Industry Experience with Quality Post-NOC Changes (Pharmaceuticals)

Dean Callaghan

CMC Manager, Regulatory Affairs

AstraZeneca

CAPRA Symposium March 1, 2010

AstraZeneca

Agenda

- Overview of Change Management
- Post-NOC Changes – Quality Document
- Experiences and Challenges

AstraZeneca

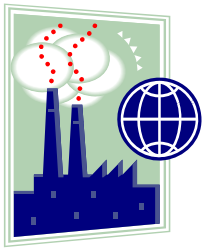
Change Management

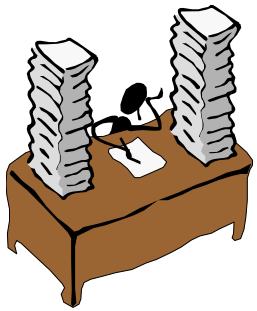
Change can come:

- Internally e.g. supply critical changes, manufacturing changes, site changes, etc.
- Externally e.g. pharmacopeial, regulatory authorities

Overview of Change Management in AstraZeneca

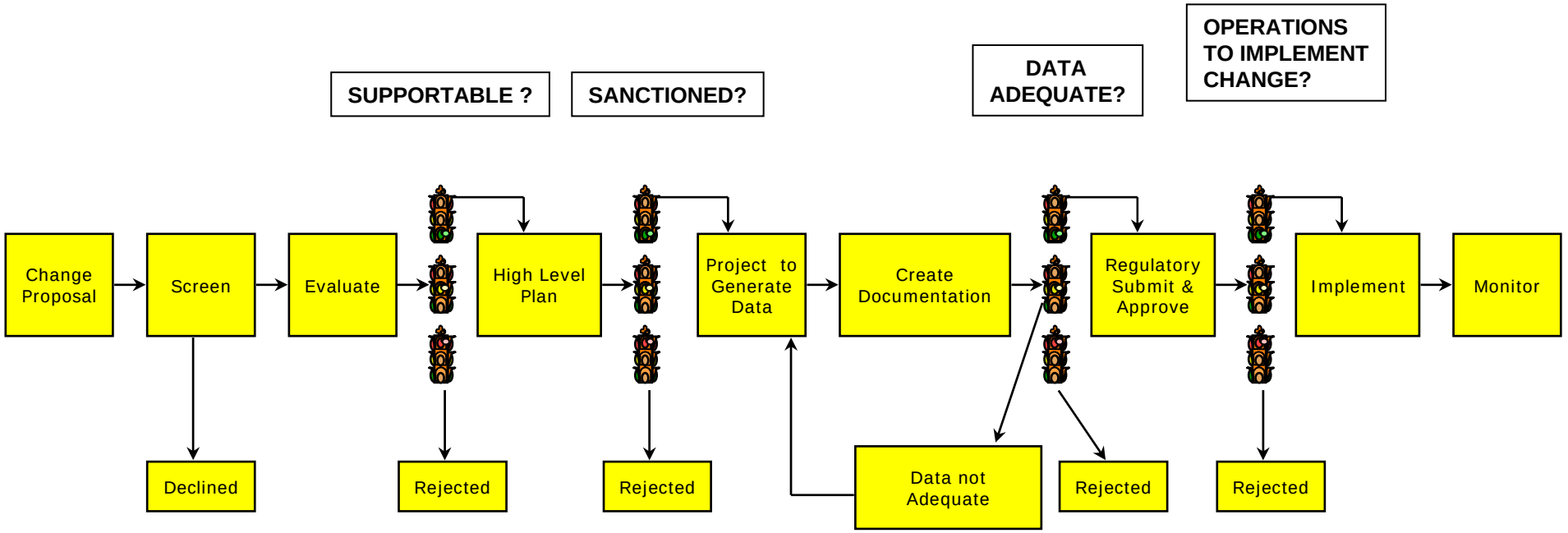
- Managing supply for well over 100 markets
- Tracking requirements and status of changes in each market
- Ensuring product meets local regulatory requirements





AstraZeneca

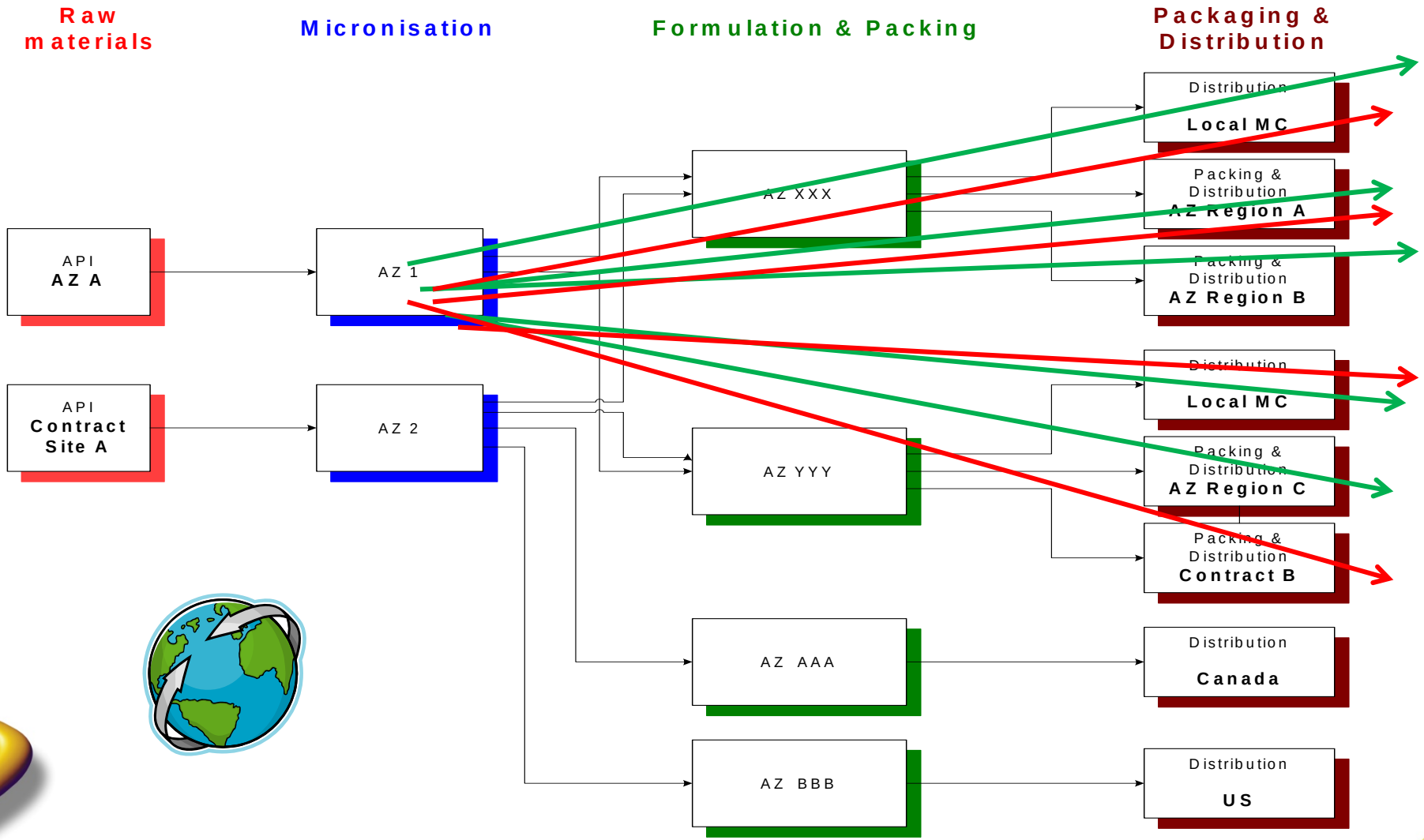
Change Management



AstraZeneca

Change Management

Supply Chain

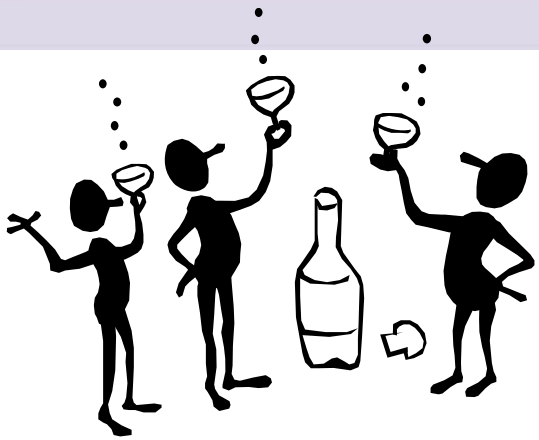


AstraZeneca

Change Management

Keys to Regulatory Success

- Proper assessment of type of change
- Appropriate supporting data
- Harmonized data package
- Accurate forecasts for approvals
- Assessment / mitigation of risk



AstraZeneca

Post-NOC Guidance

- 1994 Changes to Marketed New Drugs Policy
- January 2005 Notice (Drug Substance)
- July 2006 Screening Requirements for NC
- First Draft – 2007/03/16
  - Comments due June 2007
- Second Draft – 2008/12/02
  - Comments due January 2009
- Final Version
  - Adopted - 2009/09/02
  - Effective - 2009/09/30

Post-NOC Guidance

- Transparency
  - Opportunities for comments
  - Summary of comments available
- Harmonization
  - Definitions/Categories, ICH
- Modernization, Scientific, Risk-based approach
  - QbD, Design Space
- Implementation Period

Overview – Quality Changes

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Replacement or addition of a manufacturing site and/or manufacturer involving:			
a. production of the starting material, intermediate, or drug substance	None	1-6,8-9	Supplement
	3,5	2-6,8-9	Notifiable Change
	1-5	3-6,8	Annual Notification
b. testing (e.g., release, stability)	None	2-5,7,8	Notifiable Change
3. Deletion of a manufacturing site or manufacturer for the starting material, intermediate, or drug substance	None	None	Annual Notification

Conditions

1. No Level I or Level II changes in the drug substance specifications.
2. No change in the route of synthesis, physical characteristics, and impurity profile of the drug substance (that is [i.e.] no new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within ICH limits).
3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment of viral safety data or TSE risk assessment is required.
4. The change does not concern a sterile drug substance.
5. The change concerns drug substances that are discrete chemical entities (i.e. this does not include polymeric complexes).

Supporting Data

1. (1,5) Viral safety data (ref. Condition 3) or supporting or comparative bioavailability data (ref. Condition 5) (whichever is applicable to be included in CTD modules 1&5).
2. (1.2.5) For sterile manufacturing, evidence of GMP and/or EL information (e.g. Confirmation of a satisfactory GMP rating by the Inspectorate), and process validation and/or evaluation studies for sterilization.
3. (S) Updated or new DMF (with a Letter of Access provided in Module 1), any relevant drug substance information should be provided where available.
4. (S.2) Confirmation that the synthetic route, process controls, control of materials, and specifications of the intermediate or drug substance (as appropriate) in the manufacturing process of the proposed drug substance are the same as those previously approved or revised information if any of the attributes have changed.
5. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and testing.
6. (S.2.3) For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from

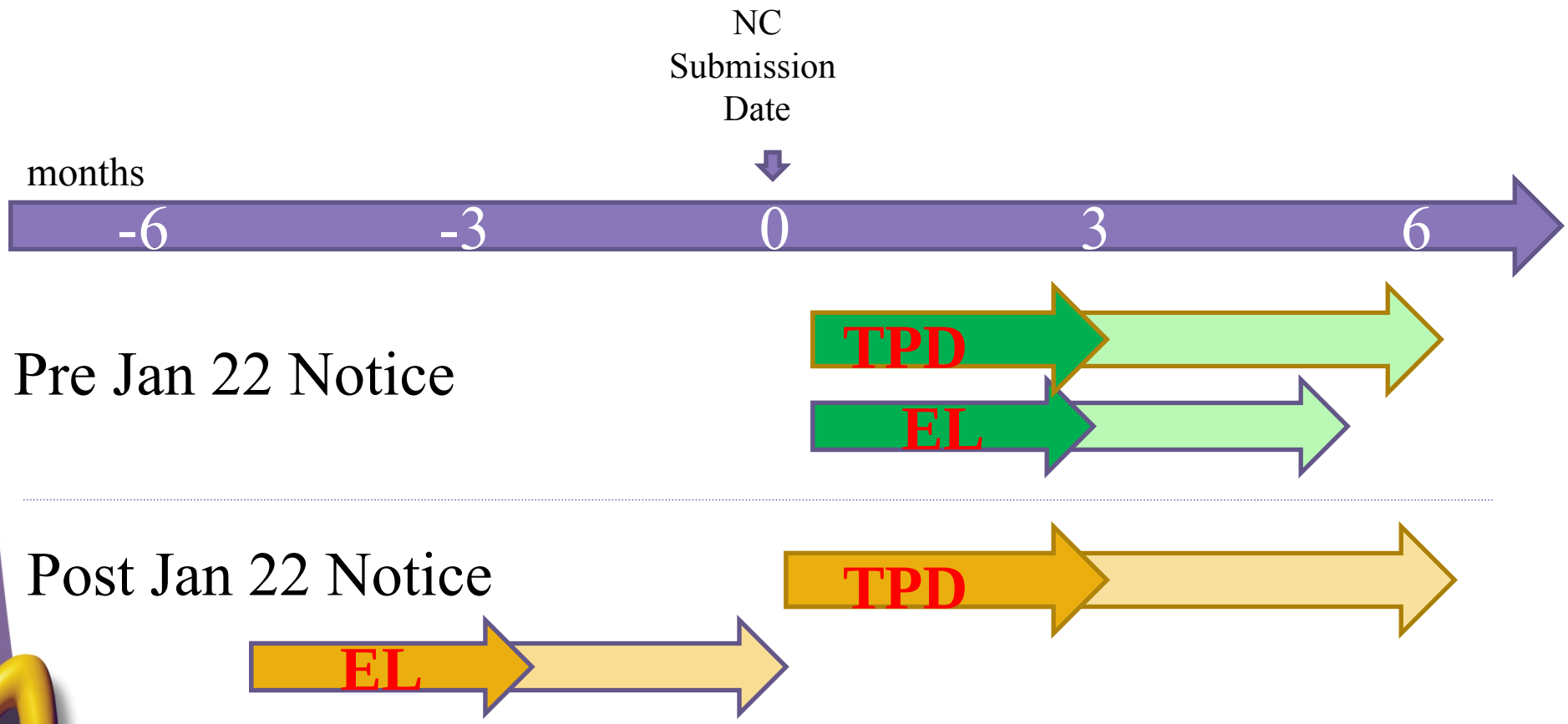
- Provides guidance on what reporting category a change should be classified as, based on conditions, and what supporting documentation is required

AstraZeneca

Experiences and Challenges

- Positive Feedback
  - Transparency, global proof of requirements
- Target date for Notifiable Changes
  - From 90 day default to 90 day target, ↓ predictability
  - Backlog at BPS, ↓ planning and patient supply
  - Options for Supply chain critical changes?
- EL Information
  - (1.2.5) For sterile manufacturing, evidence of GMP and/or EL information (e.g. Confirmation of a satisfactory GMP rating by the Inspectorate)
  - Jan 22 Notice – GMP required at time of submission
  - Substance vs. Product, MRA vs. Non-MRA
  - With backlog and EL requirements, test site change could be ~1 year

Experiences and Challenges
Establishment Licence



Experiences and Challenges

- Certificates of Suitability (CEP)
  - "At this time, the use of the Certificate of Suitability (CEP) issued by the EDQM in support of changes to the drug substance is under review in pharmaceuticals"
  - Potential to help with backlog
- QbD and Design Space
  - Incorporated comments
  - Bridging between pre and post approval
  - Harmonization
  - More experience required
- Opportunity for discussion, justification of alternative supporting documentation

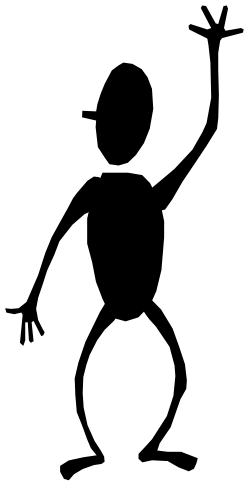
Conclusions

Keys to Regulatory Success

- Proper assessment of type of change
- Appropriate supporting data
- Harmonized data package
- Accurate forecasts for approvals
- Assessment / mitigation of risk

AstraZeneca

Thank You



AstraZeneca