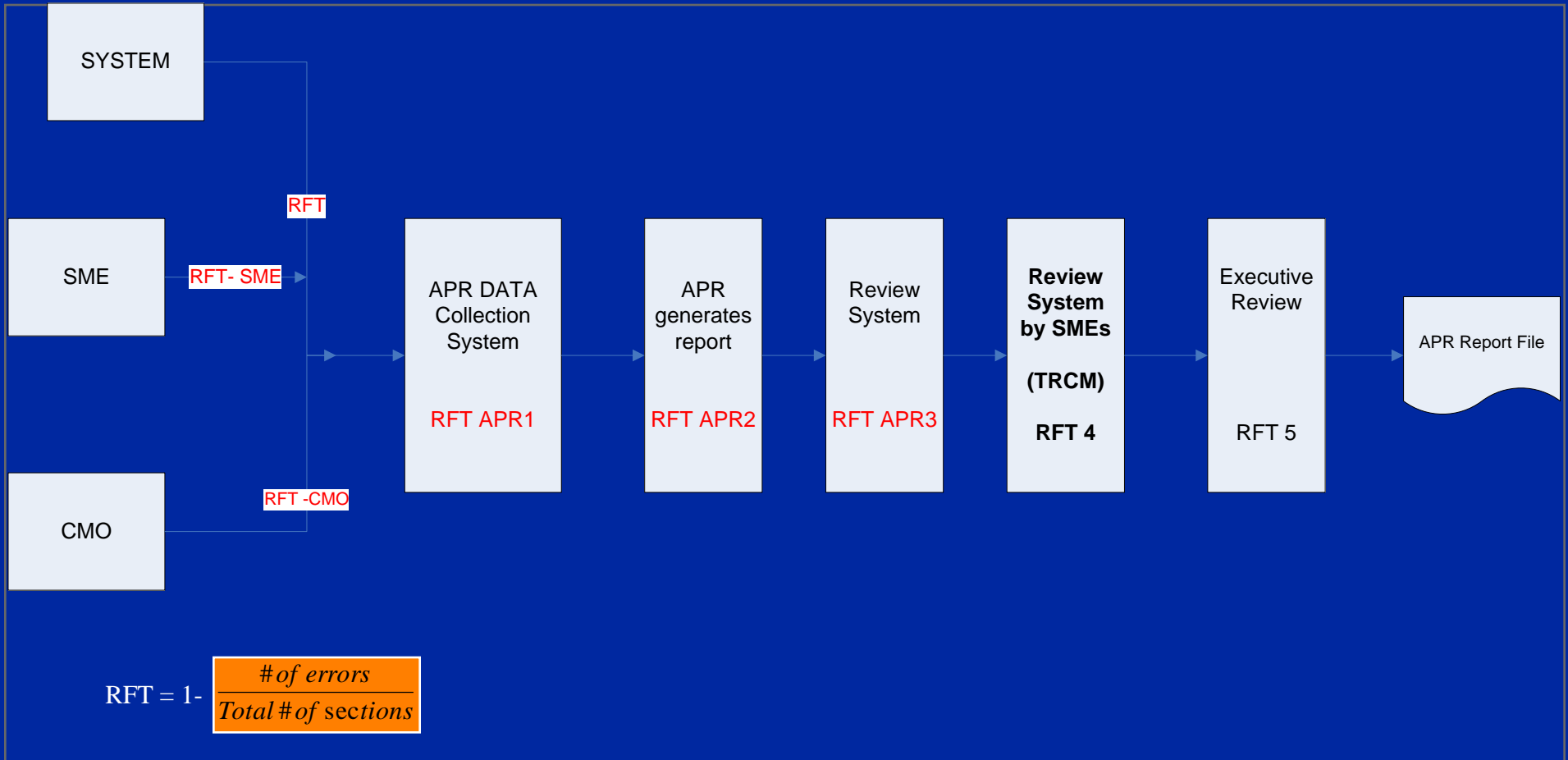
Statistical Analysis



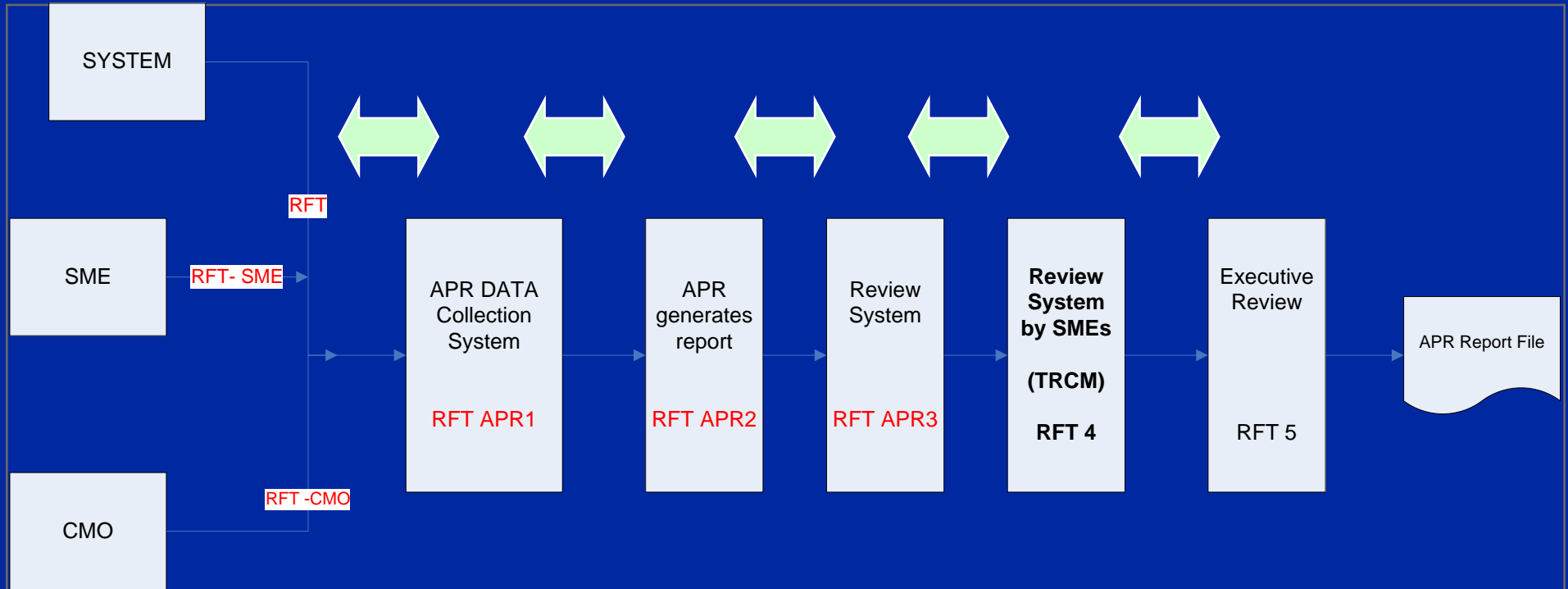
## APR Customer Feedback Analysis

- Top 3 metrics for APR evaluation:
  - Cycle Time for report generation,
  - Cycle Time for Report Review, and
  - RFT

# Voice of Customer Analysis



# Ishikawa Principle: Next Process is the Customer



Defining Customer and Supplier at each stage, we collected voice of customer based on definition to define

‘RFT’

## Design System

- Supplier–Customer relationship was defined based on ‘Next Process is Customer’ principle.
- ‘Voice of Customer’ was thus collected at each step– What does Process ‘x’ need from their supplier (Process ‘x-1’) to be able to meet its customer (Process ‘x+1’)’s CTQs.
- Combining the principle of ‘Design for Six Sigma’ and ‘Next Process is Customer’, the RFT system was designed to capture all the CTQs specified by each customer at each level.
- Thus, defining customers and suppliers at each level; strategy was to define RFT at each step.

## Design System

- The 'Voice of Customer' captured at each process step was converted into measurable CTQs (by Quality Function deployment) – Converting the 'What' into 'How' and finally measurable quantifiable deliverables for each step.
- A measurement system and acceptable levels for each CTQ was established and designed into the RFT tool.
- CMO APR's responsibilities were clarified by Executive Committee to help us create RFT dashboard for CMO based on team expectation from CMO APR.

## Design System

- Challenge: The goal was to capture all the CTQs defined at each level of 'Customer' defined within the System as the 'Critical Quality Attribute' of the RFT criteria for each APR the same. Defining how to design to give a one-place stop for the team to effectively collect the data was a challenge.
- Solution: The final version is truly a one-stop shop for the whole RFT process, run by a single key: the month which automatically populates all the products for the month with all their details in respective tabs including CMO dash-board.
- Statistical: Real-time trending for all CQA's identified as critical to RFT metric. Graphically enhanced tool.

## Design Requirements for APR RFT System

- Data collected by each team member based on RFT definition and entered in the system
- Real time trending of RFT
- Application/tools
  - RFT tool
  - Basic trending methods and tools
- Incorporate the Western Electric trending rules

## Business Requirements for APR RFT CMO

- APR RFT Main Critical Quality Attributes (CQA) for the CMOs
  - Clarity of Report
  - Correct Attachments
  - No Missing Attachments
  - No missing information
  - Cycle Time
  - Signature
  - Less than 1 call for clarification

## Statistically-based Trending System Selection

- Selection

- Chart for Individual Measurements with Control Limits based on c-chart\*
  - Application
    - One number is available to represent a given condition
    - When only one reported result is being plotted or analyzed
      - For example, mean of replicate
    - Applications include, charting each RFT by source or APR

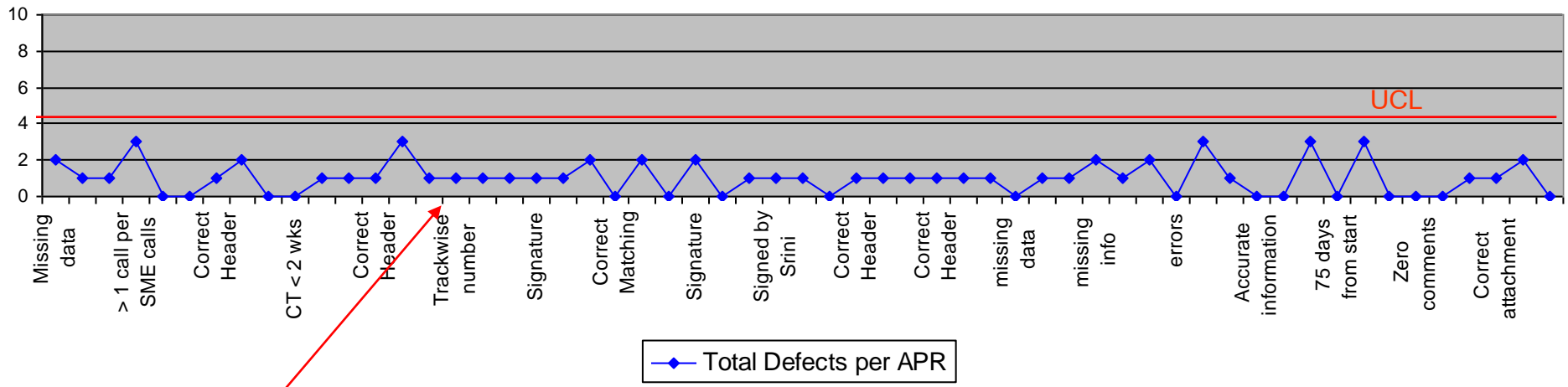
\* In [statistical quality control](#), the **c-chart** is a type of [control chart](#) used to monitor "count"-type data, typically total number of nonconformities per unit

## Statistically-based RFT Trending System Design

- Calculation of the Process Average ( $\bar{X}$ ):
  - $\bar{X} = (X_1 + X_2 + \dots + X_n) / n$  ;  $n$  = total number of measurements and  $X_i$  = individual measurements (for  $i = 1$  to  $n$ )
    - $\bar{X}$  is the centerline of the  $\bar{X}$  chart
- Calculation of the Upper Control Limit ( $UCL_{\bar{X}}$ ) for Individual Measurements ( $\bar{X}$ ):
  - $UCL_{\bar{X}} = \bar{X} + 3 \sqrt{\bar{X}}$
- Calculation of the Lower Control Limit ( $LCL_{\bar{X}}$ ) for Individual Measurements ( $\bar{X}$ ):
  - $LCL_{\bar{X}} = 0.0$

# Statistically-based Trending System Design

Total Defects per APR



LCL<sub>x</sub> = 0.0 → Lower limit for NOT RFT is 0 → 100% RIGHT FIRST TIME

## Statistical APR RFT Data Trending System

- APR RFT designed System Rollout
  - Presentation of concepts, application and expectations
- “Expectations” for Contract Manufacturers defined into CTQs.
- Preliminary Statistical Trending limits Determination
  - Historical Data/ Simulated data
- Working procedure for APR and CMO
- Roles and responsibilities

## TOOL DESIGNED

- Truly a one-stop shop for the whole RFT process,
  - run by a single key: the month which automatically populates all the products for the month with all their details in respective tabs including CMO dash-board.
- [X:\QM\QualityEngineering\APR\\_RFT\\_Project\MONTHLY\\_TOOL\FINAL\\_MONTHLY\\_TOOL-APR-CTQ-RFT.xls](X:\QM\QualityEngineering\APR_RFT_Project\MONTHLY_TOOL\FINAL_MONTHLY_TOOL-APR-CTQ-RFT.xls)

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APR RFT Summary for the month of: AUG

Enter/Select Month  
AUG-DEC

Product	Name	SME	Systems	CMO	Srini	Divina	Scott	TRCM	Execom	Total Defects per APR
1	<a href="#">Copegus Tablets, 400mg -Nutley</a>	0	0	0	0	0	0	0	0	0
2	<a href="#">EC-Naprosyn Tab, 375mg-Legacy</a>	0	0	0	0	0	0	0	0	0
3	<a href="#">EC-Naprosyn Tab, 500mg-Legacy</a>	0	0	0	0	0	0	0	0	0
4	<a href="#">Ticlid Tabs, 250 mg</a>	0	0	0	0	0	0	0	0	0
5	<a href="#">EC-Naprosyn Tab, 375mg-Leganes</a>	0	0	0	0	0	0	0	0	0
6	<a href="#">EC-Naprosyn Tab, 500mg-Leganes</a>	0	0	0	0	0	0	0	0	0
7		0	0	0	0	0	0	0	0	0
8		0	0	0	0	0	0	0	0	0
9		0	0	0	0	0	0	0	0	0
10		0	0	0	0	0	0	0	0	0
11		0	0	0	0	0	0	0	0	0
12		0	0	0	0	0	0	0	0	0
13		0	0	0	0	0	0	0	0	0
14		0	0	0	0	0	0	0	0	0
15		0	0	0	0	0	0	0	0	0
16		0	0	0	0	0	0	0	0	0
17		0	0	0	0	0	0	0	0	0
18		0	0	0	0	0	0	0	0	0
19		0	0	0	0	0	0	0	0	0
20		0	0	0	0	0	0	0	0	0
21										
22										
23										
24										
25										

NOT RFT plots- by Source

NOT RFT plots- by APR

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CMO DASHBOARD

Number	Month	Product	Type	Site	Review Period	APR Start Date	Quality Agreement	Contractor due date	Date CM APR received	CM CYC TIM
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AUG										
1	AUG	Copegus Tablets, 400mg -Nutley	Contractor	Catalent Pkg	Aug 1 2007- July 31st 2008	8/1/08	40	09/29/08		
2	AUG	EC-Naprosyn Tab, 375mg-Legacy	Contractor	Catalent Pkg	Aug 1 2007- July 31st 2008	8/1/08	40	09/29/08		
3	AUG	EC-Naprosyn Tab, 500mg-Legacy	Contractor	Catalent Pkg	Aug 1 2007- July 31st 2008	8/1/08	40	09/29/08		
4	AUG	Ticlid Tabs, 250 mg	Not CMO	Nutley	Not CMO	Not CMO				
5	AUG	EC-Naprosyn Tab, 375mg-Leganes	Contractor	Catalent Pkg	Aug 1 2007- July 31st 2008	8/1/08	40	09/29/08		
6	AUG	EC-Naprosyn Tab, 500mg-Leganes	Contractor	Catalent Pkg	Aug 1 2007- July 31st 2008	8/1/08	40	09/29/08		
7	AUG				Not CMO	Not CMO				
8	AUG				Not CMO	Not CMO				
9	AUG				Not CMO	Not CMO				
10	AUG				Not CMO	Not CMO				
11	AUG				Not CMO	Not CMO				
12	AUG				Not CMO	Not CMO				
13	AUG				Not CMO	Not CMO				
14	AUG				Not CMO	Not CMO				
15	AUG				Not CMO	Not CMO				
16	AUG				Not CMO	Not CMO				
17	AUG				Not CMO	Not CMO				

Mock data

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	G	H	I	J	K	L	N	O	P	Q	R	S
1												
2	APR Start Date	Quality Agreement	Contractor due date	Date CM APR received	CMO CYCLE TIME	CT REPORT	Signature	Accurate	Complete as per CMO Request Form	Report	Comments	
3												
4	8/1/08	40	09/29/08			OK				Does not meet CTQs		
5	8/1/08	40	09/29/08			OK	YES	YES	YES	OK		
6	8/1/08	40	09/29/08			OK				Does not meet CTQs		
7	Not CMO					NA				Does not meet CTQs		
8	8/1/08	40	09/29/08			OK				Does not meet CTQs		
9	8/1/08	40	09/29/08			OK				Does not meet CTQs		
10	Not CMO					NA				Does not meet CTQs		
11	Not CMO					NA				Does not meet CTQs		
12	Not CMO					NA				Does not meet CTQs		
13	Not CMO					NA				Does not meet CTQs		
14	Not CMO					NA				Does not meet CTQs		
15	Not CMO					NA				Does not meet CTQs		
16	Not CMO					NA				Does not meet CTQs		
17	Not CMO					NA				Does not meet CTQs		
18												
19												
20												
21												
22												

**Mock data**

## Final Outcomes:

- DFSS project completed and closed
- APR Format Standardized and Templates completed.
- CTQs for Contract Manufacturer's added to 'Business Manual and/or Quality Agreements.
- Current RFT rate deemed good.



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