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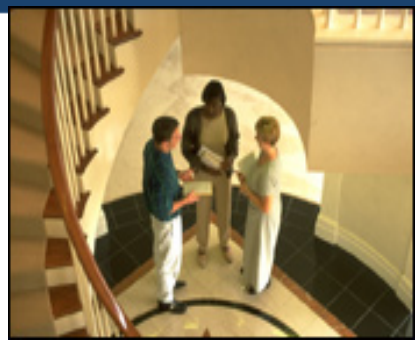

FDA – Conformia CRADA

Preliminary Phase Results

FDA Interaction, QbD, PAT, Design Space

FDA Symposium
Harvard University
August 23, 2006

FDA CRADA Study

- **CRADA is a three year study consisting of 3 Phases**
  - **Year 1 / Phase 1: Research - *FDA, Conformia, and 9 Pharma/Biotech Companies***
  - **Year 2 / Phase 2: Solution Definition - *FDA and Conformia***
  - **Year 3 / Phase 3: Education / Workshops - *FDA, Conformia, Pharma/Biotech Industry***
- **Topic: Current State Practices, Challenges and Bottlenecks in Pharmaceutical Development**
- **Pilot Group involves 9 companies and will expand to 25 companies**
- **Research based on last 9 months**
- **Sponsored by Office of Pharmaceutical Sciences (OPS), CDER**
- **Objectives: To improve overall understanding of the difficulties in governance, risk and compliance within the Pharmaceutical Development environment**

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Key Objectives & Outputs

Objective

- **Analyze Root Cause:** Identify existing root causes of bottlenecks in drug development resulting in inefficiency
- **Assess Guidelines:** Describe gaps, perceptions, and usefulness of existing guidance related to pharmaceutical development.
- **Describe Current State Practices:** Summarize current state of pharmaceutical development, challenges, opportunities, and top of mind issues facing development organizations.
- **Identify Potential Future State:** Define requirements needed for companies to implement Quality by Design (QbD) closed-loop, continuous improvement, process understanding approach to new drug development.
- **Educate:** Increase familiarity of key initiatives, new technologies and future state possibilities

Expected Output

- **Company Readout:** Identify current state practices / top of mind issues internal to participating companies.
- **Final Report / Benchmarking Briefing:** Roll up results of all preliminary phase company participants (Phase 1)and loose comparison
- **FDA Briefings:** Communicate to FDA current perceptions in understanding, expectations of future agency guidance; opportunities for streamlining guidance.
- **FDA Reaction:** Conformia to share FDA's feedback with participating companies.
- **FDA Workshops:** Conduct Internal FDA Seminars to educate FDA on key areas: Development Process, Qbd, Design Space, PAT.

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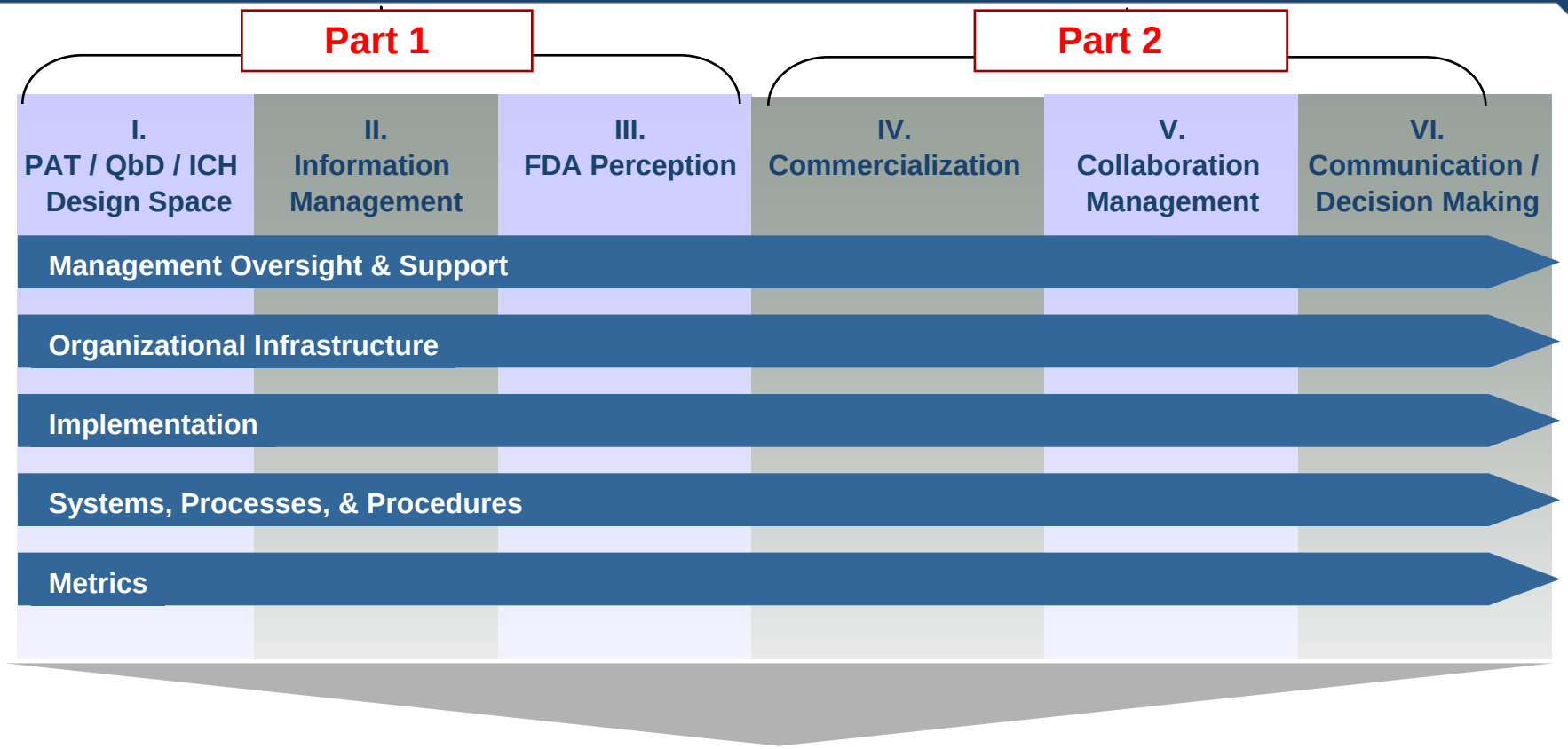
Research Agenda Split into Two Parts



- Capture Current State
- Highlight "Range" of Practices
- Measure Awareness / Perception

- Identify Enablers and Barriers
- Identify Additional Needs
- Create Platform for Ongoing Discussion

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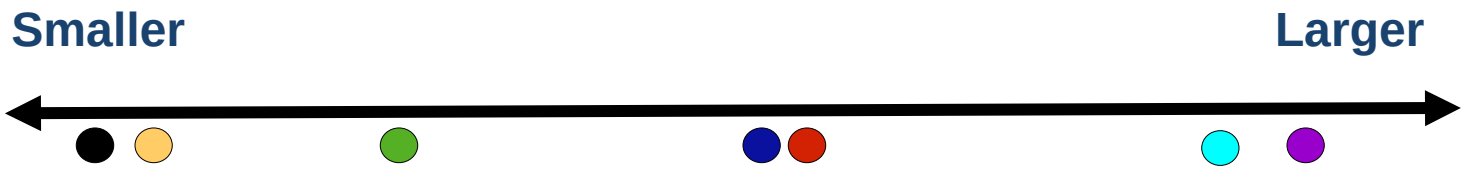
Participating Company Demographics

Relative Company Size of Pilot Group*

Complete Results from 7 Participating Companies



Collectively:

- **135+ commercial products to market**
- **Parallel and multi-site development activities occurring at all 7 companies.**
- **All 7 companies using CMOs in Development process / tech transfer**

*Based on 2005 Annual Revenue, # of Employees, Number of Development Sites, Number of Commercial Sites.

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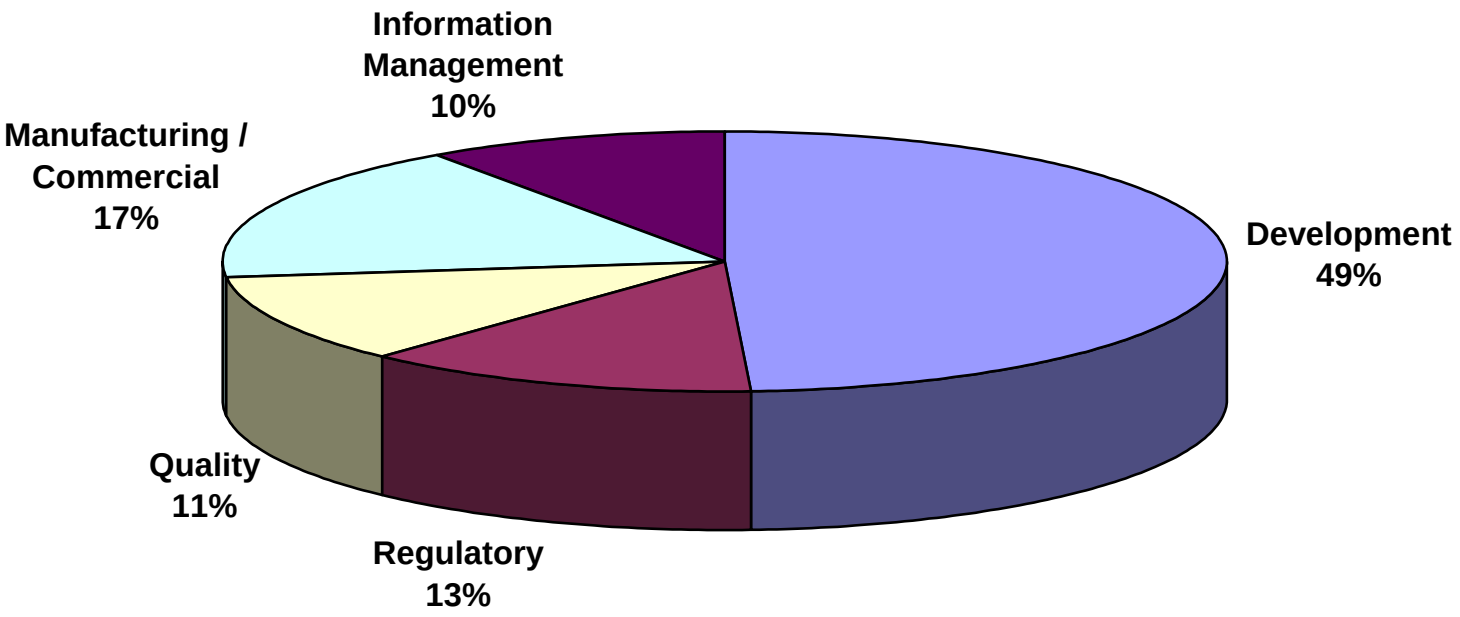
Pilot Group Research Base: 165 Interviews from 7 Companies

Breakdown of Key Respondents				
Drug Substance	Drug Product	Information Management	Regulatory	Quality
Scientists (Early & Late) Engineers (Early & Late)	Scientists Analytical Chemists	Directors Managers	Directors VP	Directors VP



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Conformia Developed Assessment Tool to Map Continuum of Current State Practices

Stages of Enablement

	1 Ad-hoc / Not Enabled	*2* Emerging	*3* Partially Enabled	*4* Enabled Integrated Enterprise-Wide
Strength of Initiative	No Formal Initiative Ad hoc processes	Exists, but silo'd.	Formalized	Stage 3 + FTE's assigned
Management Support	No strong management support	Limited management involvement or support	Top down management support across the organization	Top down executive sponsorship translated into formalized initiatives
Cross Functional Support	Grass roots effort	Limited to functional groups from a top down approach	Initiatives span cross-functional groups	Key initiatives are translated into daily functions
Interaction with FDA	Limited interaction with FDA	Interaction limited to dedicated personal from Regulatory & Quality	Numerous avenues of dialogue with FDA occurring; Mix of Science and Regulatory	Cross functional bi-directional sharing of ideas and perspective with FDA

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Preliminary Findings

QbD, PAT, Design Space, & FDA Interactions

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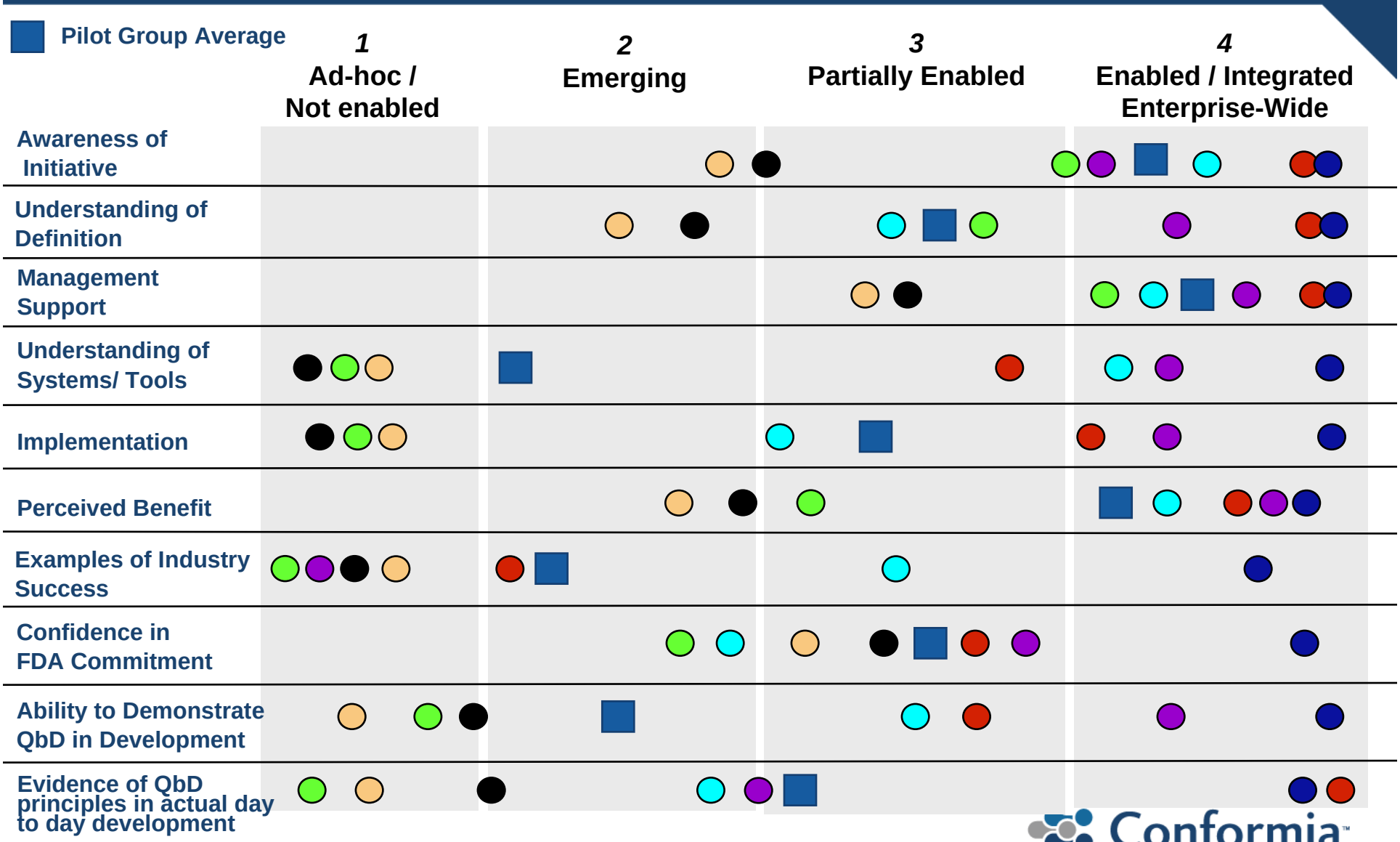
State of the Union: QbD in Development

Implementation and adoption of QbD paradigms varies widely.



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Pilot Group Observations: Key Enablers of Quality by Design

- **Some observations from Companies that have cross functional implementation of QbD across Development:**

- **Observation 1: QbD is driving paradigm** around which PAT (Process Understanding) and Design space are linked.
  - Almost consistently view PAT and Design Space as tools to enable QbD.
- **Observation 2: Externally visible** cross functional QbD initiatives / activities appear to be aligned with higher levels of adoption.
- **Observation 3: Molecule Independent i.e.** large molecule and small molecule development processes at these companies were treated the same in terms of QbD initiatives / linkage to development process maps.
  - Upfront knowledge of overall development process was available to entire enterprise

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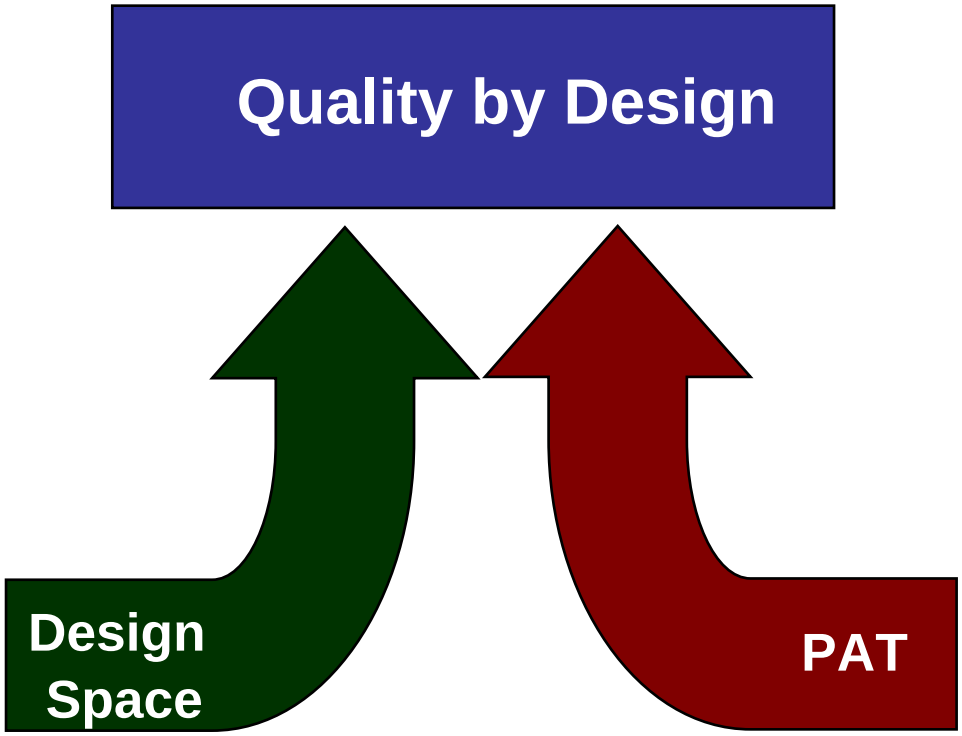
Leading respondents had a fairly consistent view of how the three initiatives are related

"Quality by Design is the overarching paradigm and Design Space and PAT are tools to achieve this end"



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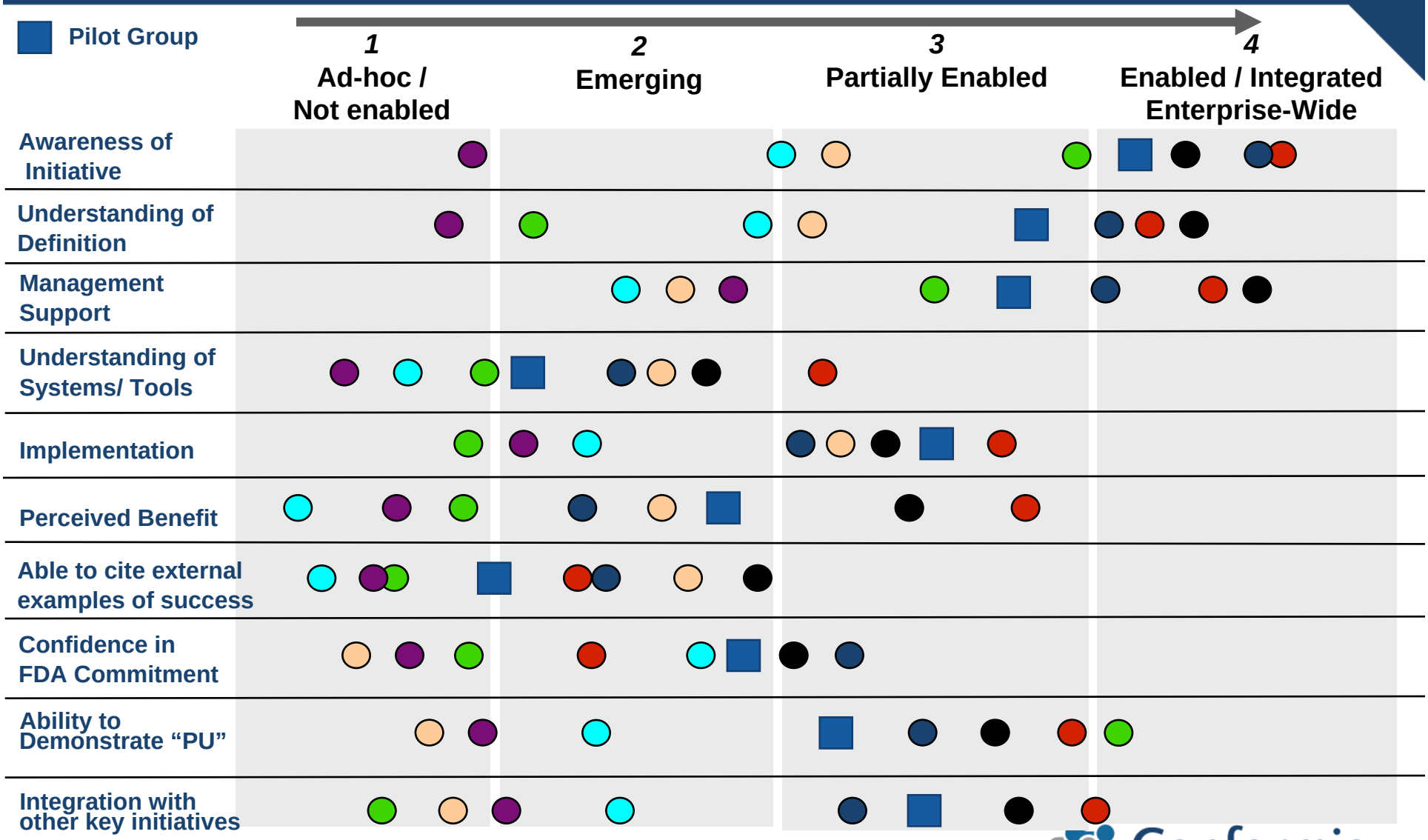
State of the Union: PAT in Development

Awareness Exists Across Development Organizations…



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Group Findings: Where to Start PAT -- Two Camps of Thought

Camp One: Implement PAT in Development

- More benefits to overall Product / Process Development
- Transferred process to Commercial Mfg more robust
- True Process Understanding in Development (could transfer the best processes / provide better tech transfer / ease burden
- Might be easier to “fold in” from the get go.
- Commercial Mfg can’t really exploit PAT / not trained that way

Camp Two: Implement PAT in Commercial Mfg

- **Easier to justify investment in technology**
- **Easier to use in environment where you have a lot of comparative data / a lot of data about products already. More accurate / less false readings**
- Not clear on how to measure / control accurately in development when process itself is still changing. More opportunity to get it right in Mfg
- Will we need to generate a lot of extra data in Development? Don’t want to implicate quality of product when methods may not be known well enough.

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Lessons Learned from Successful PAT Implementation in Development

- **Enablers:**
  - Centralized “resources” who go very deep in PAT vs everyone on the team trying to support the knowledge curve
    - PAT Team
    - Designated “experts”
  - Culture “ to expand PAT” not become the “gatekeeper”
- **Linkage with Mfg and clear Sr, Mgmt view that PAT must be owned by Development**
  - More robust use of PAT Tools in Development
  - Can’t rely on mfg to mange the variety of tools or introduce into existing product ($$$)
- **Drivers: Better appreciation of science / process understanding in Development and drive for higher quality**
  - Peering into the black box with PAT Tools
- **Expect that it will make Development more expensive, not less.**
  - But higher quality / more interesting / more opportunity for innovation / better control of process
  - Some mixed views on this.

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Brief Observations on “Design Space”

- **Of the Three Initiatives - PAT, QbD, and Design Space – latter is least understood**
  - Understanding of design space very limited
  - No consistent definition observed across participants in the group
  - Participants expressed a lack of understanding of scope, approach, and benefits to be achieved
  - Not convinced that FDA is fully behind “Design Space” concept
  - Perceived Benefits not well understood
  - Need more guidance / clarification from FDA before this will gain traction

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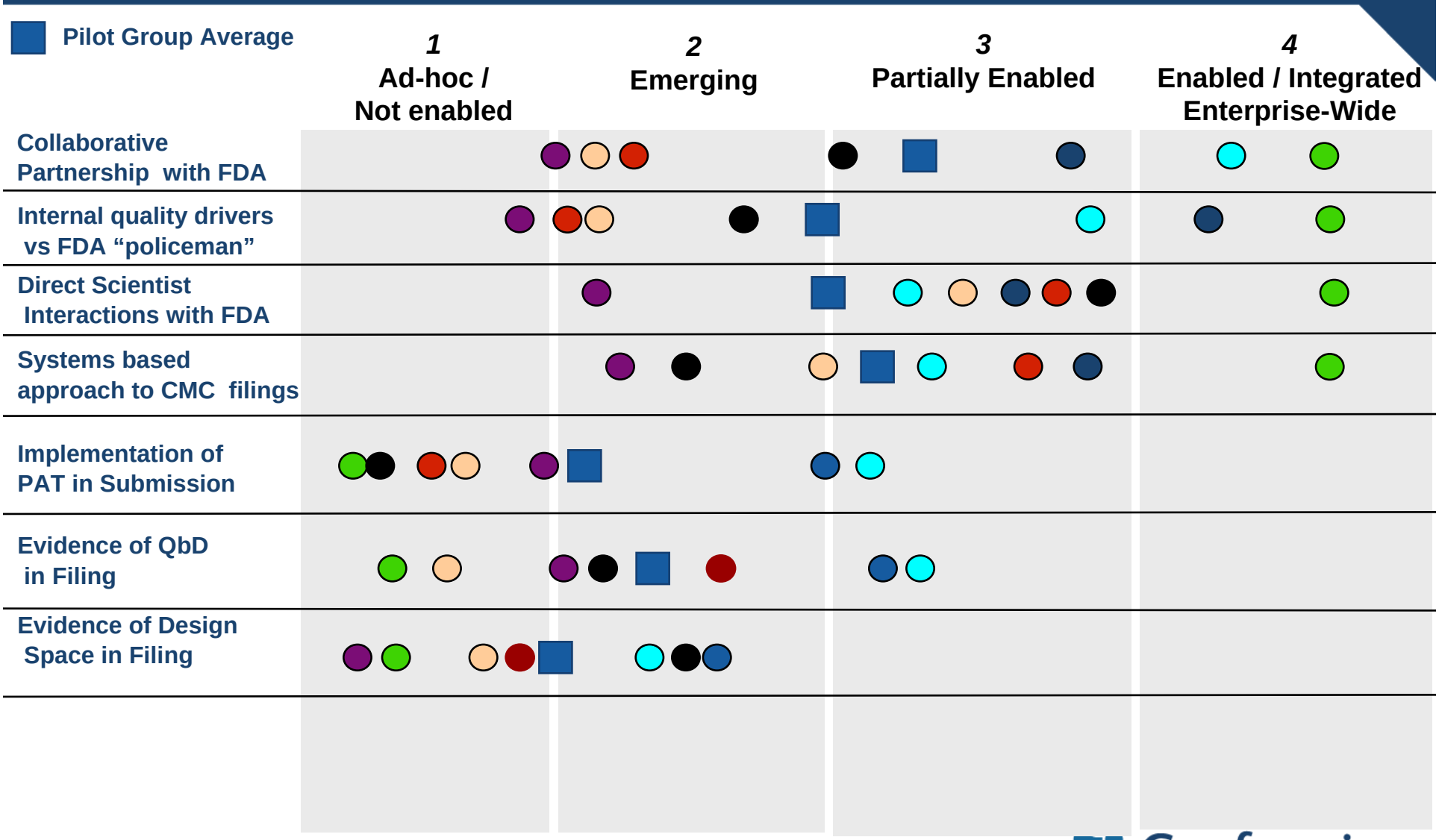
State of the Union: Interactions with FDA

Relationship with FDA varies significantly across group …



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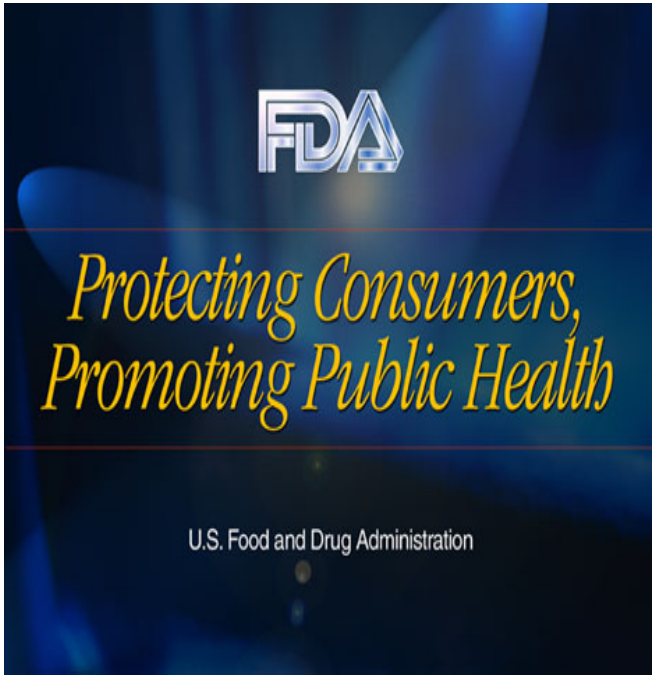
How the Pilot Group Companies Describe Their Relationship with FDA Varies Tremendously



- **"Our internal standards are higher than FDA's"**
- **"Relationship with FDA is Very Open"**
- **"Its our responsibility to educate / explain to them"**
- **"Mutual Advisors"**
- **"They are a *Trusted Partner*"**
- **"We see them as an *Advisor*"**
- **"Fair" and "Collegial"**
- **" We try to *Partner* where we can"**
- **Team Oriented**
- ***Open / but* they are still the agency**
- **"Distant: they have their roles / we have ours"**
- **"*Not Transparent* with each other"**
- **"We are Guarded with each other"**
- **"We give them the minimum they ask for, too much data is too much risk"**
- **"FDA is the Policeman"**
- **" We do what they tell us, and watch out for them when we see them coming. Occasionally we get Caught.**
  - " If they weren't in the "policeman" role, we probably wouldn't do half the things they ask, b/c to comply costs money, time, and mindshare which we would willingly spend on product development or the business"

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Key Takeaways from the Pilot Group on FDA Relationship

- About half the scientists don't seem to have many direct interactions with FDA.
- Individuals within companies varied tremendously interms of level of mutual respect. "Policeman, guarded, resentful of getting too many questions, etc."

- **Direct quotes:**
- "In our company there is an underlying perception that there is a need to "say the right thing" (i.e. what FDA wants to hear)
- "We are very reactive. If FDA says jump, we ask how high. Not why. I wish we pushed back more with the science, but we don't.
- "Every time the FDA asks us to do something it costs us more money, so we limit our conversations and just try to get through the process"

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Examples of Development Interactions Pilot Companies are Availing with FDA *(Partial List)*

- **Tutorials to CMC and OBP Review team:**
  - PAT
  - Design Space
  - Quality By Design
- **"Day in the Life of a Drug" Tours at Pilot Plant & Mfg Facilities**
- **Sharing Development / Commercialization Strategy (Education of Policy, Reviewers and Inspectors)**
- **Visiting Scientist at FDA**
- **CRADA Participation**
- **Sitting on Committees: ISPE Interaction / Well Characterized Biologics / ASTM (Standards / Best Practices)**
- **Pilot Program for QbD**
- **PAT Case Studies**
- **Industry Representation on FDA Advisory Committees**

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