Case Study: FDA ANDAs and legacy QbD approach

Overview

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Generic Drug development

- ANDA Portfolio
  - Temozolomide is IDT's first proprietary generic product
  - First in a portfolio of 24 approved US specialty generic drugs
- **Fundamental** and **transformational** change to the IDT strategy, business and prospects

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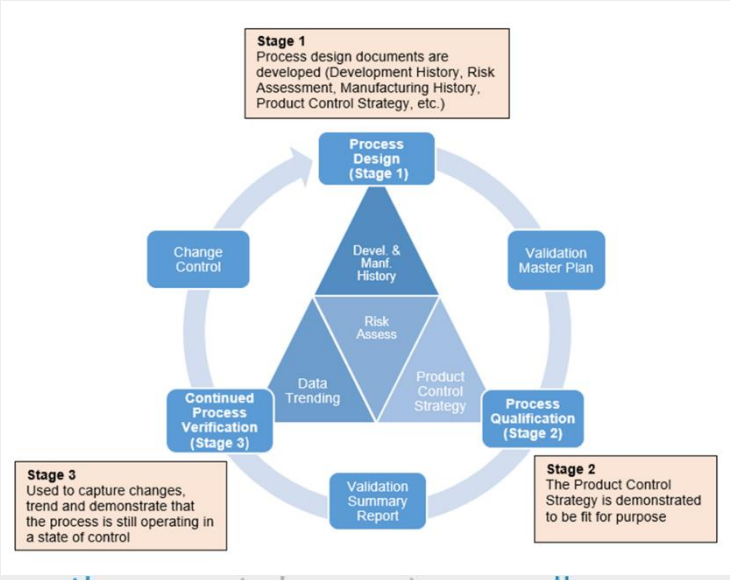
Decision to use QbD approach

- Process Validation a must
  - Ensuring processes are capable of repeatedly and reliably producing a finished product to required quality.

- IDT decision for risk based approach. IDT are implementing the 3 Stage approach which involves QbD in the first stage (Process Design)

- Three Stage Validation Lifecycle approach:
  - **Process Design**
  - **Process Qualification**
  - **Continued Process Verification**



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Case Study 1 - Temozolomide

- Temozolomide is a cytotoxic product used primarily in the treatment of glioblastoma multiforme and refractory anaplastic astrocytoma.
- Capsule product developed
  - 5mg, 20mg, 100mg, 140mg, 180mg and 250mg
  - some presentations share the same blend (more in each capsule)
  - some share the same capsule size (different colours)
- Registered (FDA) in November 2013
- Approval received April 2016 - launch activities underway
- Partnership with Mayne for US distribution

Case Study 1 - Temozolomide

- PV Stage 1: Process Design
  - The development of Temozolomide centres around eight major processes:

  - Process steps impacting a Critical Quality Attribute (CQA) of the product were ascertained, followed by risk assessment on process manufacturing steps to determine Critical Process Parameters (CPP). This was based on pilot scale and engineering batches and exhibit batches for initial submission.
  - Understanding the product and process enables a Product Control Strategy
- Commitment not to progress to Stage 2 PV until Stage 1 understood, therefore determining number of batches

Case Study 1 - Temozolomide

- PV Stage 2: Process Qualification
  - Launch stock used for validation to minimise wastage
  - Matrix approach developed based on learnings from Stage 1
  - Use of similarities and differences to produce an efficient and effective validation set

Strength	PV requirements - Blending	Size of capsule	PV requirements - Encapsulation	Pack sizes (number capsules in amber bottle)	PV requirements - Packaging	
					Capsule count	Capping/Labelling
5 mg	3 batches[1]	3	2 batches[2]	5 & 14	4 packed batches for 5s & 14s	3 batches (total)
20 mg	1 batch[1]	2	1 batch[2]	5 & 14	2 packed batches for 5s & 14s	
100 mg	4 batches	1	4 batches (1 each strength)	5 & 14	4 batches (both formats to be captured)	
140 mg		0		5 & 14		
180 mg		0		5 & 14		
250 mg		0		5		

1 Based upon similarities in physical properties of the blend & 5 mg worst case.
2 Based upon smaller capsule size being worst case and lower fill weight having the tighter range. However, all batches will support fill weight control

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Case Study 1 - Temozolomide

- Challenges
  - Internal development so much to learn about the product
  - Need for scale adjustments between PV1 and PV2 due to long approval timeframes
  - Many strengths, expensive materials
  - ‘Optimise rather than compromise’ approach to process validation costs

Case Study 2 - Doxazosin

- Oral medicine used for the treatment of high blood pressure (hypertension) and urinary retention associated with benign prostatic hyperplasia (BPH)
- 1mg, 2mg, 4mg, 8mg tablet presentations
- ANDA acquisition late 2014
- Packing & Distribution partnership with ANI, US market
- API procurement and development in 2015
- FDA Submission (PAS) 2016, expected approval and launch 2017

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Case Study 2 - Doxazosin

- PV Stage 1: Process Design
  - Development to ascertain critical process parameters such as blending time, material order of addition, blending speeds, storage temperature, compression machine speeds etc
  - Product Control Strategy including incoming controls such as raw material specifications
  - Testing of Critical Quality Attributes such as blend uniformity, tablet appearance, tablet weight, friability, hardness
  - AQLs were set for defect types such as capped tablets, broken tablets, colour variation, specks, chips, mottling etc.
- Results linking into PV Stage 2 which will be conducted on launch stock

Case Study 2 - Doxazosin

- Challenges
  - Tech transfer package yet limited tribal wisdom
  - Development still required
    - Stage 1 PV still critical in understanding critical aspects of local process
  - Packing partnership, shared process validation
  - Management of changes
    - Optimisation now versus post approval
    - Context of future scale-up

Case Study 3 - Pindolol

- Oral medicine indicated for the management of hypertension
- Tablet 5mg and 10mg presentations
- CMO partnership
- Distribution partnership with ANI, US market
- API procurement and development in 2016
- FDA Submission (CBE30) 2016, expected approval end of the year

Case Study 3 - Pindolol

- Validation Master Plan (VMP) developed as a governance document detailing IDTs requirements and expectations regarding overall process validation activities. VMP acts as a bridging document for IDT QMS and CMO.
- Overlay of Stage 1 & Stage 2 process validation disciplines across CMO existing practices (eg: justification for ‘3’ batches)

Case Study 3 - Pindolol

- Challenges
  - Integration of VMP with QbD foundations, with CMO not previously adopting this approach
  - Agreement of document review and approval process
  - Limited previous history of product and registered process

IDT where to from here

- Next Steps
  - PV Stage 3: Continued Process Verification
  - Advocating for strong Process Validation disciplines for our products regardless of site of manufacture or packing
  - Investing in Process Validation capability as a core strength for IDT

Thankyou

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