Navigating the CMC and Regulatory Challenges of a Breakthrough Therapy Product for Multiple Myeloma

WCBP 2019

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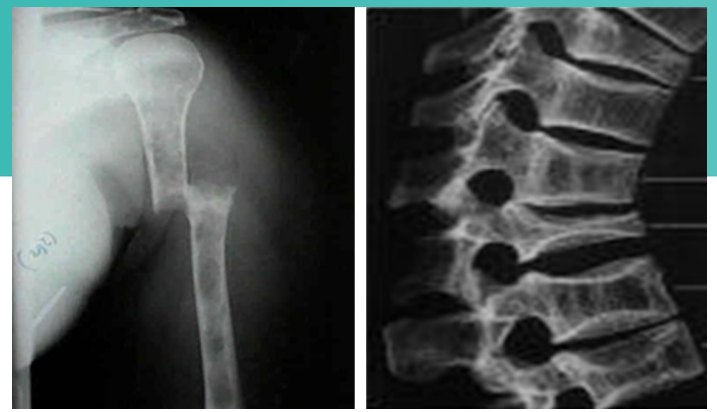
Overview

- Breakthrough therapies create opportunities & challenges for CMC development and manufacturing from both a technical and organizational view
- Breakthrough Therapies have a simple strategy: GO FAST!
- Benefits from more frequent meetings with FDA but acceleration still impacts:
  - CMC process scaling up & technology transfer
  - Establishing specifications & regulatory filing with limited time/data
- Having experience with previous Breakthrough filings helps
- New modalities are often coupled with breakthrough products – the future is now with more to come!

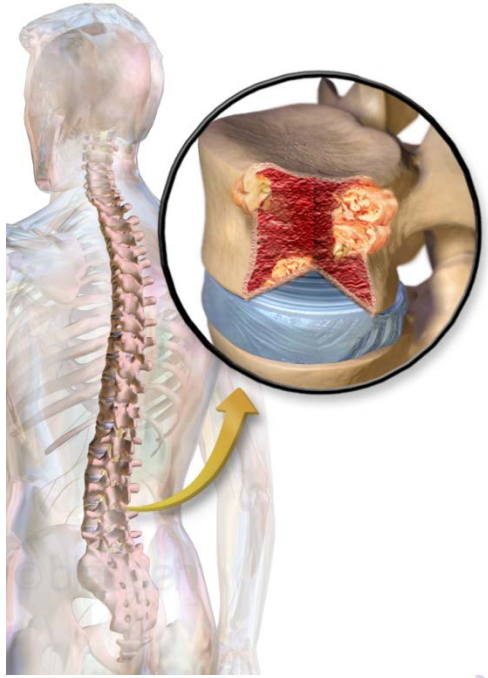
Multiple Myeloma

- 10-15% of all hematological cancers
- Most prevalent hematological malignancy in people over 65 years old
- 185,000 patients (prevalence) and over 47,000 new cases (incidence) estimated in US, EU-5 and Japan in 2019
- Despite new treatments MM remains incurable - mean life expectancy ~3-5 years

Urgent need for new treatments



The bones are destroyed due to infiltration by malignant cells resulting in painful fractures and spinal compressions



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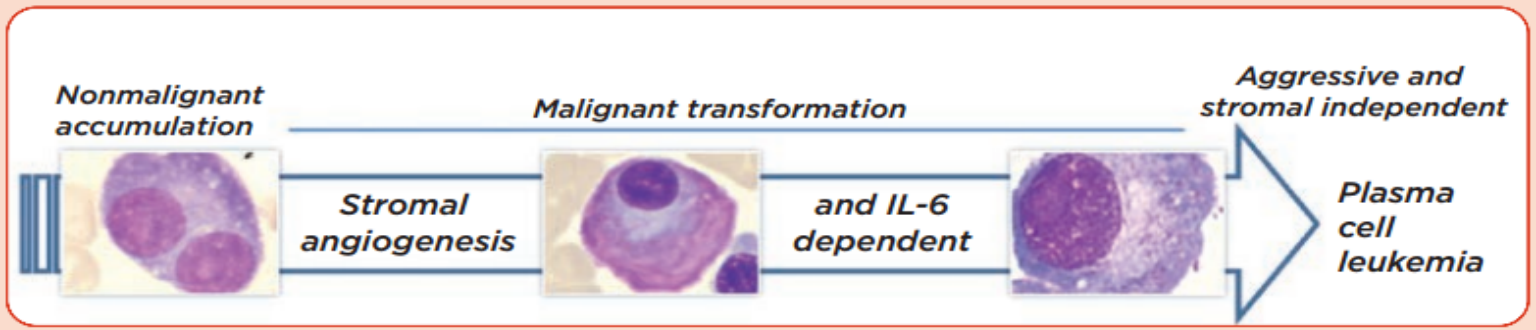
Multiple Myeloma Disease Continuum & Disease Characteristics



Multiple myeloma precursor diseases

MGUS

- < 3 g M protein
- < 10% clonal BMPCs
- No MM-related end-organ damage
- 1%/yr risk of progression to MM

Smoldering myeloma

- ≥ 3 g M protein or > 10% clonal BMPCs
- No MM-related end-organ damage
- 10%/yr risk of progression to MM in the first 5 yr

Multiple myeloma

- ≥ 10% clonal BMPCs
- M protein in serum and/or urine
- ≥ 1 CRAB features of disease-related organ damage
  - C: Calcium elevation > 11.5 mg/L or ULN
  - R: Renal dysfunction serum creatinine > 2 mg/dL
  - A: Anemia Hb < 10 g/dL or 2 g < normal
  - B: Bone disease lytic lesions or osteoporosis

62 mo | 44 mo | 29 mo

LIFE EXPECTANCY

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Project “Mermaid”

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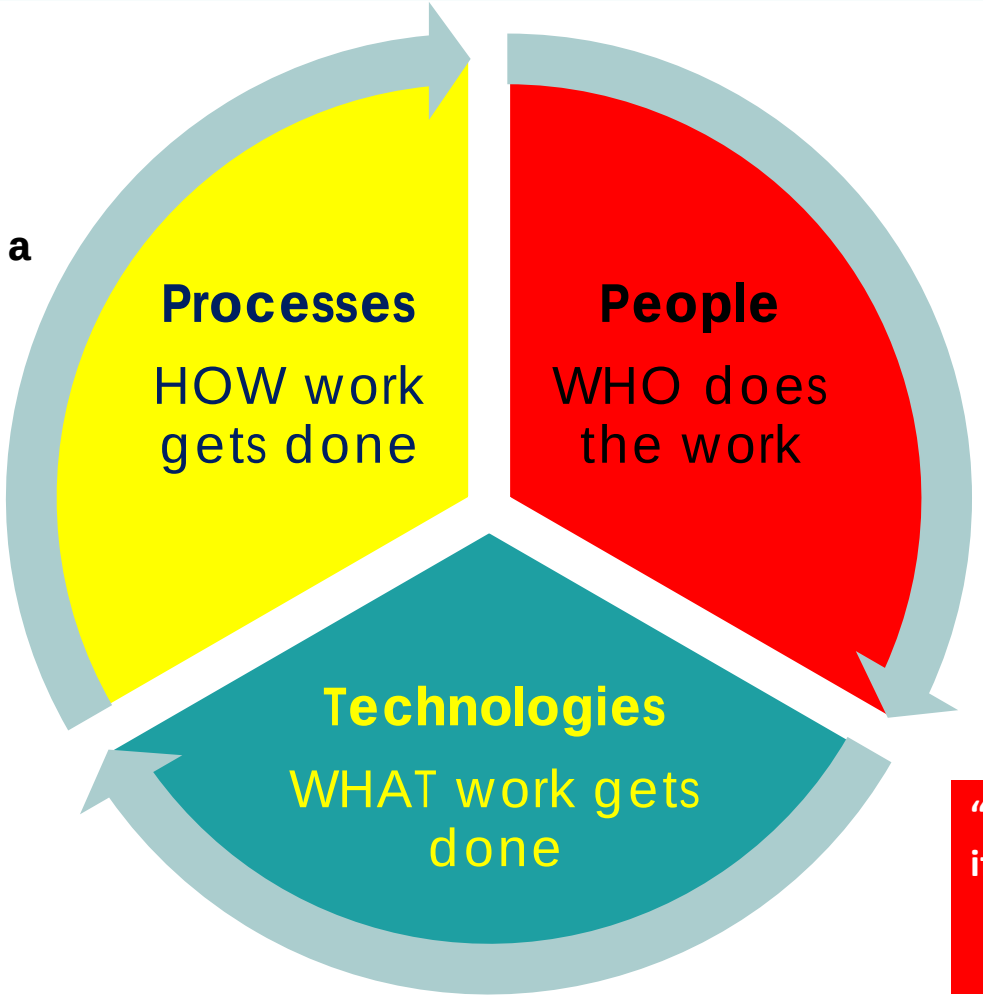
It is always about People, Processes, & Technologies

Efficient processes enable a more effective team



People drive innovation and the introduction of new technologies

"You win with people...the quality of the people is very important in building your team."
Herb Brooks
Coach, US Olympic Hockey Team
Gold Medal 1980

"It is amazing how much can be accomplished if no one cares who gets the credit."
John Wooden
Former UCLA Men's Basketball Coach

New technologies enable the introduction of more effective processes

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Expanding the “Team” concept beyond one company

Building biomanufacturing capacity—the chapter and verse

Michael E Kamarck

Biopharmaceutical manufacturing capacity has moved through three discrete chapters in its 25-year history. Could the next chapter herald formal manufacturing-capacity sharing among companies?

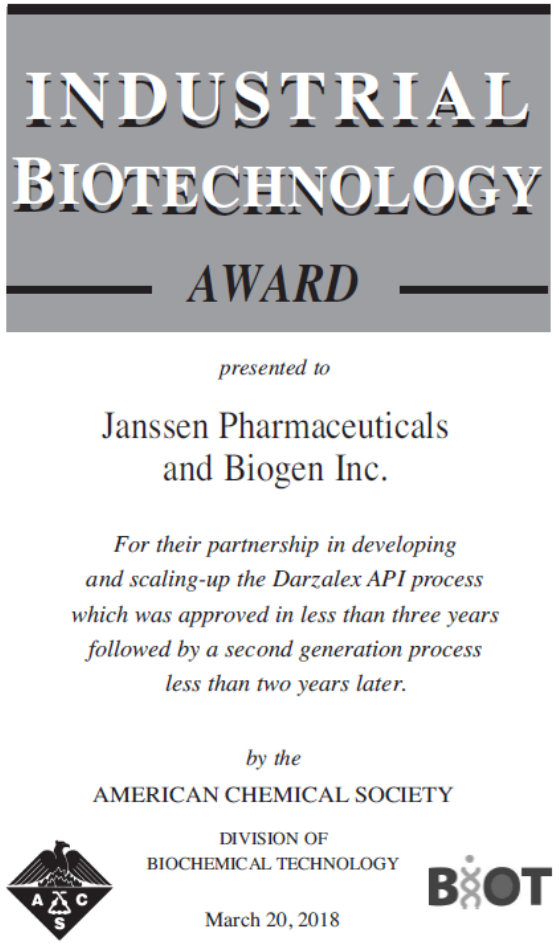
NATURE BIOTECHNOLOGY VOLUME 24 NUMBER 5 MAY 2006

But, in today's chapter of biopharmaceutical history, capacity sharing is becoming a more fluid trend.

Janssen–Biogen: Overview of a Successful Collaboration

A Successful & Productive Partnership Since 2010

- More than 30 Tech Transfers
- 12 Pilot Plant Campaigns including Tox
- Accelerated TT Approaches
- 4 “Direct Lab to 2K” Molecules
- 4 Process Robustness Assessments
- More than 20 cGMP Clinical Campaigns
- 8 Process Validation Campaigns at two Biogen sites
- 3 Commercial Products: Darzalex, Tremfya, & Tecfidera



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Technical Challenges

- Need to rapidly develop process controls for multiple potential CQAs in USP, esp oligos = need for very fast turnaround of process sample testing
- Need to rapidly move both USP & DSP to JNJ platform, change order of DSP steps, and add frozen VIN intermediate
- Confirm robustness of HCP removal
- Control impact of raw material variability on product quality profile
- Gen2 process was even more demanding in terms of a need for tighter process controls because of high titer and high VCD
- Implementation of biocapacitance control
- Complex scale-up and TT of a high VCD process
- Modifications to DSP required to manage high titer without adding equipment

Business Process Lessons Learned

- Select the right team for the task
- Align early around Regulatory Strategy
- Standardize around a Platform
  - Unit operations
  - Raw Materials
  - Equipment & Vendors
- Understand implications of scale-up as well as E2E details
- Externalize routine tasks when possible
- Effective data management
- Flexible leadership model
- Use Governance Effectively

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Business Process Lessons Learned Drive New Practices for Accelerated Programs

- Select the right team for the task
- Align early around Regulatory Strategy
- Standardize around a Platform
  - Unit operations
  - Raw Materials
  - Equipment & Vendors
- Understand implications of scale-up as well as E2E details
- Externalize routine tasks when possible
- Effective data management
- Flexible leadership model
- Use Governance effectively

- Select the right team for the task
- Align early around Regulatory Strategy
- Adopt "Psychology of Standardization"
  - Borrow platform modules where possible
  - Track risks of novel raw materials & equipment
  - Vendors – often fragile supply chains
- Understand implications of scale-up/out as well as E2E details – distributed supply chain
- Externalize routine tasks whenever possible
- Effective data management more partner-focused
- Flexible leadership model
- Use Governance effectively

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DARZALEX Approvals

2015
- **BLA Approval**
- Monotherapy for treatment of MM to those who received at least **3** prior lines of therapy
- Approved 4 months after submission with priority review!

2016
- Approval for Len+Dex or Bort + Dex combination therapies (US)
- Treatment of MM who received at least **1** prior line of therapy (US)

2017
- Approval for Pom+Dex combination Therapy (US)
- Treatment of MM for patients who received at least **2** Prior therapies including Len and proteasome inhibitor (US)

2018
- Approval in combination with bortezomib (Velcade), melphalan, and prednisone (VMP)
- Frontline Treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT)

Approved in 77 countries, 35 frontline approvals

>60,000 Patients treated to date!

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Thank you!