# CDER
# Office of Pharmaceutical Quality
# Office of Surveillance

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FDA Inspections Summit

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# Agenda

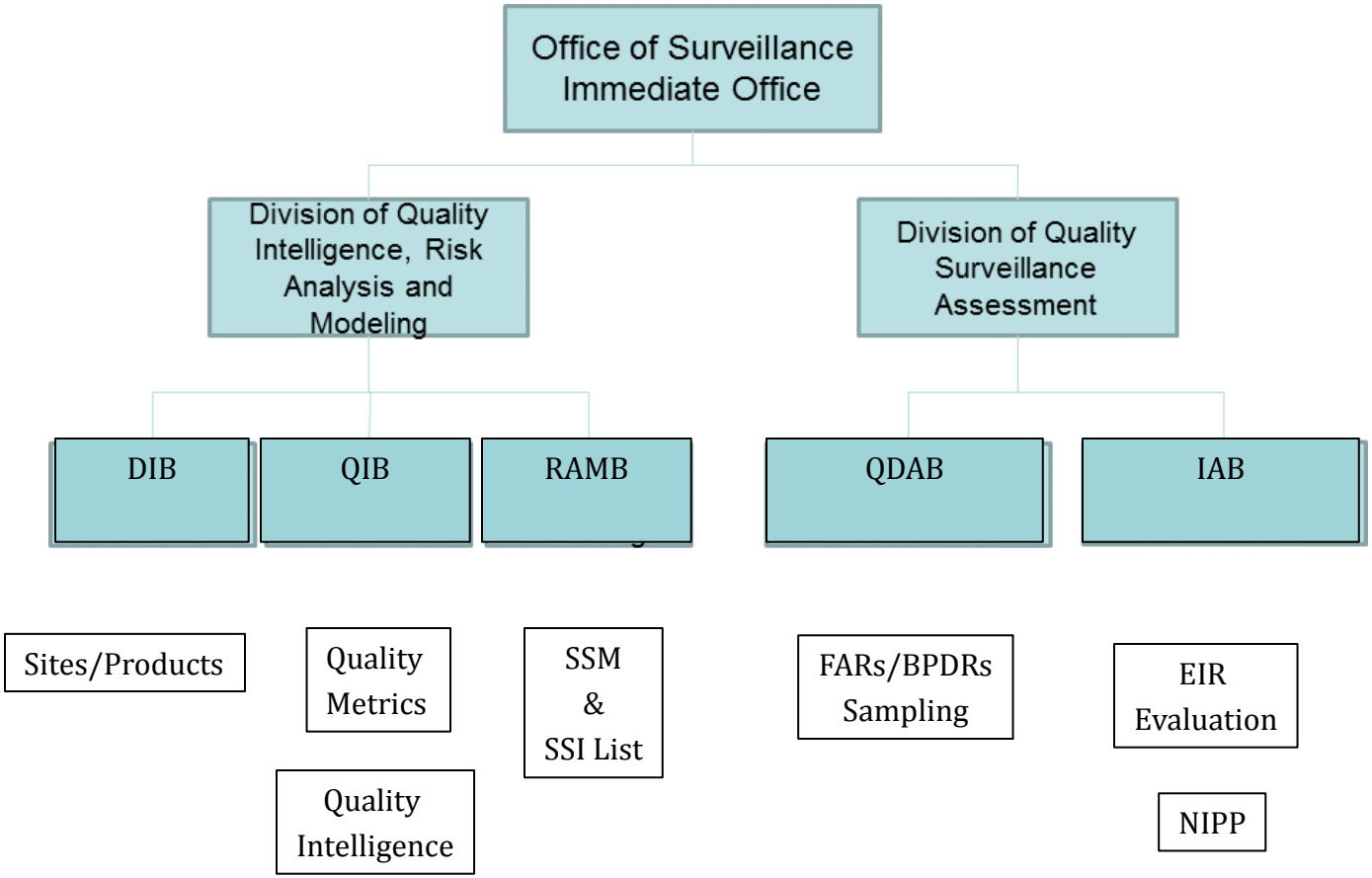
- Office of Surveillance – Mission and structure

- Quality Metrics
  - Background/Objectives/Mission
  - Potential data analytics

# Office of Surveillance

- Who/what is out there?
- What are we seeing?
  - Granular, at product or site level
- Where should we go?
- What might we find?
  - Adding context to granular data
- What should we do when we get there?

# OS Structure and Activity



# Quality Metrics

- Initiative to collect information that is currently available on site for inspection
  - Utilizes FDASIA section 706 authorities
- To set up a signal detection program as a directional vector
- Scope of program for statistical analysis (approximate)
  - 5,000 sites
  - 60,000 products
    - 5-10 sites per product
  - 10 Data Fields
  - Annual reporting by quarters (except for APR metric)
- IT support to accept data, aggregate, statistical analysis, and output

# Program - Objectives

- Use quality metrics and other risk factors to select sites for reduced inspection frequency.
- Monitor and detect variation in product quality.
- Estimate the state of quality and establish baselines across industry.
  - Communicate internally and externally
- Determine when/if post-market regulatory change filing requirements can be reduced for specific products, processes or sites.

# Potential Questions To Explore

- What effect does process segment (e.g. biological, synthetic) have on the outcome of each metric?
- What effect does dosage form or activity (API, FDF, Packaging) have on the outcome of each metric?
- What effect does each metric have on drug recalls (past, present or future)?
- What effect does each metric have on post-approval quality defects – FARs, BPDRs, etc.?
- What effect does time post-approval have on the outcome of each metric?
- What correlations, if any, exist between metrics?
- Do metric interactions exist?

# CDER's vision for QM program

Short-term:

- Investigate and segment our inventory into relevant subpopulations – manufacturing type, dosage form.
- Study the potential relationships the metrics have with our internal quality outcomes (e.g. inspection outcome, FARs, recalls, shortages, etc.) for relevant subpopulations.
- Estimate the predictive power of each metric for relevant subpopulation

Long-term:

- Develop a signal detection program using established statistical techniques (e.g. SPC charts)
- Potentially predict quality outcomes with the use of quality metrics and other internal variables

# Regression Analysis: Objectives

I. Determine the strength of relationships among continuous predictor variables and the potential for multicollinearity.

II. Identify differences in continuous predictor averages between categorical variables for stratified analyses.

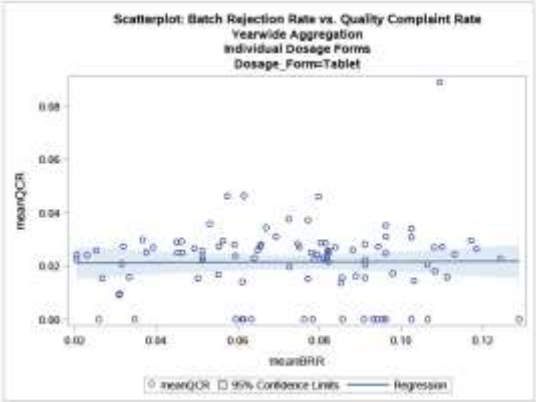
III. Identify significant risk factors (predictors) for the following site and/or product-level outcomes:

A. Past-year Drug Shortage
B. Post-Approval Incidents (Field Alert Report or Biological Product Deviation Report)
C. Recalls
D. Citations following Site Inspection

**<u>Preferentially using a penalized approach to model building</u>

# Regression Analysis: Tools

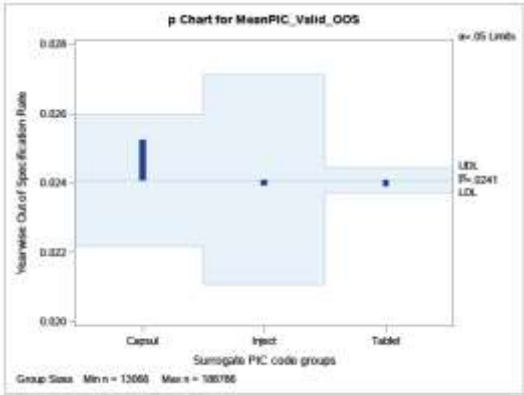
## Scatterplots




## Pearson Correlation

| Pearson Correlation Coefficients<br>Prob > \|r\| under H0: Rho=0<br>Number of Observations | |
|---|---|
| | BRR |
| OOSR | 0.04873<br>0.6844<br>72 |

## Analysis of Means (P-Charts)




## Variance Inflation Factor & Tolerance Analysis

| Dependent Variable: IO | | |
|---|---|---|
| Tolerances | | |
| Variable | Type I Tolerance | Type II Tolerance |
| Intercept | 133 | 1.6347403878 |
| meanFEIBRR | 1 | 0.9741857886 |
| meanFEIOOSR | 0.9746366321 | 0.9681728725 |
| FEIAPR_OTR | 0.9961572259 | 0.9923421872 |
| Dummy001 | 0.9936955257 | 0.9936955257 |
| Dummy002 | 5.974017E-15 | 0 |

## Logistic Regression (Binomial & Ordinal)

| Analysis of Maximum Likelihood Estimates | | | | | |
|---|---|---|---|---|---|
| Parameter | DF | Estimate | Standard Error | Wald Chi-Square | Pr > ChiSq |
| Intercept | 1 | -13.5910 | 1.8876 | 51.8399 | <.0001 |
| BRR | 1 | 0.3101 | 4.6001 | 0.0045 | 0.9463 |
| OOSR | 1 | 16.2482 | 14.7865 | 1.2075 | 0.2718 |
| QCR | 1 | 1.8364 | 23.1361 | 0.0063 | 0.9367 |
| Time_Since | 1 | 0.0418 | 0.00568 | 54.0481 | <.0001 |

| Odds Ratio Estimates | | | |
|---|---|---|---|
| Effect | Point Estimate | 95% Wald Confidence Limits | |
| BRR | 1.364 | <0.001 | >999.999 |
| OOSR | >999.999 | <0.001 | >999.999 |
| QCR | 6.274 | <0.001 | >999.999 |
| Time_Since | 1.043 | 1.031 | 1.054 |

## Poisson Regression

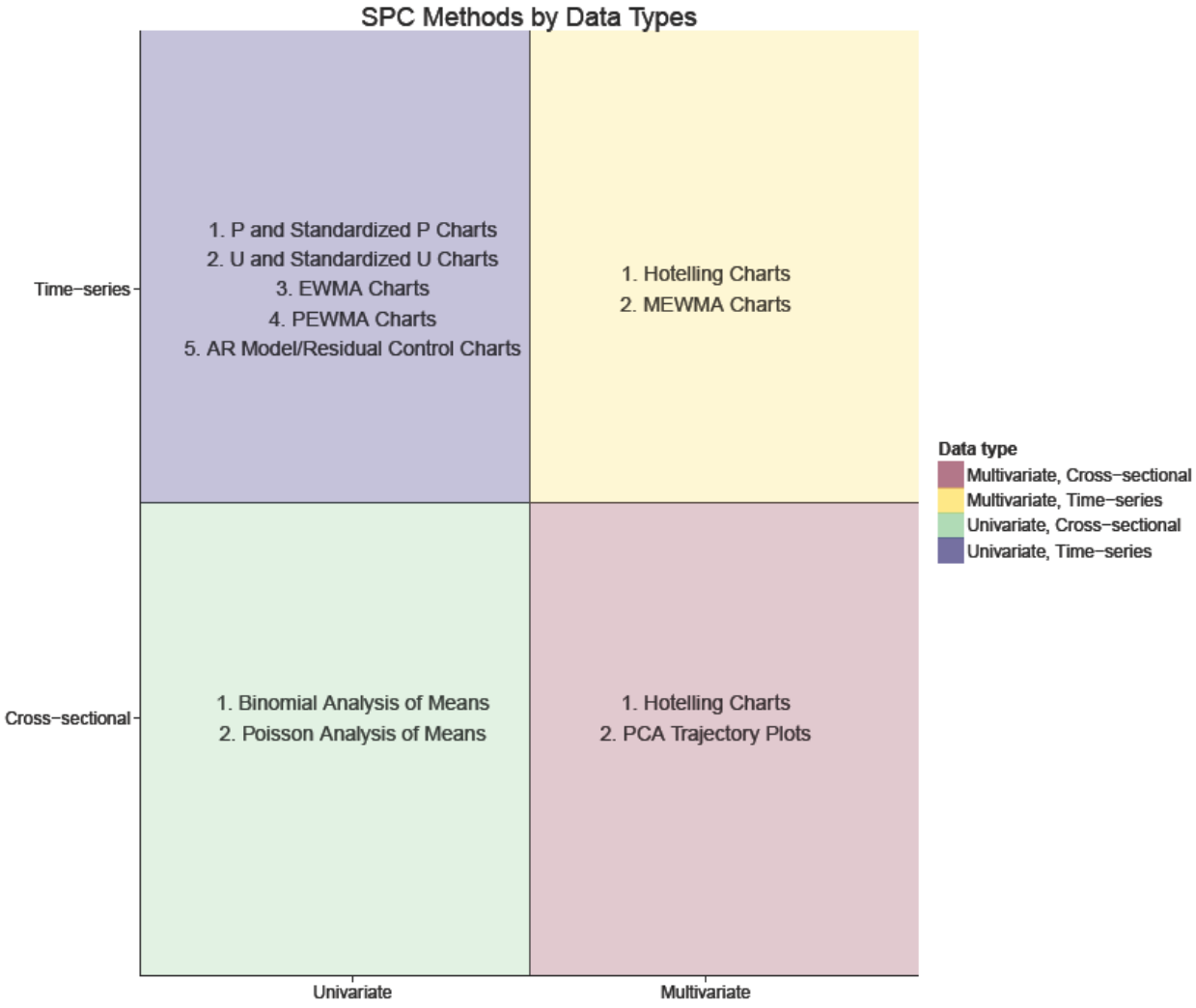
| Analysis Of Maximum Likelihood Parameter Estimates | | | | | | | |
|---|---|---|---|---|---|---|---|
| Parameter | DF | Estimate | Standard Error | Wald 95% Confidence Limits | | Wald Chi-Square | Pr > ChiSq |
| Intercept | 1 | 1.5143 | 0.1472 | 1.2257 | 1.8029 | 105.77 | <.0001 |
| meanBRR | 1 | -0.2215 | 1.6962 | -3.5460 | 3.1029 | 0.02 | 0.8961 |
| meanQCR | 1 | 5.7126 | 3.2162 | -0.5910 | 12.0162 | 3.15 | 0.0757 |
| Scale | 0 | 1.0000 | 0.0000 | 1.0000 | 1.0000 | | |

| Label | Mean Estimate | Mean Confidence Limits | |
|---|---|---|---|
| RR BRR .01 | 0.9978 | 0.9652 | 1.0315 |
| RR QCR .01 | 1.0588 | 0.9941 | 1.1277 |

# Statistical Process Control: Objectives

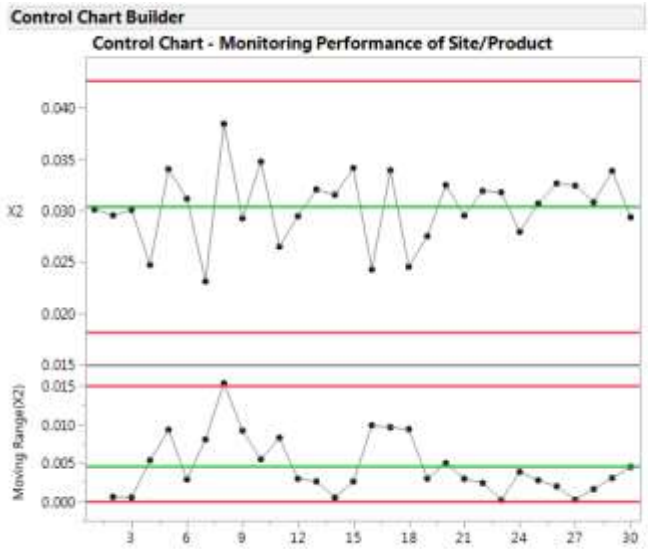
- Use statistical process control methods to monitor quality metrics that are arriving externally at multiple observation levels
  1. Quality metrics and subgroups can either be **1. quantitative** or **2. categorical**
  2. Observation levels (or subgroups) can either be **1. quarters** or **2. other rational groupings** (such as an aggregate of FEIs for each application)
  3. Techniques include both **1. univariate** and **2. multivariate**
- Approach
  - First focus on multivariate control charts (when possible) then the univariate control charts to reduce Type I and Type II error rates

# Statistical Process Control: Methods

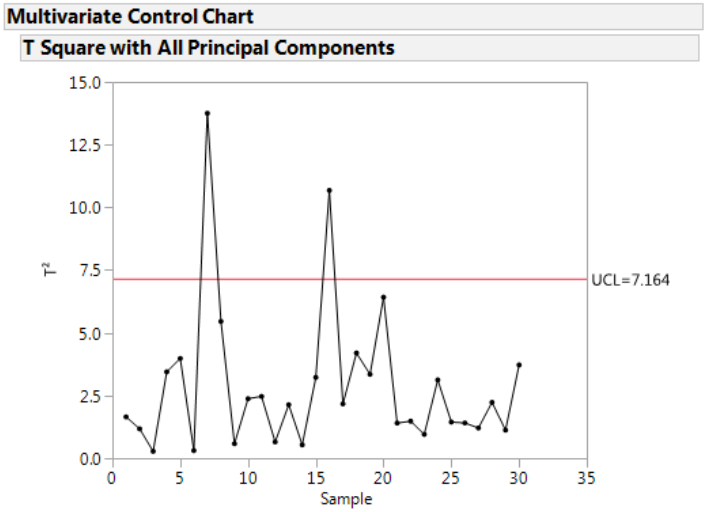


# Statistical Process Control: Time-Series Example

## Univariate




## Multivariate




Note: UCL is calculated based on Alpha=0.05

**Principal Components: on Covariances**

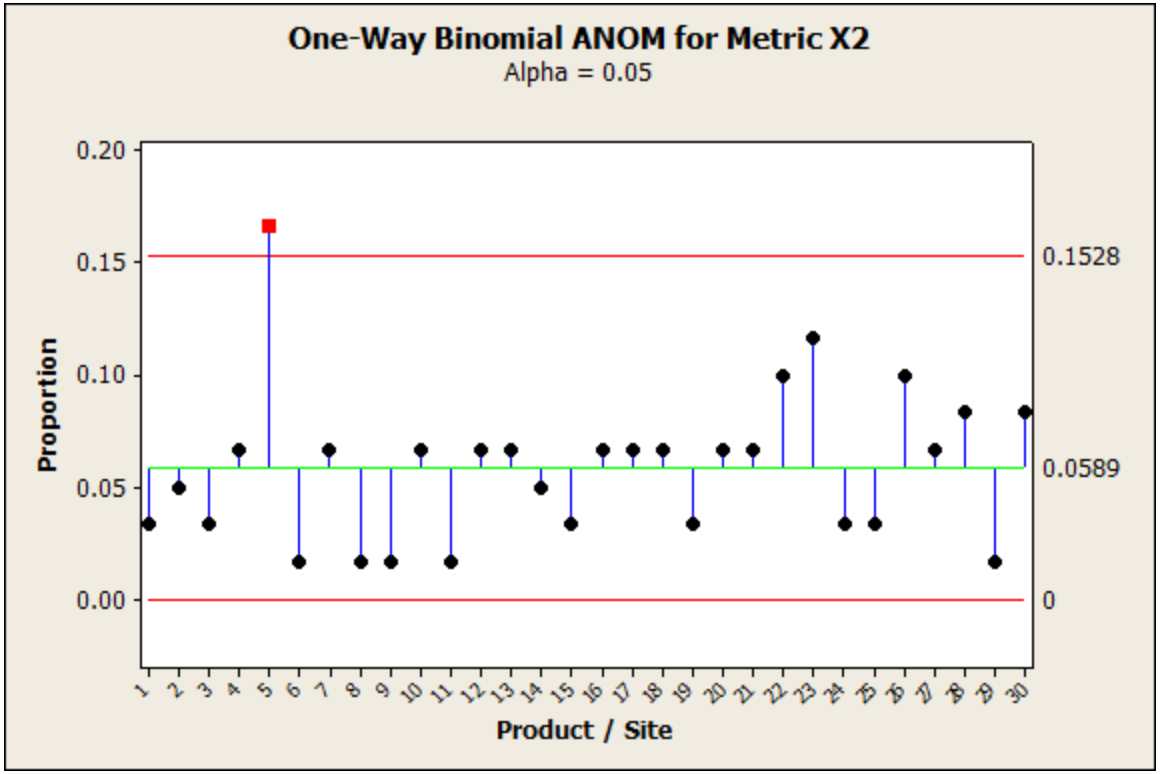
| Eigenvalue | Percent | 20 40 60 80 | Cum Percent | ChiSquare | DF | Prob>ChiSq |
|---|---|---|---|---|---|---|
| 0.0136 | 99.068 | | 99.068 | 252.510 | 5.000 | <.0001* |
| 0.0001 | 0.861 | | 99.928 | 36.454 | 2.000 | <.0001* |
| 0.0000 | 0.072 | | 100.000 | 0.000 | 0.000 | . |

**Eigenvectors**

| | | | |
|---|---|---|---|
| X1 | -0.12224 | 91.31285 | 34.15584 |
| X2 | 0.06975 | -9.85973 | 316.0305 |
| X3 | 8.55958 | 1.38434 | -2.08765 |

Note: Eigenvectors were divided by square root of eigenvalues.

# Cross-Sectional: Example



# Proposed Implementation of QM Program

- This is a surveillance program… not an enforcement program
- Submission of metrics would not result in
  - 483 observations or other enforcement actions
- Submission of metrics would result in
  - Diminished risk rank score in SSM (routine surveillance inspection scheduling)
  - More metrics = greater reduction
  - Metric data itself would not influence reduction
    - Until learning period complete and relationships established… this will take time
- First principle… more information is better than less information
- Signal detection leads to OPQ QIT (quality collaboration program)

# Acknowledgements

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