Considerations for use of Artificial Intelligence and related Technologies in Pharmaceutical Manufacturing

Rajesh Kuppuswamy, Ph.D.

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Agenda

- Technology maturity in pharmaceutical operations
- Driving innovation through technology in pharmaceutical operations
- Implications of *US FDA's Draft Guidance* on use of AI to support decision making

Technology maturity is continually evolving with adoption across Manufacturing and Quality organizations

Proven Technologies*

Pharma 4.0: Asset management, real-time monitoring

Digital Twins: Production simulation, remote maintenance

Computer Vision: Visual inspection in production, packaging

Knowledge Graphs: Impact of relational attributes on product quality

Robot Operating System: Automation of tasks in QC and Manufacturing

Evolving Technologies*

Generative AI and other evolving capabilities added to proven technologies

Parametric testing: Ability to release product without QC testing

Audit and Compliance: Continuous and automated testing, raising preemptive alerts, always ready for audits

Risk Management and Continuous Improvement: Automated feedback mechanism to adopt learning and integrate with processes

Next Generation Technologies*

Primarily driven by Agentic AI and multi-agent orchestration

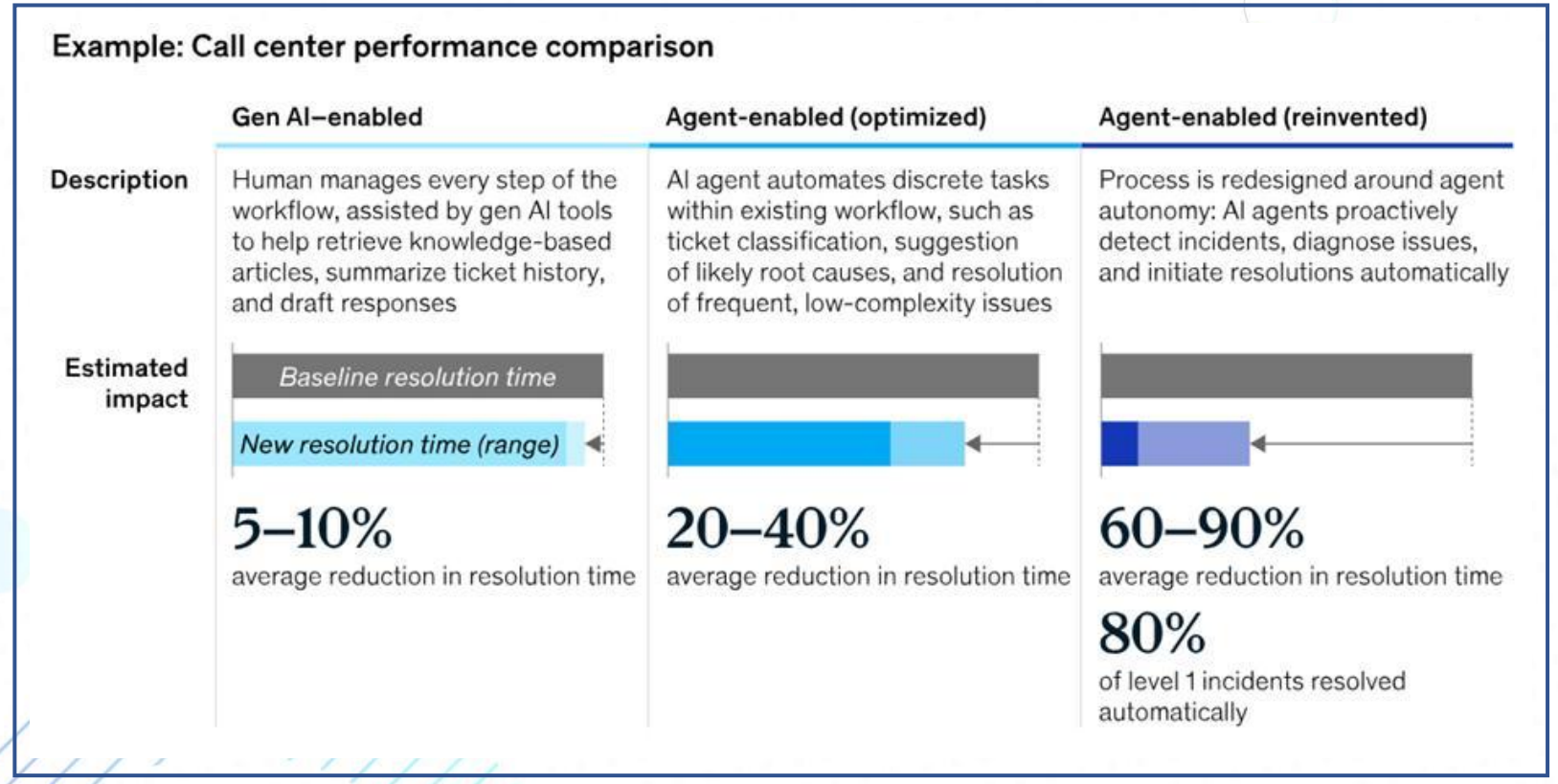
In-process monitoring and incident management: Ability to detect potential anomalies and address with little human interference

Production Planning, procurement: Ability to pre-screen, summarize and extract clauses of interest across contracts, assess risks

Health Safety: Ability to create training videos, proactive identification of potential risks and incorporating CAPA

*** Examples, not exhaustive**

The likelihood of adoption of next generation technologies is directly linked to their ability to enable *process reinvention*



Source
https://www.mckinsey.com/capabilities/quantumblack/our-insights/seizing-the-agentic-ai-advantage

Examples of process reinvention in Pharmaceutical Operations

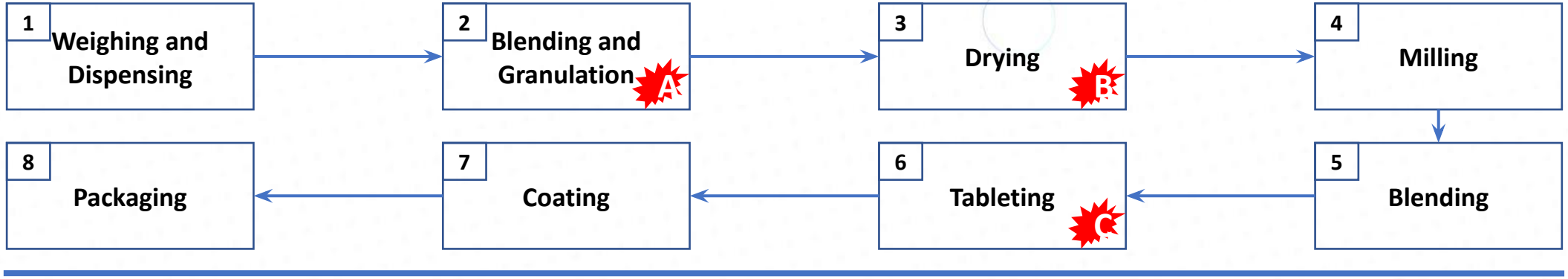
Manufacturing reinvented: Enabled by Agentic AI and multi-agent orchestration, ability to make adjustments within the design space, as required, 100% quality assurance of finished product

Analytical methods reinvented: Completion of design, execution, validation without human interference

Quality and Regulatory reinvented: Completion of design through submission of ANDA documents, including the ability to identify gaps, initiate and execute process workflows to close gaps

Manufacturing reinvented in the context of three examples

Tablet Formulation: Cases include issues in ambient conditions, machine malfunction, quality of excipient



Scenario A
Granulation is impacted due to input air temperature and humidity, resulting in OOS of PSD; objective is to obtain a final blend with optimal PSD

Scenario B
Malfunction of the dryer, inability to attain required LOD in the prescribed drying time

Scenario C
Excipient (binder) quality issues leading to hardness / friability problems

Manufacturing reinvented in the context of three examples

Tablet Formulation: Cases include issues in ambient conditions, machine mal-function, quality of excipient

Scenario A

Granulation is impacted due to input air temperature and humidity, resulting in OOS of PSD; objective is to obtain a final blend with optimal PSD

Options to address the issue

- Alter granulation conditions to rectify particle size
- Adjust milling conditions to compensate
- While altering or adjusting with the design space, study the impact on other properties such as moisture, compressibility
- Orchestrated by autonomous agents, pick the most optimal correction option

Scenario B

Mal-function of the dryer, inability to attain required LOD in the prescribed drying time

Options to address the issue

- Extend drying time within the design space
- Study the impact of higher moisture on compliance and on quality; if unacceptable, abandon process
- Communicate downstream for further planning and scheduling

Scenario C

Excipient (binder) quality issues leading to hardness / friability problems

Options to address the issue

- Predict / calculate impact on other attributes such as dissolution, disintegration before proceeding or abandoning the batch
- If proceeding:
  - Alter tableting speed, within the design space
  - Alter coating conditions, within the design space

US FDA's Draft Guidance on the use of AI: Practical implications*

Among various computational models used in the drug product life cycle, this guidance focuses on the use of AI models to produce information or data intended to support regulatory decision making regarding safety, effectiveness, or quality for drugs.

https://www.fda.gov/media/184830/download

1 Define the question of interest	2 Define the context of use (COU)	3 Assess the AI model risk	4 Develop a credibility plan for the model	5 Execute the plan	6 Document results, discuss deviations	7 Determine model adequacy for COU
Guidance: The question of interest should describe the specific question, decision, or concern being addressed by the AI model. **Scenario A question**: Does the granulation end product produce granules per established PSD? If not, will the model address corrective actions?	**Guidance**: The COU should describe in detail what will be modeled and how model outputs will be used. It should also include a statement if other information will be used in conjunction with the model output to answer the question of interest **Scenario A COU**: The model will solely determine PSD. The model will provide options to the operator for corrective actions.	**Guidance**: Risk is based on decision consequence and model influence **Scenario A risk assessment**: Impact of incorrect PSD would be high on product quality. Though the model is entrusted with determining appropriateness of PSD, the operator in the loop takes a final call on options. Therefore, the model risk for this COU could be treated as medium.	**Guidance**: ***Sharing the plan with Agency*** – Multiple options, discussed separately ***Credibility plan*** – Model description and development including training data sets and training methodology, Model evaluation **Scenario A credibility plan**: That the chosen example here is a model of medium risk, granular details of development and evaluation, including the human involvement will be evaluated	**Guidance**: Interaction with the Agency is encouraged for thoroughness of the credibility plan and the timing of activities included in the plan **Scenario A plan execution**: That the model aims to determine PSD and also determine corrective actions, strict adherence to the agreed credibility plan will be expected; as part of execution, document challenges and means to circumvent or address those	**Guidance**: Document the results of the credibility assessment plan and any deviations from the plan. **Scenario A results and discussion**: This is an opportunity to refine the plan and share findings which may determine the adequacy of the model (next step)	**Guidance**: Based on the results recorded in the credibility assessment report, a model may or may not be appropriate for the COU **Scenario A model adequacy**: Discuss findings and seek approval or pursue alternative appropriate next steps

*** Scenario A from the examples discussed earlier**

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Development and Discussion of Credibility Plan with the Agency: Life Cycle Management and Early Engagement

Life Cycle Management

- Life Cycle Maintenance should be made available for review as a component of the manufacturing site's pharmaceutical quality system, with a summary included in the marketing application such as the ANDA
- With increased product and process knowledge, Sponsors may propose model-related elements to be considered established conditions, along with a plan to manage changes to these established conditions over the drug product life cycle

Early Engagement

- Formal meetings: Initial Targeted Engagement for Regulatory Advice (INTERACT), Type C meeting
- Other meetings: Digital Health Technologies (DHTs) Program, CDER's Emerging Technology Program (ETP) and CBER's Advanced Technologies Team (CATT)

Happy to answer questions!