Technical Transfer- A tablet process transfer case study

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4 July, 2016

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What is a technical transfer?

- Technical transfer is about enabling someone else to do what you are able to do using their:
  - facility
  - quality management systems and documents
  - supply chain
  - equipment
  - people
- To transfer a product well you should know its
  - QTPP - Quality Target Product Profile
  - CQAs - Critical Quality Attributes
  - CPPs - Critical Process Parameters

About the project

- Gates foundation donated money for the manufacture and supply of anti-retroviral medicines to Africa
- Aim: To improve on and supply lifesaving medicines to Africa
- Product: 3x Anti-retrovieal tablet products 'Breakline' anti-retroviral tablet
- Objectives:
  - To develop breakline tablets to suit children, adults and the African environment
  - transfer the tablet production process to an African manufacturer

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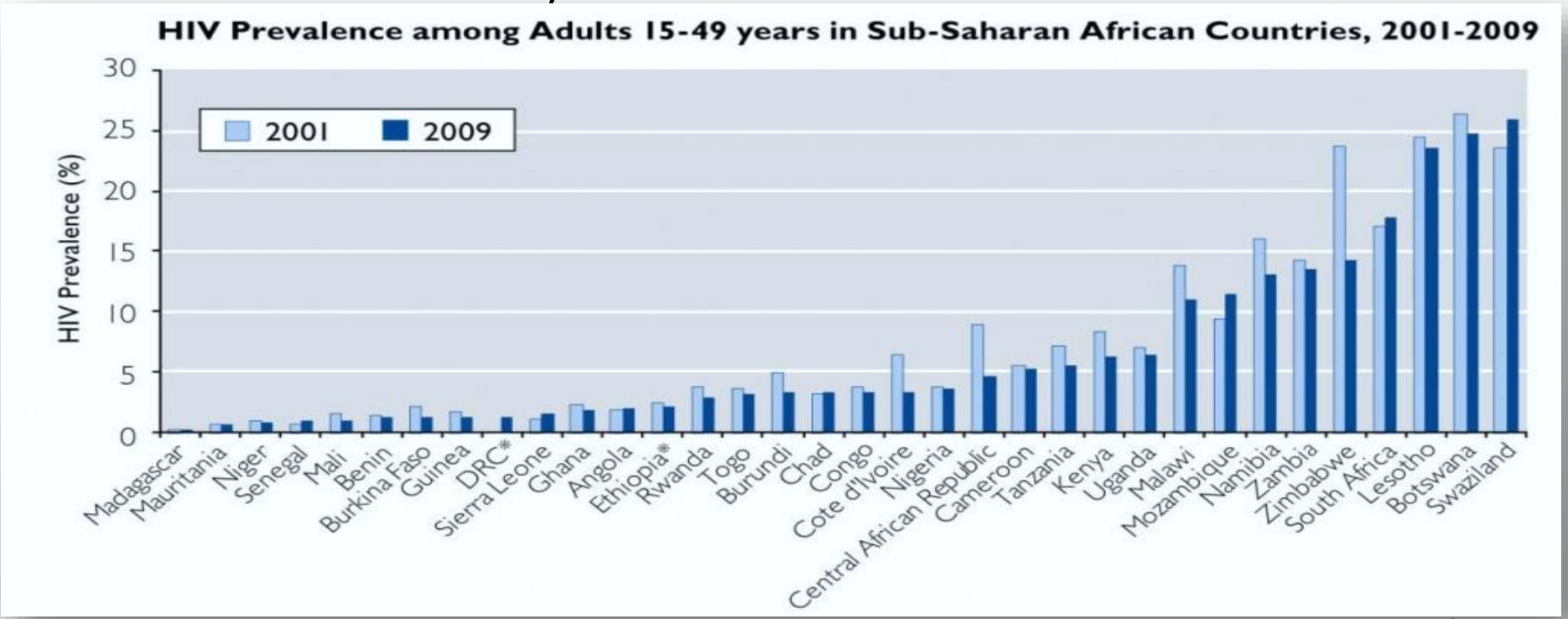
Why is HIV such a problem?

- Life expectancy
- Households
- Healthcare
- Schools and education
- Labour and productivity
- Economic development

Why is HIV such a problem?

- In 2011 over 23.5 million people were living with HIV
  - including 2,300,000 children
- In 2012 over 260,000 children were infected



Quality Target Product Profile (QTPP)

- Product type suitable for Africa i.e. cheap, stable, simple to administer and to distribute
  - ✓ Tablets as a dosage form meets these requirements
- Product design suitable for patients
  - × Existing tablets were not suitable for children (overdose)
  - ✓ Solution - redesign adult dose to be broken cleanly into to two.
- Retain product shape and coding
- Need to minimise falsification, corruption, fraud
  - ✓ Solution - Make product easy to identify, coat red, tamper evident packaging

Direct compression advantages and challenges

Advantages over other types of manufacturing processes

- Cheap
- Fast
- No granulation stage
- Simple process
- Familiar
- Stable
- Taken orally

Technical challenges

- Rely on the ingredients for flow, binding, dissolution, disintegration
- Need good powder flow
- Increased likelihood of post blending segregation
- Dusty

Critical Quality Attributes (CQAs)

Safety **Qu**ality **I**ndentity **P**urity **P**otency (SQUIPP)

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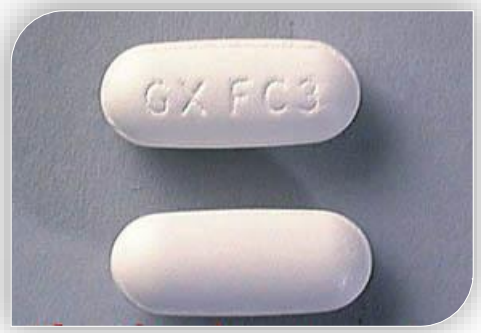
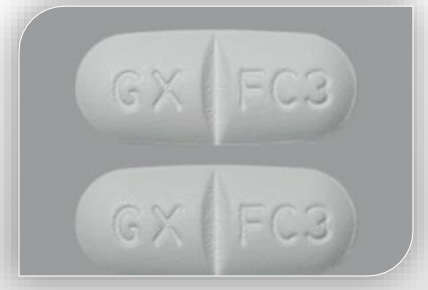
CQA- Tablet design (potency)

For children, tablets were made to be broken





CQA- Tablet design challenges

- internal stress within tablets
- variation of take-off
- likelihood of picking and sticking
- tablet thickness
- complexity of set-up
- variation at press take off point
- weight variation – especially once 'snapped'
- chance of braking tablets

About the direct compression production process

- 1- Dispense and mix API and excipients
- 2- Powder mix compressed into tablets
  - direct as there is no further processing i.e. slugging, granulation, etc
- 3- Tablets coated
- 4- Tablets packaged
- 5- Packaged product distributed

Critical Process Parameters (CPPs) - affect the CQAs

- Lubrication mixing time
- Compression forces
- Compression speed
- Moisture content of blend

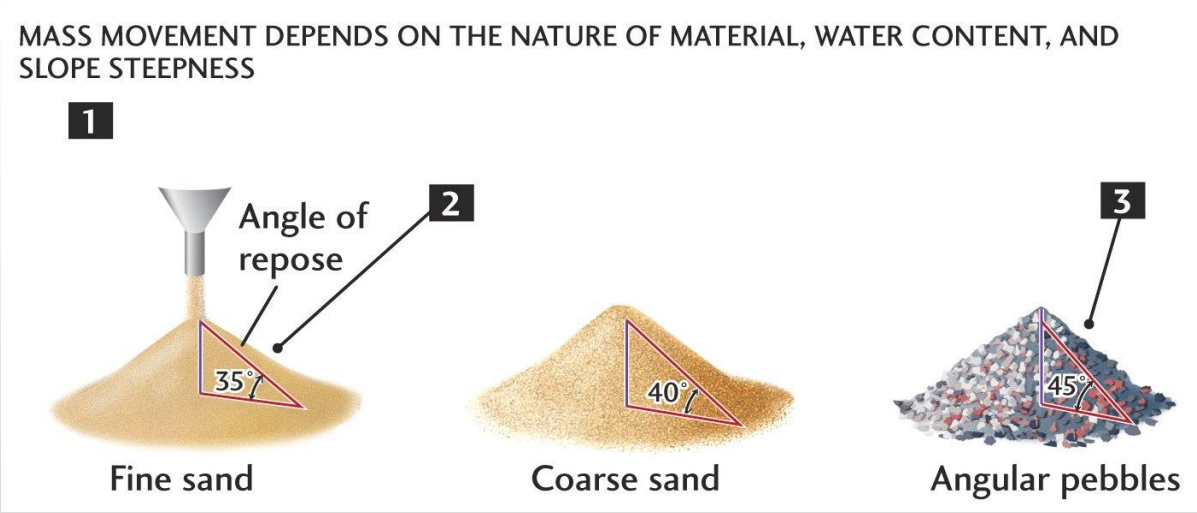
Process challenges to overcome

- ✓ IBC volume changes
- ✓ Powder flow changes
- ✓ Change of compression equipment
- ✓ IPC changes
- ✓ Coating changes

Material change challenges

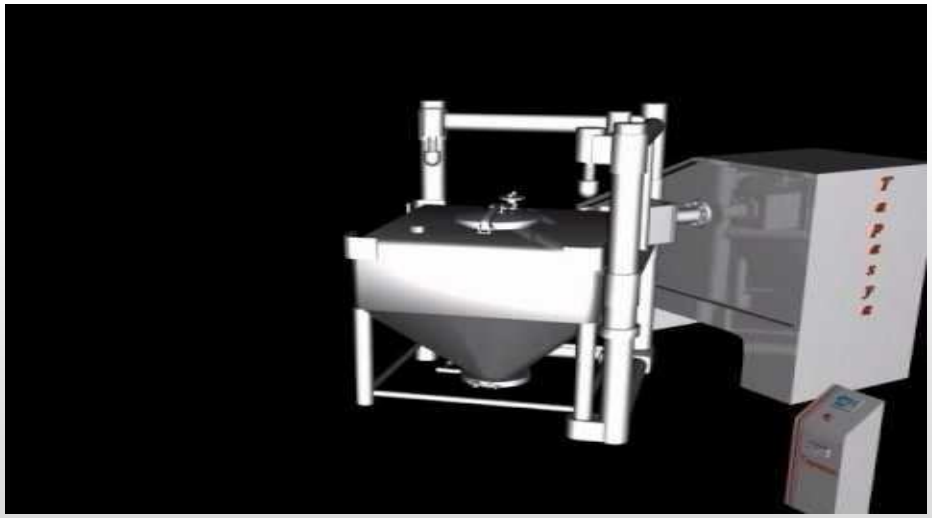
Changes of materials affects powder/product

- physical characteristics
- flow characteristics
- disintegration time
- dissolution profile
- moisture content
- static charge
- thickness (tablet)



Mixing and lubrication challenges

- IBC size affects mixing performance
  - Adjusted using scale up formula
- Blend uniformity testing
  - Chamber testing rods – can't readily test a single tablet dose size
- Determining optimal lubrication time



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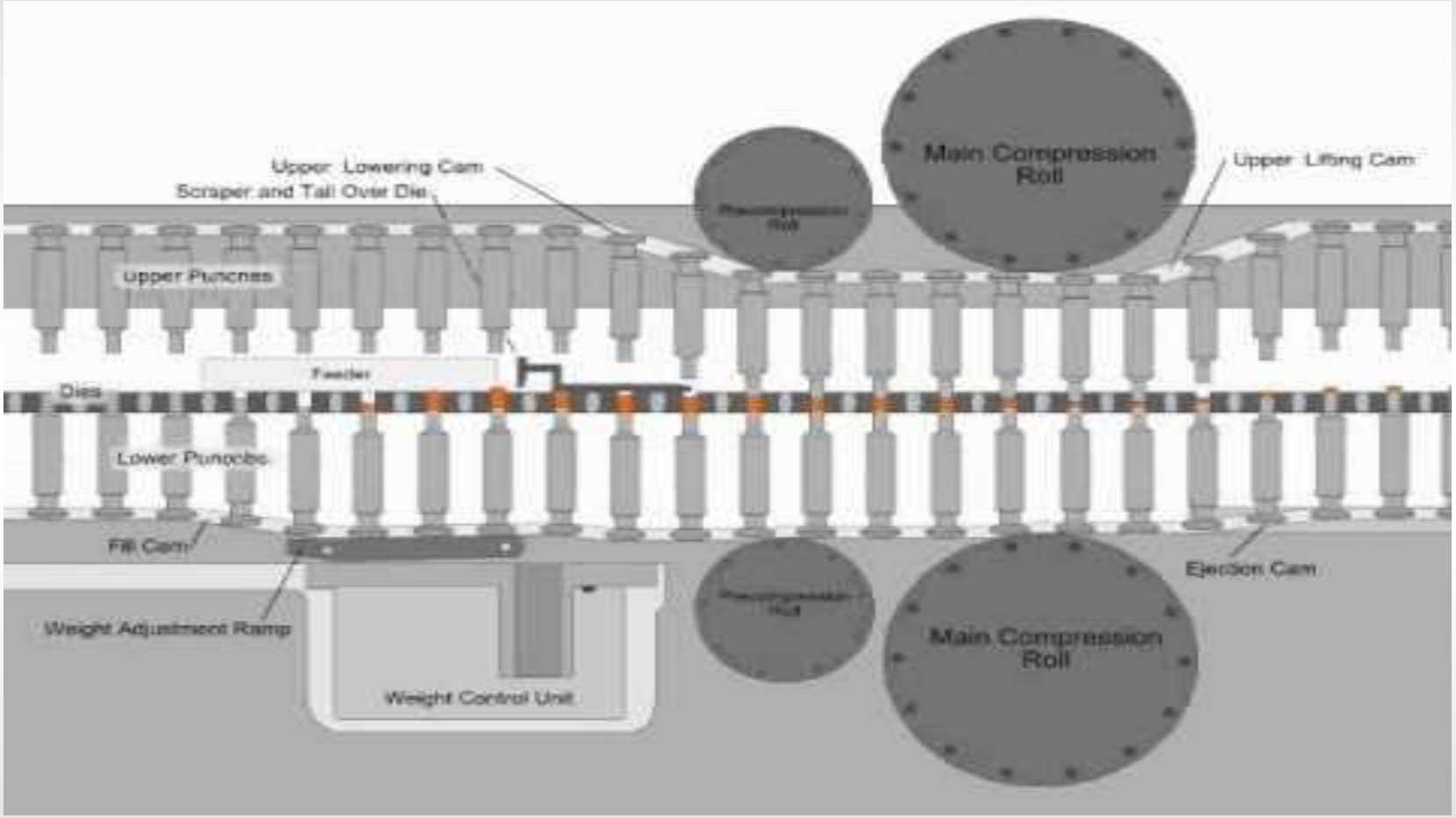
Tablet press animation



Compression challenges

- Significant bridging in drop tube:
  - Vacuum build-up above powder bed
    - vacuum broken using a filter through the IBC's manhole cover
- Drop angle and distance change
- Press change:
  - Tablets jumping out of product shoot
    - Installed a deflection plate
  - Tablet picking
    - Code legible, weigh variation within limits
    - Lettering style changed to reduce future risks

In Process Check (IPC) challenges

- Different start-up process
  - $Target\ fill\ depth = Target\ weight \times (\text{Actual fill depth} \div \text{actual weight})$
- Centralised testing area
  - Not in room testing
- Change in test equipment
  - Harder to compare with original process

Coating challenges

Change in coating machine

- Affects fill volume - Trained staff in gun and baffle setup
- Affects unloading - force applied to tablets during emptying

Change in coating colour

No spray pattern test

Coating challenges

Outcome

- ✓ Adult/Paediatric product transfer successful
- ✓ Product knowledge improved by all parties
- ✓ Cost per batch reduced significantly
- ✓ Corruption risk minimised (red coat)

- ✓ In 2012, over 68% of people with HIV had access to anti-retrovirals

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Thank you for your time. Questions?

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