



Introduction to Just In time Manufacturing

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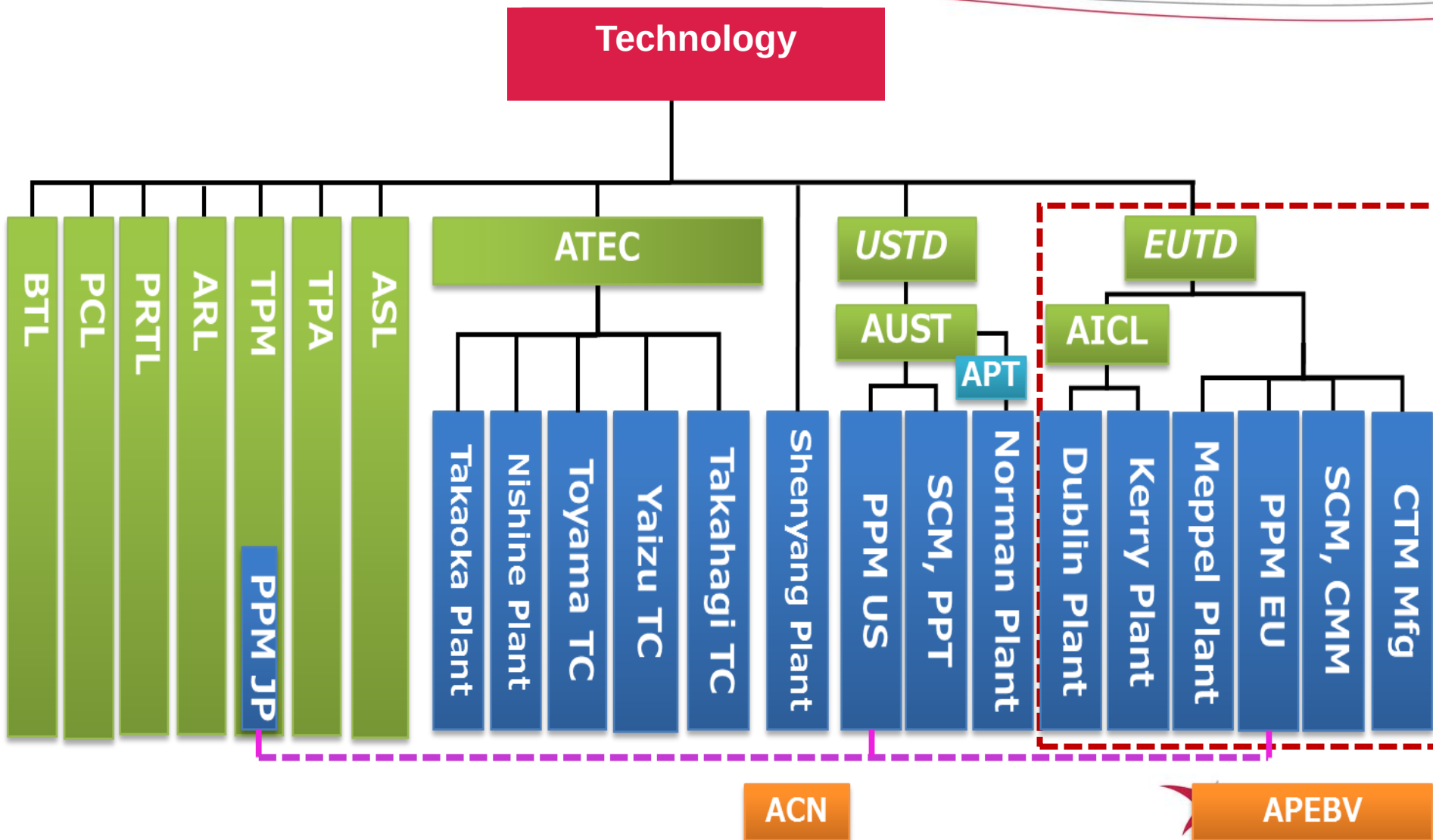
Next steps

Questions

Astellas in a Nutshell

- One of the top 20 pharmaceutical companies in the world
- Sales FY2015 of \$10 billion
- Global category leader in Transplantation and Urology
- All of the Company's sales are composed of sales of ethical pharmaceutical products
- Sizeable operations in Japan, Europe and North America
- Approximately 16,000 employees worldwide
- R&D budget of \$1.7 billion (2015)

Organization of Global Technology Division, Astellas



EUTD Locations

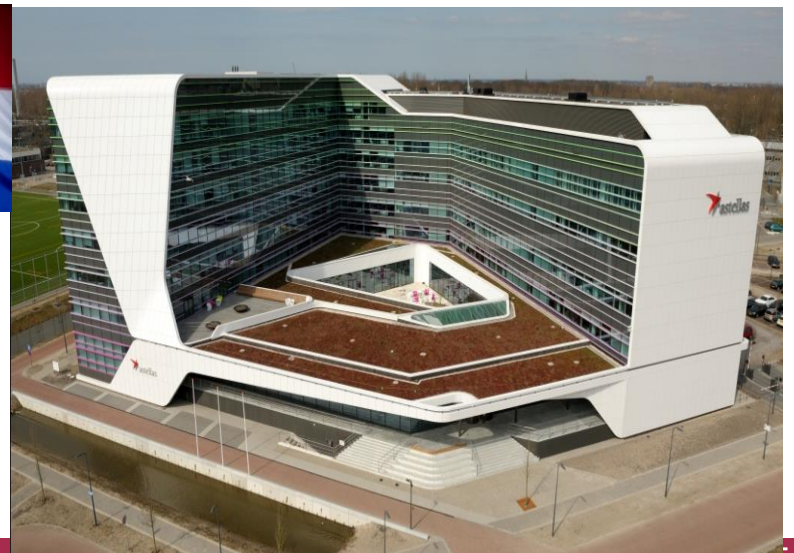


Kerry, Drug Product plant (300)



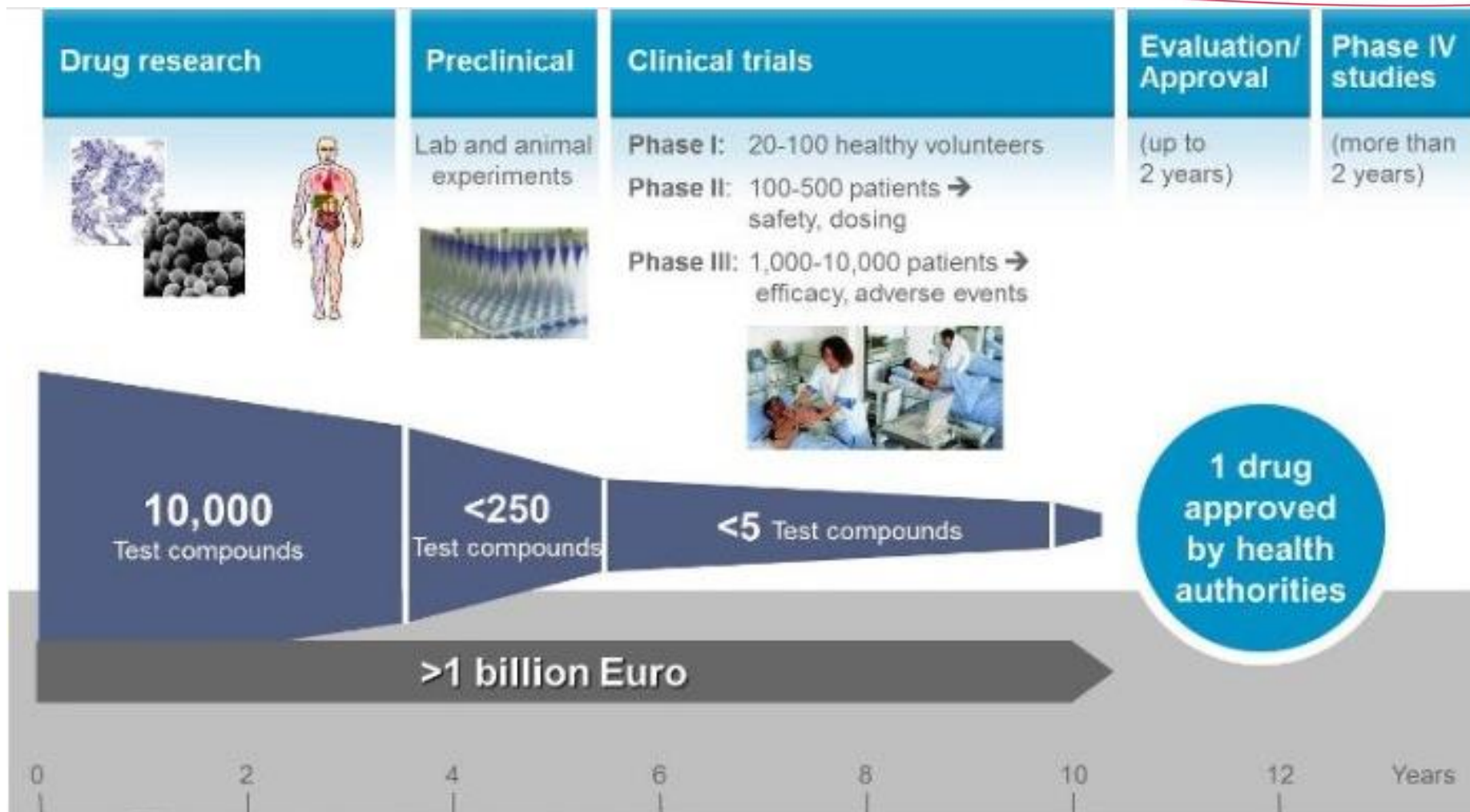
Dublin, Drug Substance plant (75)

Meppel, Drug Product plant (300)



Leiden, CTM Manufacturing (37)

General Drug development



Source: European PhRMA, Profile Pharmaceutical Industry 2010

(Astellas) Clinical standards SAD/MAD - PoC

SAD:

8 dose levels in 8 subjects each, sequential

1 DDI group (n=8-12)

1 food effect group (N=8)

**nr of product needed :
up to 1000**

MAD:

4 groups of 12 subjects, sequential

**nr of product needed
>1000**

EU: SAD, DDI, FE and MAD in one integrated protocol

SAD and MAD can be partially overlapping

PoC:

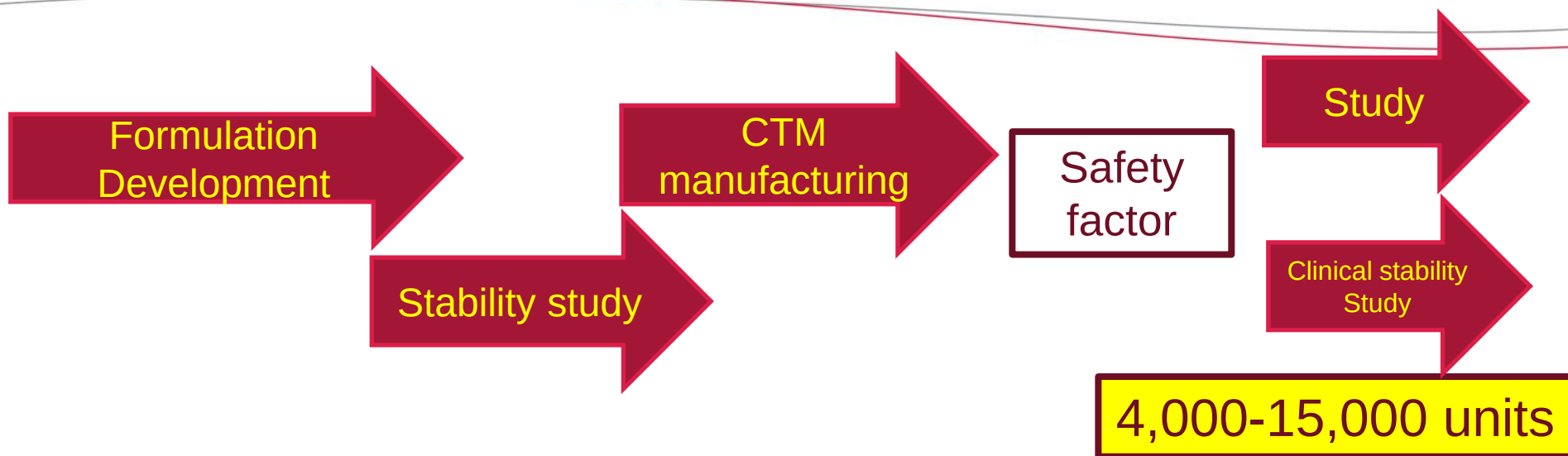
4 weeks treatment

**nr of product needed
>10000**

Up to n=150

One region, >3 centers

Issue description: Phase 1 study with n = 8 healthy subjects



Possible strategy(s) to save time and improve efficiency, *Just in time manufacturing*

Simplified formulation, chemical in capsule (CiC):

- DS directly weight in capsule
- Limited IMPD and QC strategy
- Large time saving (+6 months) because of only limited develop times

Centralized manufacturing

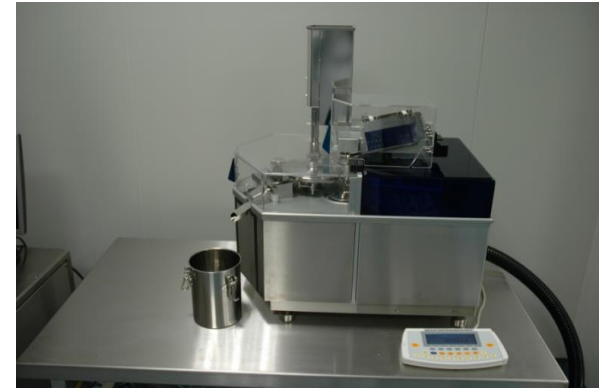
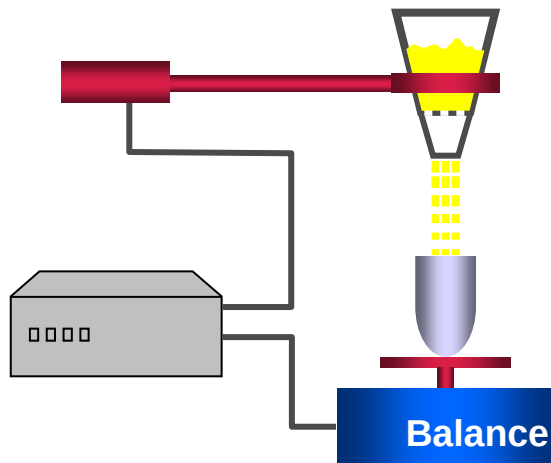
- Central team
- One stop shop principle
- Stock control
- No dependency on clinical site selection

Manual capsule filling at clinical site (extemporaneously)

- Limited capacity
- Quality outside control sponsor
- Pharmacy typically not a site selection criterion

Central capsule filling (CiC), 5 days program

1. Receive of clinical order
2. Manufacture requested order(s) with Xcelodose
3. Primary packaging of order(s)
4. Test and release
5. Ship

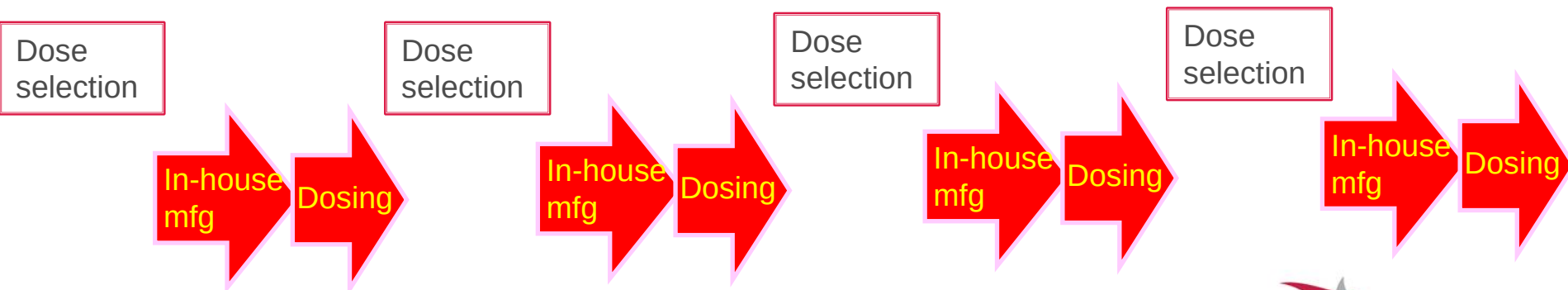


Approach of 5 days program

- **Dedicated teams consisting of : QA, Manufacturing, QC**
- **Simplified IMPD**
 - Less details, flexible
 - Aligned with all stakeholders
- **Simplified QC strategy**
 - No upfront DP stability study (standard shelf life 1 month according to guidelines confirmed by DS stability)
 - Limited release test only identity testing, strength is based upon direct weight of DS in capsule.

Case study : From dose selection to CTM at study site in 5 days

	Prep	Day 1	Day 2	Day 3	Day 4	Day 5
Alignment on CTM supply strategy (lowest dose and estimated maximum dose)						
IMPD writing and submission including regulatory assessment						
Preparation phase of all documentation						
Start: Receipt of CTM request form or announcement of request (e-mail)						
Start regular documentation and master documentation						
CTM manufacturing						
Analysis of packed product						
Review of executed batch documentation						
Review of analytical data : ID check						
Review of documentation for release of drug product						
Shipment of drug product and required data package						



Conclusions / evaluation based on 3 clinical studies

CMC

- Very low amount of DS waste
- Manufacturing and dosing went well and within timelines
- CTM supply only worked out due to intensive communication between all involved parties, especially to align QC strategies, IMPD.
- Communication between all stakeholders (dedicated teams) very efficient
- Only applicable for BCS class 1

Conclusions / evaluation based on 3 clinical studies

Clinical

Very positive feedback from Core team and Study team

Ultimate flexibility was highly appreciated by study manager.

Preference for central manufacturing as compared to manufacturing at the clinical site as:

- It will limit the choice in clinical units
- Only feasible for early single center FIM SAD, difficult for MAD and POC
- Extemporaneous formulation might be considered for first two low starting dose levels in a FIM study.

Next steps

Same capsule composition will be used for phase 2A study:

Until pivotal study product can still be changed, may be bridging needed in vitro or in vivo.

Challenge for Xcelodose capacity

- Discussion on going regarding investment in equipment with larger capacity output to keep the speed.

Discussions on going to use same strategy with blend in capsule (BiC)

- More upstream development needed
- QC strategy less simple
- Most likely 6 days instead of 5 days
- Other BCS class compounds possible

Any questions or comments?

Knowledge is
having the right
answer.

Intelligence is
asking the right
question.