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Approval of a Greenfield Biologics DS Site in Asia

6 December 18

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Talking points

- Background
- The Assignment
- Assessment
- Game Plans
- Unexpected Concerns
- Three-Party Compliance Collaboration
- Inspection Readiness
- Final Result
- Epilogue

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Background

- Samsung Biologics was founded in April of 2011, and Groundbreaking for Plant 1 was in May of 2011
- Roche signed agreement in October 2013 to transfer an already approved monoclonal antibody drug substance to Samsung Biologics
- The only other customer of Plant 1 was BMS – for DS and DP
- Ground breaking for Plant 2 was in October 2013; not in scope for initial assignment

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Samsung Biologics

Plant 1 – June 2013

Songdo Plant 1

Completed Plant #1 and Admin Building

- Ground Breaking : May 2011
- GMP Ready : June 2013 (25 months)
- Mechanical completion : 13 months
- Facility Validation : 12 months

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The Initial Assignment *(since it grew…)*

- Complete the Tech Transfer of Roche product in order to meet market demands and free up capacity for new molecules
- Receive regulatory approval from FDA within 24 months – the goal was Q4, 2015

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Initial Assessment – November 2013

Encouraging:

- Plant was well constructed; presented very well
- Team was enthusiastic, well educated and quick learning staff
- ~ 5% Experienced workforce from USA (in mid-level leadership roles)

Concerning:

- Plant floor was not well organized and had some basic safety and Quality deficiencies
- Ninety percent of workforce was new to pharmaceuticals and young
- English language skills of local staff varied widely – from perfectly fluent to reticent to speak
- Cultural and behavioral differences; not consistent with GMP mindset
- Minimal (<4 days) time spent on the Quality due diligence audit. It was performed on site prior to signing agreement
- No in-depth plan in place for path forward

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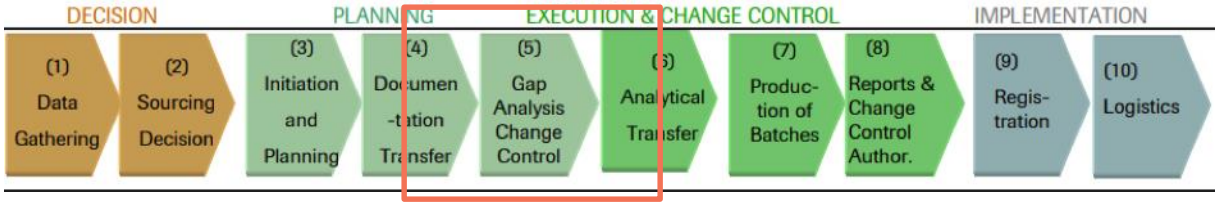
Game Plan - 2014

- Tech Transfer Plan – Technically driven with QA Oversight



  - Process capability and gap assessment for existing site equipment
  - Risk Assessments for Facility, Process, Methods, etc.
  - Analytical Method Transfer Plan
  - Engineering runs and PPQ plan
- Quality Systems Comparison and Updates
- Quality Agreement
- Creation of Batch Records - bilingual
- Inspection Readiness secondary priority - initially

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Unexpected Challenges

Samsung, was new to the biopharmaceutical industry and their knowledge and experience was limited. This created challenges not typically seen during a standard tech transfer.

- Numerous gaps were identified in:
  - **Quality Systems**
  - **Batch Records & Review Process**
  - **Knowledge transfer process, training & operator capability**

Associated with these gaps were the concerns that the operators and associates could not consistently demonstrate basic knowledge of GMPs and technical expertise

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Closing gaps within the Quality Systems

- As part of Roche's Quality Risk Management Plan a standardized Gap Assessment was performed to assess Samsung's quality system against Roche's PQS requirements.
- 1900 QS requirements were checked
- Hundreds of QS requirements missing in Samsung QS
- A systematic approach was necessary to prioritize the closure of gaps in three stages.
  1. Prior to Engineering runs
  2. Prior to Qualification Runs
  3. Prior to FDA inspection)

Tedious – but worth the effort long term

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Closing gaps in the Batch Record Review Process

- Engineering Run executed batch records had fundamental GDP errors that were not caught by the Samsung review process.
- Roche decided to review all Samsung batch records until the process was determined to be under control
  - 50+ batch records per DS batch
  - developed feedback loop and metrics
- Used risk ranking and filtering methodology and a protocol to qualify Samsung
- Ultimately reviewed over 2000 batch records before batch record review was completely qualified

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Closing gaps in Knowledge Transfer, Training and Operator Capability

- QA support was not in place to provide adequate coverage for a 24 hour process – Roche QA and MSAT implemented coverage schedules
- Operators had not received sufficient training to successfully complete certain operations (i.e column packing) – brought in vendor training experts
- General procedures were not written sufficiently and could not be successfully followed.
- General GMP mindset (this can take years to fully understand and learn); too many new employees to provide sufficient “learn by example” OJT for GMP- Lots of reinforcement

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So Many Topics – Too Few People

- The Roche Quality Team for the Samsung project was 4 FTE in the US, 4 FTE in Korea and 4 Contractors
- For specific topics, Roche Quality experts were drafted
- After PPQ runs, Roche immediately started ongoing production to build inventory
- There was still a large amount of work to get ready for inspection
- Roche, Samsung and the other client, BMS, only had so many resources – so we could not duplicate or miss areas to get ready for inspection

What to do?

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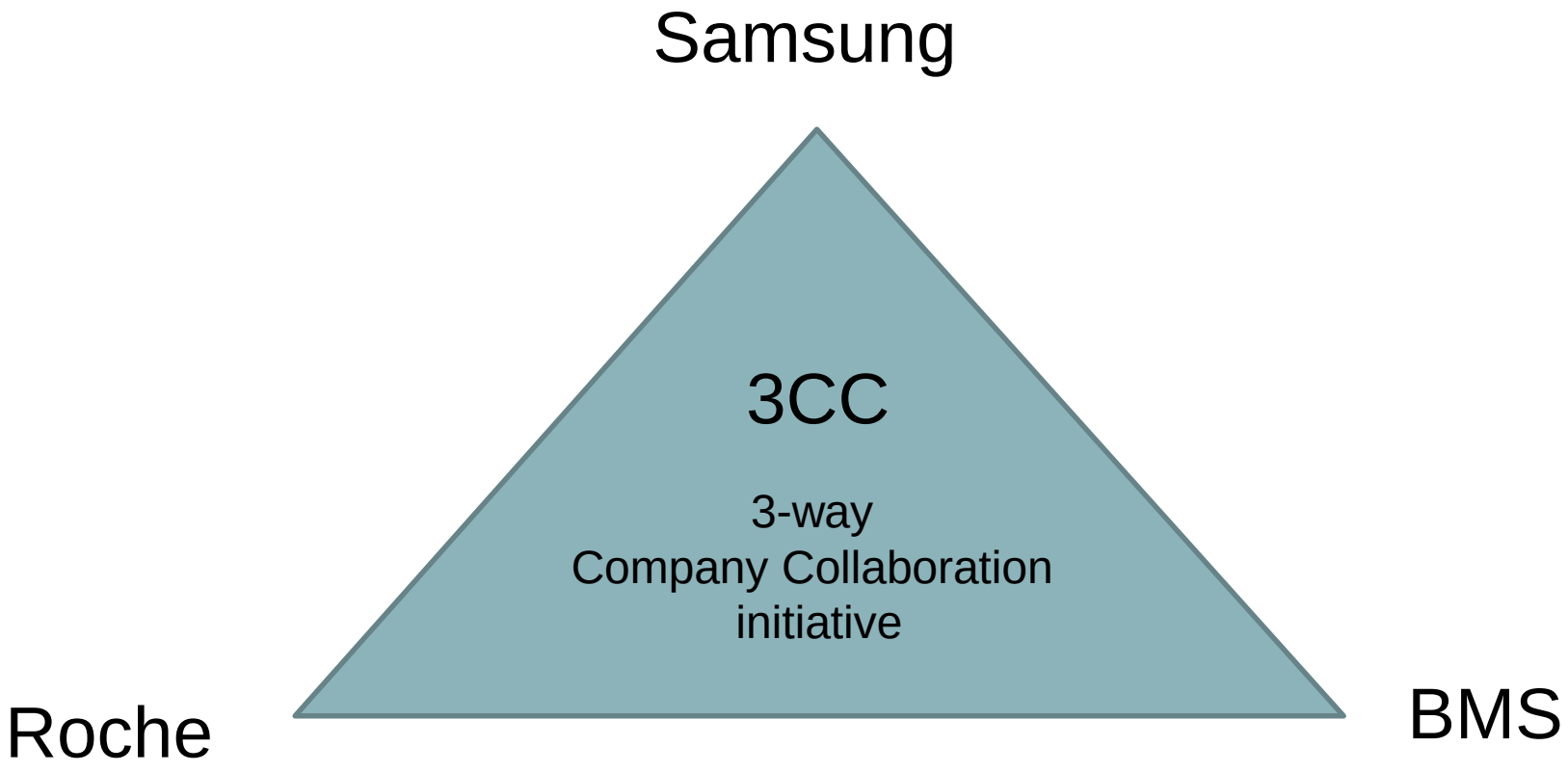
Coordinating Readiness Resources



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3CC: 3-way Company Collaboration

(for PAI Readiness and Continuous Quality Improvement Plan)

- 3-Way NDA approved
- Used risk ranking and filtering exercise to determine *non-product specific* priorities for Samsung PAI preparation
- Resources coordinated across company lines
  - Roche driven Kaizens on Deviations, Change Control, CAPA, etc.
  - BMS driven Kaizens in Quality Control, etc.
  - Jointly driven Inspection Readiness Activities
- Ongoing communication on issues, prioritization and plans

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3CC used for FDA PAI Readiness Plan

- Mapped all the inspection topics to presenters
- Practiced the opening presentation
- Practiced the tour route using show-and-tell boards
- Practiced with all presenters; interviews conducted until they were comfortable

Roche utilized internal network expertise to supplement the 3CC resources in completing preparation activities!

- The Samsung FDA PAI for the Roche DS occurred in October 2015

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Got 483? - No!

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EMA Inspection – New Challenges

- AIFA was the inspecting body
- Dual inspection with BMS – 3 Party Compliance Committee comes in handy!
- Dual DS and DP inspection!
- BMS and Roche anchored the inspection strategy room
- Tougher inspectors so we received some observations

Roche and BMS both received DS approval from EMA

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Epilogue

- Samsung Biologics now has 3 Plants up and running in Korea
- Their total bioreactor capacity is 360000 liters
- They have multiple clients, multiple approvals
- The product we transferred now has biosimilar competition
- Samsung Bioepis has become a major biosimilar company

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Current Songdo Complex

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Learnings

- Personnel GMP awareness, mindset and discipline is a must that takes time and effort
- Cultural and language differences always needed to be factored in
- Work on the Quality System and Quality business processes really helped
- Strong project governance helped keep the team together
- Face to face interactions worked far better than phone conversations
- Collaboration and Partnership can work across companies