The opportunities and challenges for the implementation of ICH Q12 from an AstraZeneca perspective
How big an issue is lifecycle management for AZ?

BIG and getting BIGGER!

Requiring approval before implementation

2018 CMC LCM

Notifications, do and tell changes, low risk

Why do we spend so much time doing so much work to mitigate so little risk?
Reminders…

Q8 Suggestion
“…This guideline also indicates areas where the demonstration of greater understanding of pharmaceutical manufacturing science can create a basis for flexible regulatory approaches”

Q12 Objective
“..enhance industry’s ability to manage CMC changes effectively under the firm’s PQS with less need for regulatory oversight prior to implementation”

This is about using our understanding (as envisaged under Q8) to effect more risk assessment in the management of change and allow the industry to innovate through life-cycle
The problem with Q8…

Demonstration of product knowledge

Typical agency question: “Please specify your normal operating range (NOR) in 3.2.P.3.3.”

Having declared this, how do we manage this parameter?
The opportunity with Q12…

Demonstration of product knowledge

- Normal operating range stated openly
- Risk assessment leads to clear classification of this as EC or not (in PLCM)
- Agreement with reviewer on how with will be managed during lifecycle
- Useful for clarifying risk designation for deviations
Opportunities from Q12 for AstraZeneca

• A positive way to leverage our scientific approach to development into simplified lifecycle management enabling continuous product improvement

• Clarity & Consistency for change management
  – Agreement on established conditions (ECs) resulting from development data and risk assessment
  – Agreement on the management of ECs
  – Opportunity to leverage the PQS to implement changes and take these off the critical path
  – Encapsulate this in one document (PLCM) in order to help simplify change assessment and facilitate inspections

• Increase business focus on changes that truly matter, rather than those with little risk to patients
Challenges on implementation (internal)

- Skepticism from stakeholders
  - We invested heavily in “QbD” and returned little “flexible regulatory approaches”
  - Will this result in more or less confusion
  - Unclear what the “look and feel” of this will be
  - What about international?

- Needs a change in mindset from our stakeholders
  - Changes based on risk assessment and reference to PLCM
  - A move away from Module 3 being “the source of truth”

- Potential for divergence between similar products
  - Could be different process and product knowledge for similar products
  - Similar life-cycle changes could, therefore, have different classifications
Challenges on implementation (CMOs)

The management of Contract Manufacturing Organisations could lead to issues

**Conservative**
- They have to manage a diverse range of contract givers leading to potential for diverse approaches to risk and LCM
- They have increased inspection frequency, greater potential for issues to be raised
- Not always part of the original development so not aware fully of the history
- Different appetite to risk – can be lower because of the potential impact on multiple other clients

**Control**
- Working under a different PQS
- Communication
Challenges on implementation (external)

• Clarity and Consistency
  – Will we have a similar view on Established Conditions and management of these between agencies?
  – Will agencies start to want more “defence”?  
  – How will we manage this if we cannot achieve the same view?
    • We already have this to some extent with specifications
    • This will require similar thinking, but over a wider scope

• How do we move this thinking forward in the non-ICH world?
  – The utility of Q12 is significantly impaired if there is no acknowledgement of this elsewhere
  – Implementation of LCM changes may be impaired to meet non-ICH country requirements
  – “reference country approval” will be difficult to overcome may be a need to open our agreements with other agencies
Challenges on implementation (external)

- GMP Inspection now a norm from multiple international agencies
  - Focus is on the PQS and the management of changes
  - Increasing scrutiny of this in the context of filed information
  - Will there be issues caused by our use of “established conditions” and risk based concepts not fully endorsed in international?
Big Question - Where is Module 3 in all of this?

- Initial basis for approval
- Contains all background information supporting EC classifications
- Source of reference for PQS documents
- Source of reference for inspections
- Will be updated independent of ongoing regulatory submissions (non EC updates) in line with PQS changes

MOD 3

- Pivotal document for LCM
- Agreed ECs & change classification, PACMPs, commitments etc.
- Source of truth for regulatory impact assessment
- External source for LCM

PLCM

Is this necessary?
ICH Q12 is gathering momentum– FDA Pilot

• FDA issued a request for participation in their “Established Conditions Pilot Program”
• AZ are looking to engage with this as a way of:
  – Seeking a better understanding of how to frame change management in a Q12 context with the agency
  – Having a view on the Agency’s “red lines” around this topic
  – Being in a position to validate some of our thinking and use that for further discussion/engagement internally and externally

First we need clarity on how to approach this, and then we can strive for consistency of review!
ICH Q12 is gathering momentum– Changing Thinking

• Even in draft form Q12 is starting agencies thinking about the lifecycle management of drug products
  – Review of the Japanese application form
  – WHO initiatives & role of “reference country”
  – Informing thinking on accelerated development and lifecycle management
  – Prompting drafting of new guidances (e.g. FDA’s established conditions draft guideline)
  – Lots of discussion!
Next Steps for AstraZeneca

• Internally
  – Sell, sell sell!
  – Remain positive and help our internal stakeholders understand how Q12 can help us

• Externally
  – Be part of the pilot and use this to enable dialogue
  – Look to how we can pre-position Q12 in our filings
  – Actively promote this thinking where we can
Ultimately, we need to be positive…

…Rome was not built in a day
…neither with ICH Q12!

It will take time to get this right, but it’s time worth spending.