EMA /US FDA Workshop on

support to quality development in early access approaches

Innovative validation

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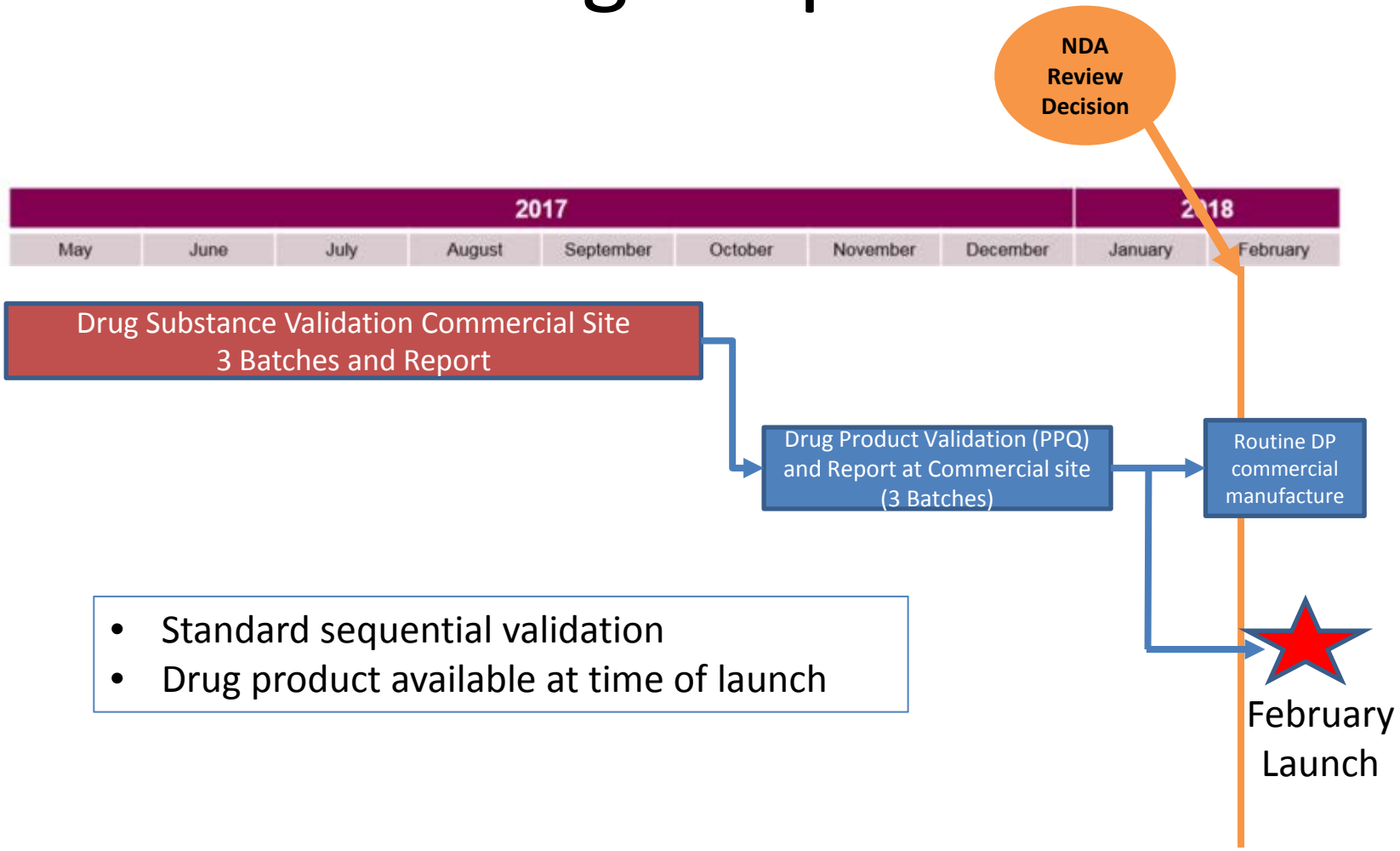
Scenario

- In-licenced product, brought into AstraZeneca late in development
- Shown to have great potential, particularly in niche indication
- AstraZeneca planned an NDA submission at the end of June 2017 with an expected Priority Review.
- Based on standard timings, approval was expected late January 2018.
- Drug Substance and Product validation was planned to ensure launch in February 2018
- At pre-NDA meeting FDA suggested AstraZeneca submit a request for BreakThrough Therapy Designation in parallel with NDA .

Original plan



- Standard sequential validation
- Drug product available at time of launch

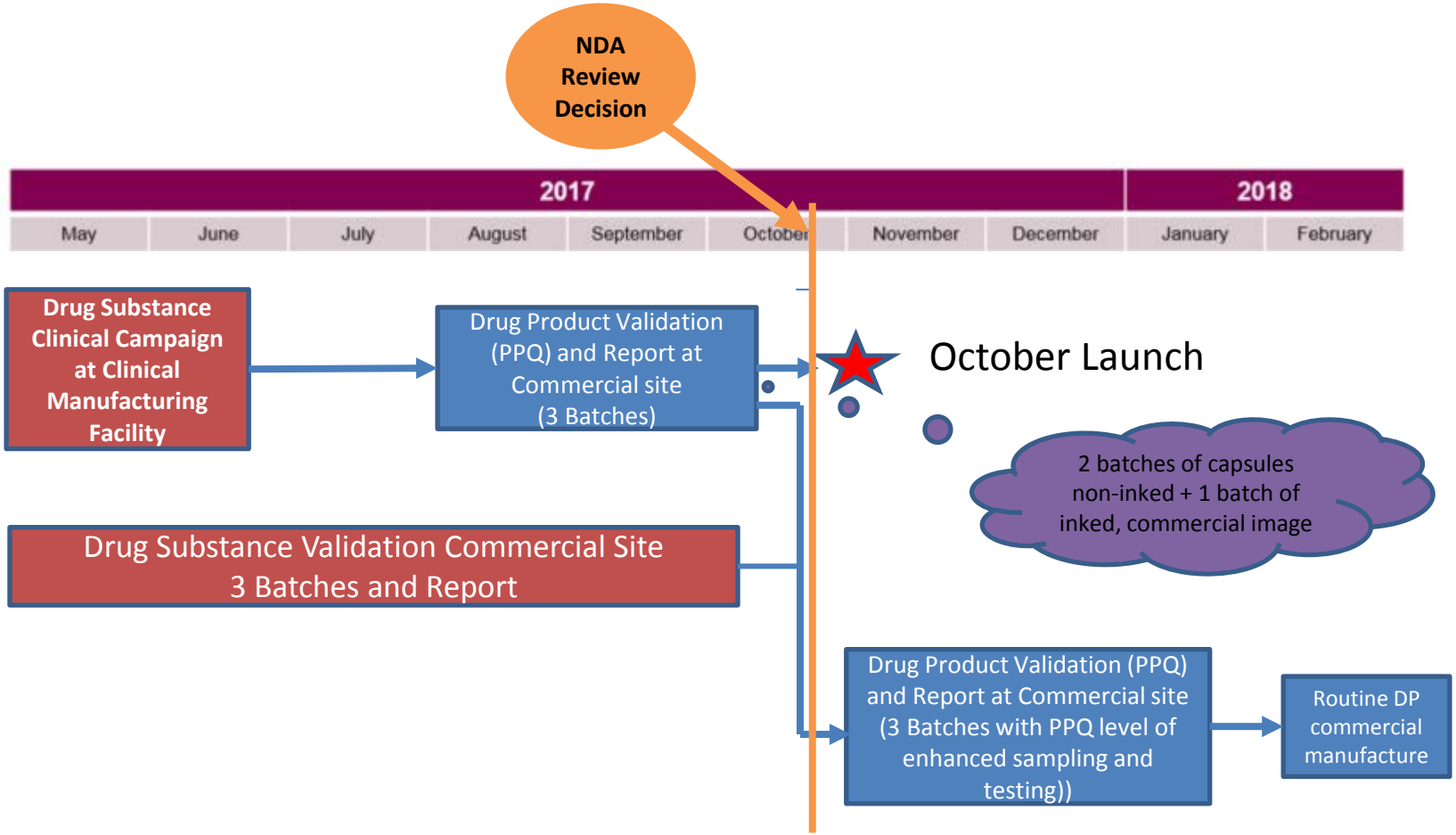
Breakthrough Designation

- NDA was accepted in early August with Breakthrough Designation AND priority review.
- FDA indicated that their review would be complete by late September
- This meant a gap to supply of around 4 months!

- Real “Good news/Bad news” scenario!

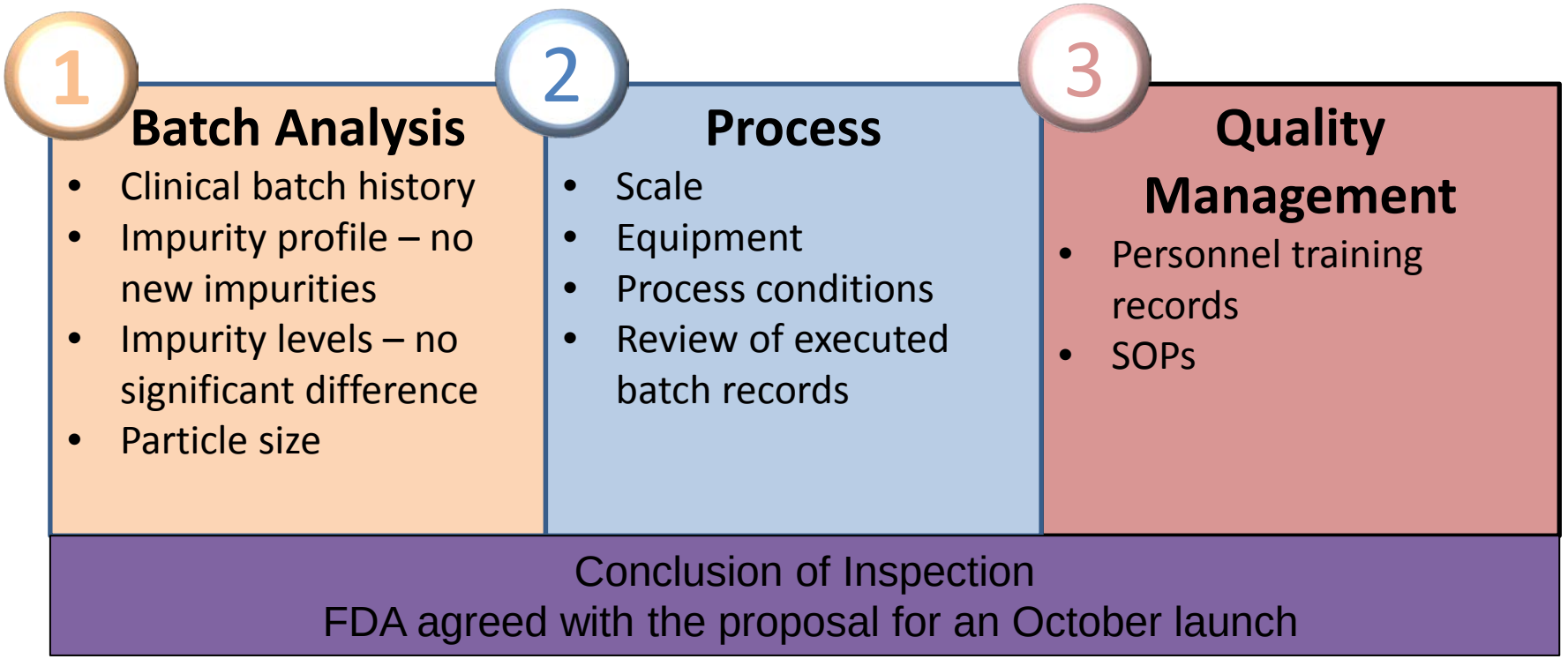
- Briefing Document and Type A meeting request submitted to FDA 7 August.
- FDA granted a meeting on 17 August, 10 days after meeting request.
- All parties focussed on finding a way to get product to patients and meet quality objectives
- Lots of information provided up front to enable an informed discussion

Revised Plan



Review & Inspection Engagement

- Batch Data & some executed batch record sent to FDA in advance of inspection
- Clinical and Commercial facility – same campus facilitated inspection



Keys to Success

- Focus on the patient
  - Clear to everyone that the patient had to come first
- Sound science and balanced risk basis for proposal
  - Clear comparability in the quality systems and quality management applied at the various sites
  - Clear similarity between the products manufactured at the various sites
- Engagement of Multiple Stakeholders
  - Timely interactions with agency to discuss this issue
  - Access to information in advance of inspection
  - Reviewers, inspectors, subject matter experts and site quality were able to have open and engaged discussions throughout the process, particularly during the inspection

…even better if

- So much of the basic guidance on this is common between regions
- The risk/benefit ratio for innovative proposals to meet quality challenges isn't region dependent change
- Maybe multiple stakeholders should also include multiple agency involvement?
- Greater cooperation between agencies and the applicant could facilitate greater and faster access for patients to these cutting edge therapies

Conclusion

- Maintaining focus on supplying the patient is key throughout the process of securing valid product supply
- Solid science and balanced risk-assessments need to underpin any innovative validation approach
- All stakeholders need to engage openly throughout the development to ensure that all information is discussed in a balanced and critical manner
- Because of shortened timelines and potential for complex proposals, it is vital to recognise the value that multiple stakeholders can bring to the inspection and assessment of new products
- Guidance exists to facilitate all this, though the extent to which this might be obviously applicable to accelerated developments may need clarification

Backups

Outline of Proposal made to FDA

- Proposal to FDA for October Launch
  - Validate Drug Product at the commercial facility with clinical drug substance
  - Validation to include 3 batches – 2 non inked + 1 inked, commercial image.
  - Use the 1 inked batch manufactured with clinical drug substance for launch.
  - Perform enhanced sampling and testing of subsequent 3 batches using validated drug substance manufactured at the commercial facility

- Supporting information to back-up proposal
  - Comparison of DS Clinical and Commercial Facilities and Equipment.
  - Discussion of minor process differences used at 2 facilities
  - Comparison of batch analysis drug substance - Batch history 13- batches, proposed clinical batch for validation, an early pre-validation batch from commercial facility
  - Critical assessment of Drug Product manufactured with drug substance from 2 facilities (blend uniformity, capsule weight uniformity, content uniformity, dissolution) to show equivalence

Key to Success – Sound Science & Risk Assessment

- Process validation takes place on a background of sound science and risk-based assessment

  "The approach to PPQ should be based on sound science and the manufacturer's overall level of product and process understanding and demonstrable control. "

  "As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes"

- Demonstration of a sound scientific basis and balanced risk assessment should always be the cornerstone to acceptable process validation rather than a predetermined number of batches

Key to Success – Engagement of Multiple Stakeholders

- The engagement of multiple stakeholders during inspection and review helped to ensure an open dialogue on risk
- This was initiated by open discussions on the problem and possible solutions
- In this case, the need for a product specific pre-approval inspection facilitated this engagement and increased the speed with which issues could be resolved
- Mechanisms also exist in the EU for this kind of interaction, to some extent

Key to Success – Engagement of Multiple Stakeholders

- Community Inspection Procedures allow for product inspections for
  - the verification of compliance to GMP
  - the verification of adherence to details in the Module 3
- Also allows for the involvement of assessor in these inspections “In certain circumstances…”
- Little or no mention of the involvement of the applicant in this
- In an accelerated framework, this could be expanded to facilitate multiple party involvement in the review
- Minimises the likelihood of a “for cause” request for inspection from the assessor which could delay approval and supply of product to patients