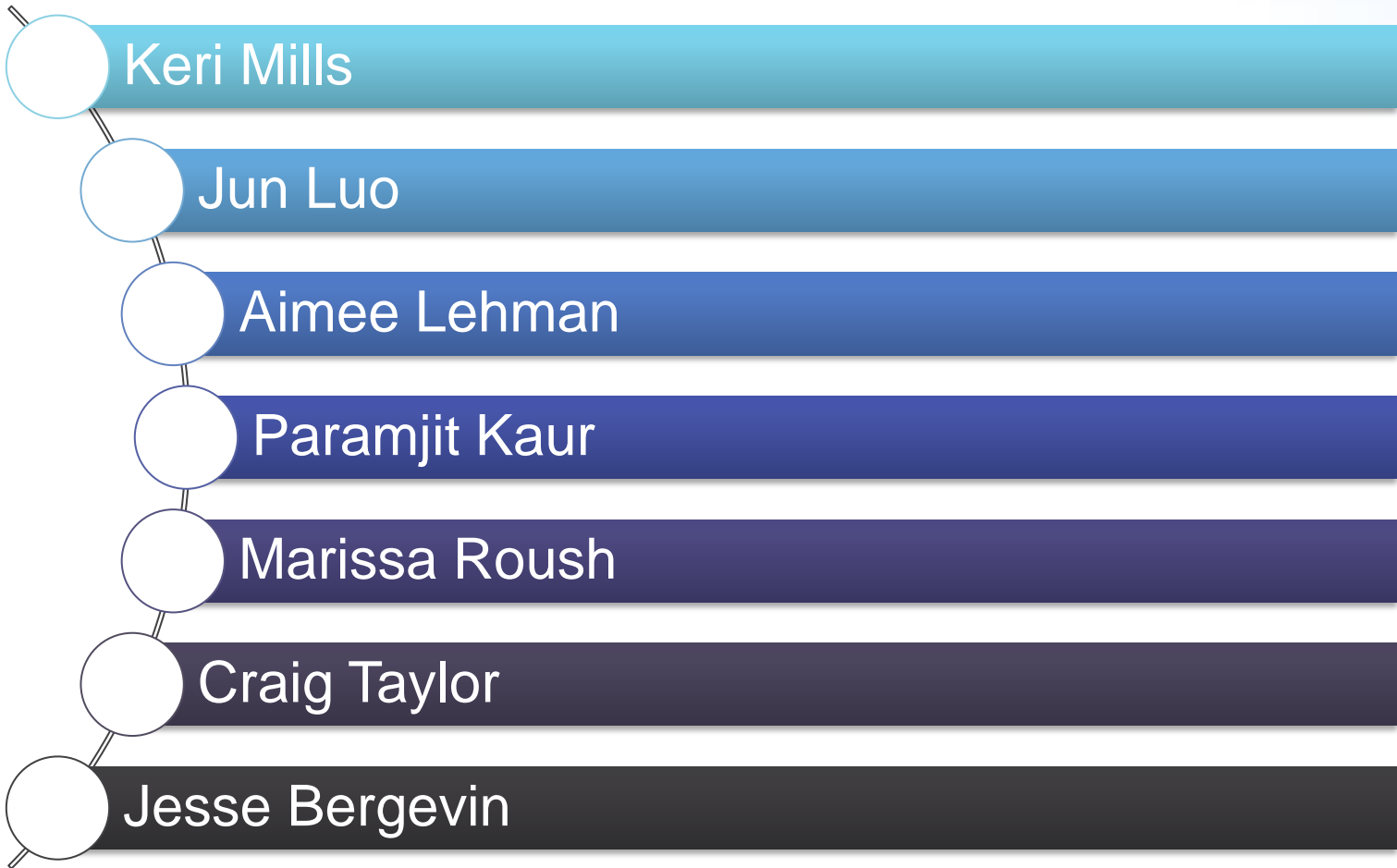**Genentech**
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Using JMP to Analyze Raw Material Variability in Cell Culture Process

Jason Gu
SAS JMP Discovery Summit 2014

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Agenda

Overview

Problem Definition

JMP to the Rescue

Summary

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Background

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Who We Are

Genentech Inc,

- Founded in 1976 by biochemist Herb Boyer and venture capitalist Bob Swanson.

- First produced synthetic human insulin in 1978.

- Acquired by Hoffman-La Roche AG in 2009.

- Therapeutic focus areas: Oncology, Immunology, Neuroscience, Metabolism, and Infectious Disease.

Our Mission is:

To be the leading biotechnology company, using human genetic information to discover, develop, manufacture and commercialize biotherapeutics that address significant unmet medical needs. We commit ourselves to high standards of integrity in contributing to the best interests of patients, the medical profession, our employees and our communities, and to seeking significant return to our stockholders based on the continued pursuit of operational excellence.
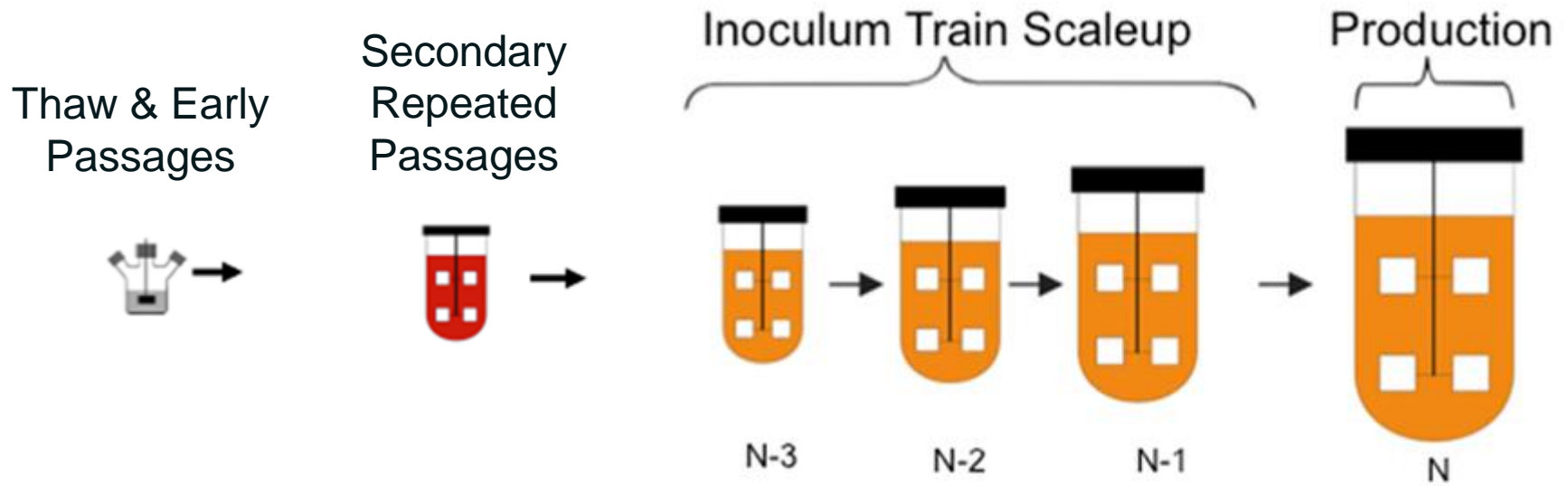
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History of Vacaville Site

- Site completed in 1998. First plant (CCP1) licensed in 2000.

- Second plant (CCP2) completed in 2007.

Some Vacaville Facts

- Combined, CCP1 and CCP2 makes Vacaville the largest drug substance plant in the world with an combined 344,000 L of capacity.

- Highest throughput plant in the Roche-Genentech network.

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Thaw & Early Passages

Secondary Repeated Passages

Inoculum Train Scaleup

Production

N-3   N-2   N-1   N

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- Drug Substance (API) Manufacturing is a complicated process involving many raw material ingredients.

- Some raw materials are sourced through external vendors while some are prepared on-site.

- Variability of a single component raw material could lead to variation of process performance or product quality attributes.

- Studies into lot-to-lot raw material variability frequently focus on the undefined components of the media or on complex multi-component powders.

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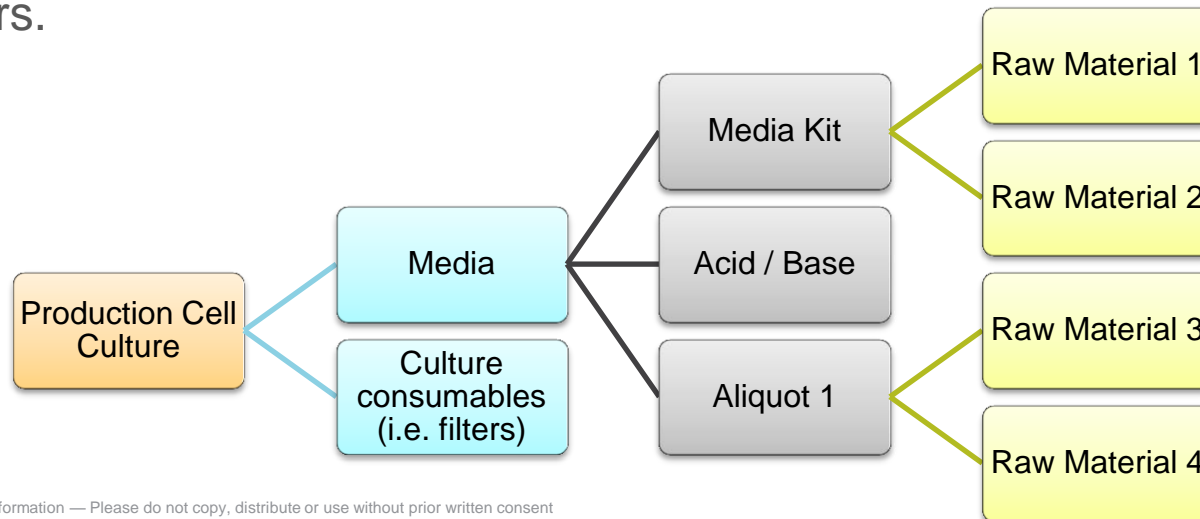
How the data is stored:

- All material production / consumption data is stored in our Production Operations Management System.

- Data is stored in a parent / child relationship format.

- All Key Performance Indicators (KPIs) are calculated and stored within Manufacturing Sciences Process Data Systems.

- Information is linked using batch identifiers.

Product	Ingredient	Level
---	N Culture	0
N Culture	N Culture Media	1
N Culture	Consumables	1
N Culture Media	N Media Kit	2
N Culture Media	Acid / Base	2
N Media Kit	Raw Material 1	3
N Media Kit	Raw Material 2	3
N Culture Media	Aliquot 1	2
Aliquot 1	Raw Material 3	3
Aliquot 1	Raw Material 4	3

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Problem

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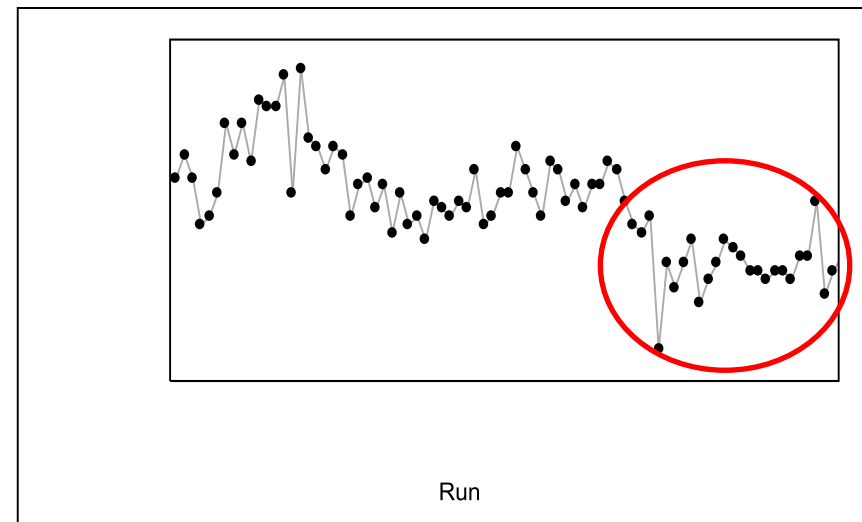*A Member of the Roche Group*

Observation

Observed Low Performance (Cell Line A)

- Seed & inoculum: Lower growth and cell viability (especially N-1).

- Production: lower growth and titer (inherent from low seeding density & low initial viability)

N-1 Final Viability

Run

N Product Titer

Run

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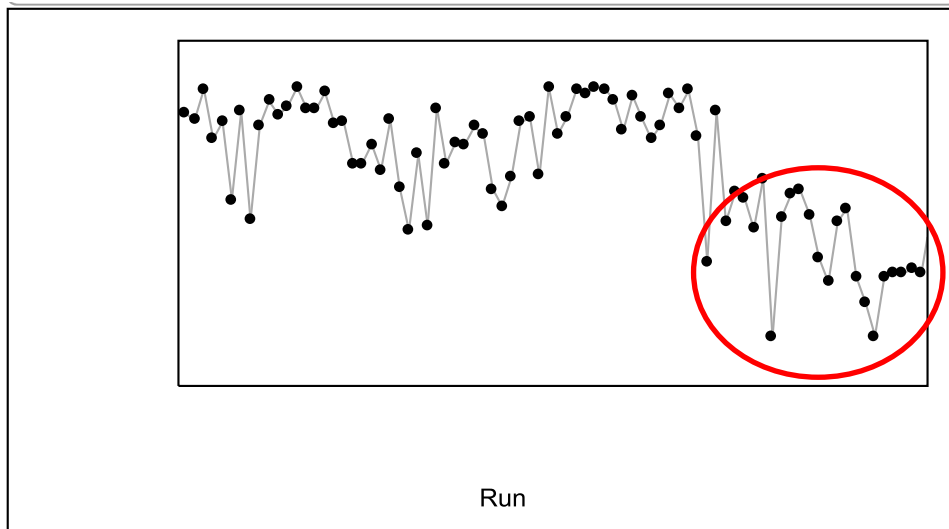
- Plots a SPC control chart for a key performance indicator or product quality attribute and displays a mosaic plot of the ingredients that went into that particular batch.

- Each color of the mosaic plot represents a different lot of material.

- Useful as an initial screening for raw material variability contributions.

- Requires a specific data structure and makes use of a hierarchical query in SQL (Connect By)

- Script is affectionately known as "the kaleidoscope"

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Raw Material Trace Analysis v2
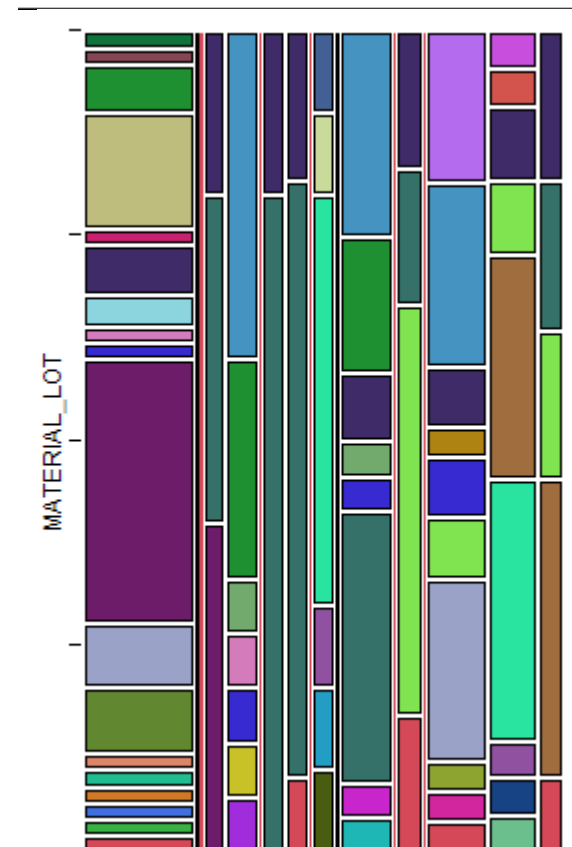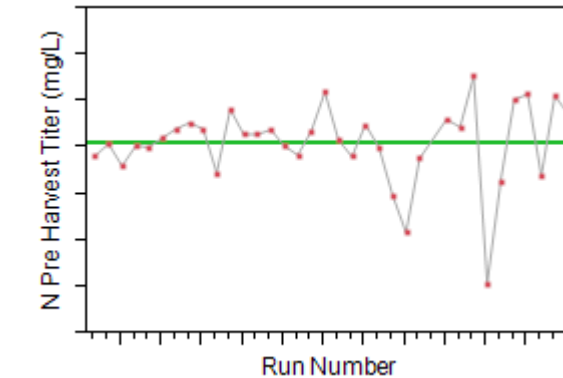
Raw Material Trace Analysis with a Single Component

- Once a culprit / suspect raw material ingredient has been identified, the search can be refined to hone in on that particular ingredient.
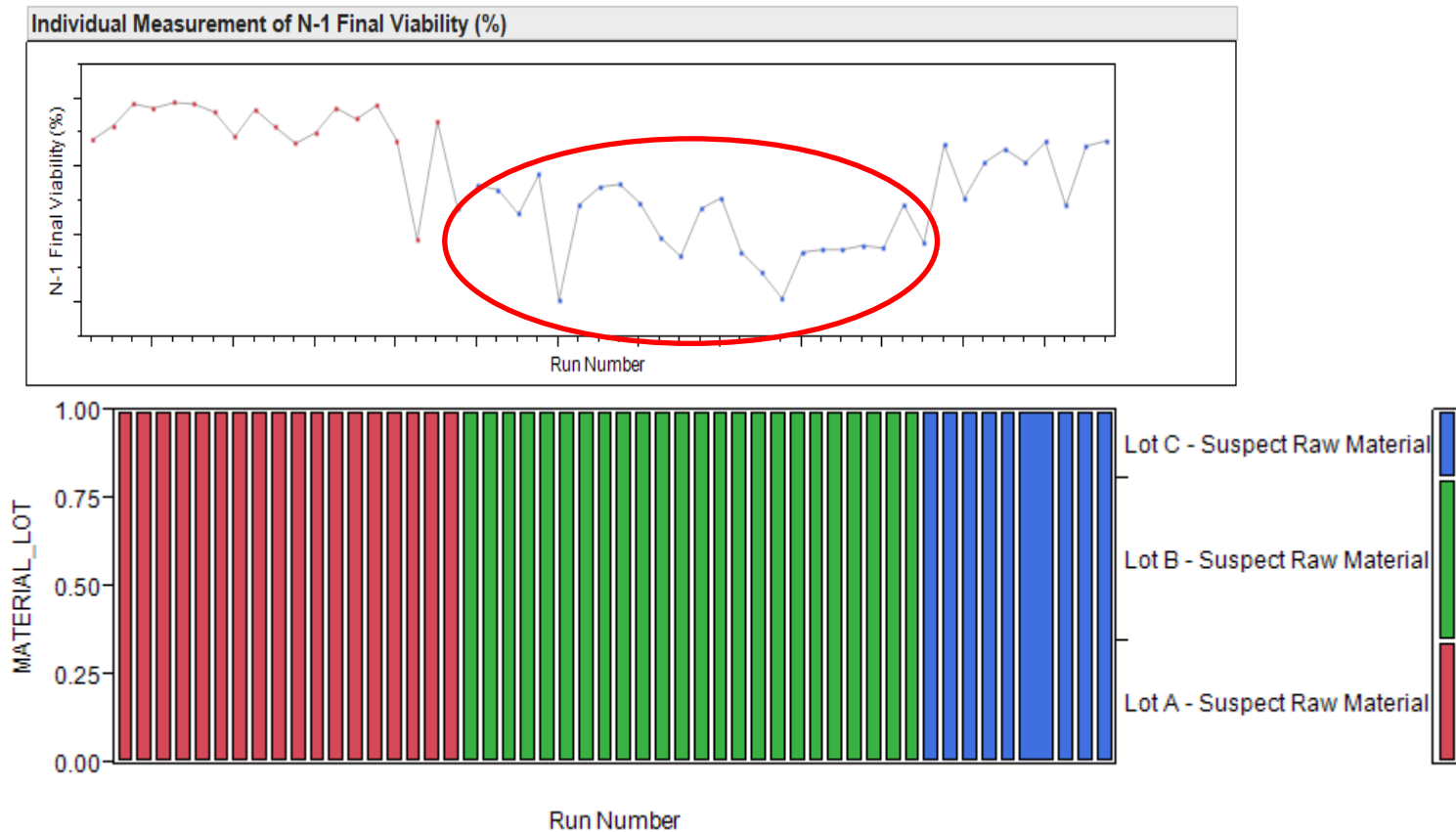
Refinement (v3)

Script Refinement

- Next step: figuring out the exact quantity of what raw materials that went into each lot.

- Poses a challenge from a technical standpoint as the raw materials that could go into multiple lots is only represented once by using the connect by query.

- Solution: iterate the query for each batch, a bit time consuming but calculates the correct quantity for each lot.

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Conclusions

- The manufacturing of monoclonal antibodies is a process that involves many different types of raw materials. Differences in these raw materials can contribute to significant variability to the process.

- Using JMP in conjunction with a material genealogy database, we can quickly plot a visual that aids in detecting changes in raw materials and their correlation with any process shifts.

- Connect By is an very useful SQL query for tracing genealogy.

- Be wary of raw materials that could potentially be parsed, recombined and re-used. Careful tracking of material genealogy is essential to figuring out what the process actually consumed.

- Future state: Be able to analyze process performance with quantifiable raw material quality attributes.

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