DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Single-use and Sustainability

Core design philosophies for the new DSM Biologics facility

Ben Hughes
Senior Process Engineer
DSM Biologics

PDA Australia Chapter Meeting:
Single-Use Systems for Pharmaceutical Applications
20th March 2012

HEALTH · NUTRITION · MATERIALS

Presentation Overview

- DSM Biologics
- New Brisbane Facility
- Design philosophies
  - Single-use
  - Sustainability
- Conclusions

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

DSM – A Global Presence

- To create brighter lives for people today and generations to come
  - Connecting unique competencies in life sciences and material sciences
    - Nutritional products, specialty chemical synthesis, polymers and pharmaceuticals
  - Annual net sales exceeding €9 billion
  - ~23,000 people employed
    - 49 countries, 5 continents
- DSM Pharmaceutical Products:

Biopharmaceuticals:
- Groningen, Netherlands
- Delft, Netherlands (R&D)
- Capua, Italy
- Brisbane Australia (as of 2013)

Pharma Chemicals:
- Linz, Austria
- Venlo, Netherlands
- Regensburg, Germany
- Geleen, Netherlands (R&D)

Corporate Headquarters & Dosage Form Manufacturing:
- Parsippany, NJ
- Greenville, NC

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Sustainability - from responsibility to business driver

- DSM manages its business with a focus on a triple bottom line: People, Planet and Profit
- Sustainability is DSM's core value
  - Driving economic prosperity, environmental progress and social advances to create sustainable value for all stakeholders

DSM Recognized for Sustainability

2010 Dow Jones Sustainability World Index
#1 in the Global Chemical Industry

ACS Green Chemistry Institute' Pharmaceutical Roundtable

- DSM receives Profiles in Sustainability Award 2011 for Green Innovation
- DSM receives European Outsourcing Award 2010 for carbon footprint reduction
- DSM to build "Biologics Plant of the Future" in Australia
- DSM receives Profiles in Sustainability Award 2010 for Green Chemistry Toolbox
- DSM receives SafeBridge "Safety" Certification for handling of potent compounds
- DSM joins ACS Green Chemistry Institute® Pharmaceutical Roundtable

FTSE
World Business Council for Sustainable Development

Good Corporate Citizenship
Endorse obligations in the chemical industry's International Responsible Care® Program

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

DSM Biologics Services

- Contract development & cGMP manufacturing
  - Multi-product facility, bioreactor capacity to 1000L
  - Biological APIs - proteins, monoclonal Abs
  - 25 years experience, successful 2010 FDA and EMA audits

- Proprietary Technology development and licensing
  - Intensified platform processes:
    - XD® culture
    - RHOBUST® Direct Capture chromatography
    - The Kremer Method™

- Flexible manufacturing with Mammalian cell line expertise
  - Single-use technologies (SUT)
  - Suspension cell line focus

Groningen, Netherlands

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

New Brisbane Biologics Facility

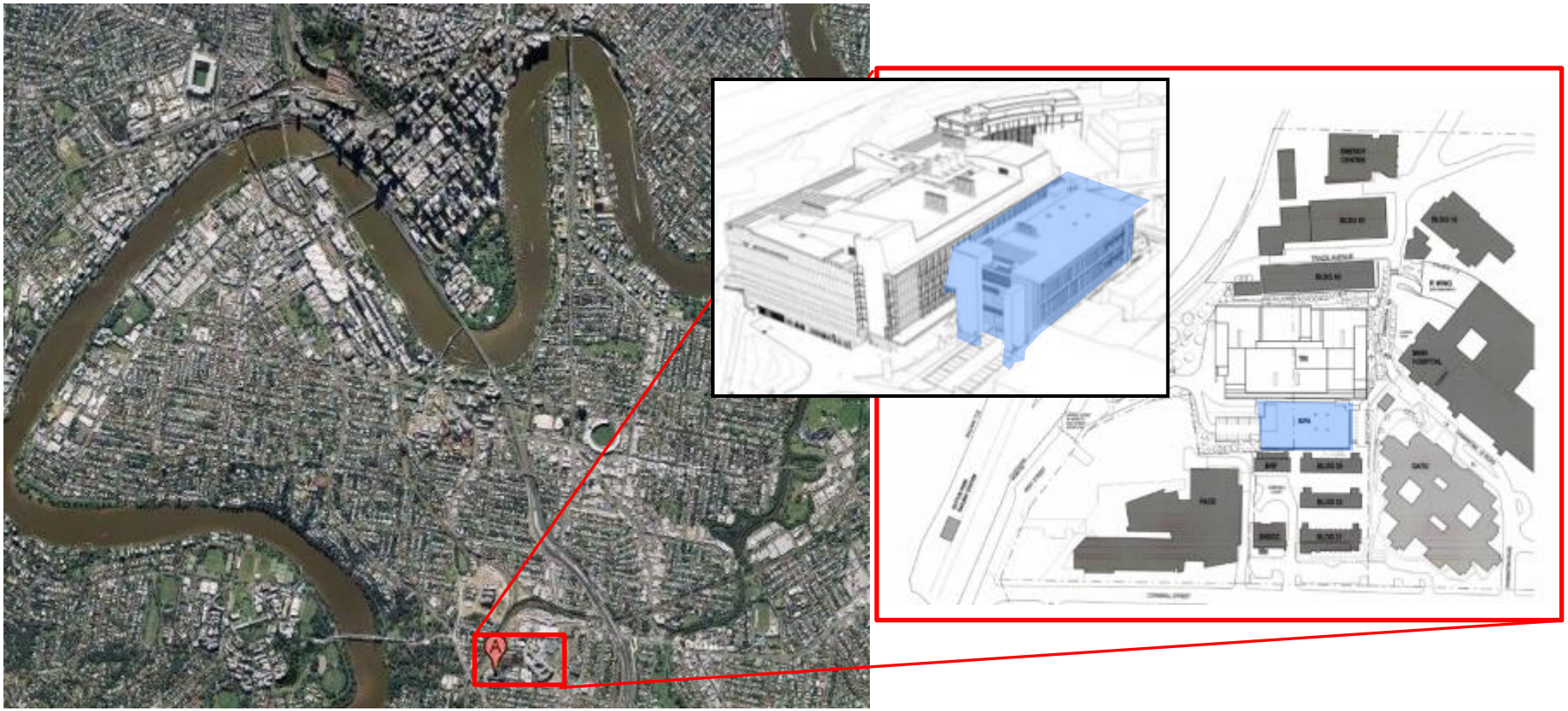
- Construction underway for new cGMP manufacturing facility

- Partnership between DSM and BioPharmaceuticals Australia (BPA)
  - BPA established by Qld Government to construct a manufacturing facility and identify an experienced international CMO partner
  - DSMB selected to design and operate the facility
  - Facility funding provided by Commonwealth of Australia and Queensland government

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

DSM Biologics Facility Location

- Princess Alexandra Hospital Campus, Brisbane

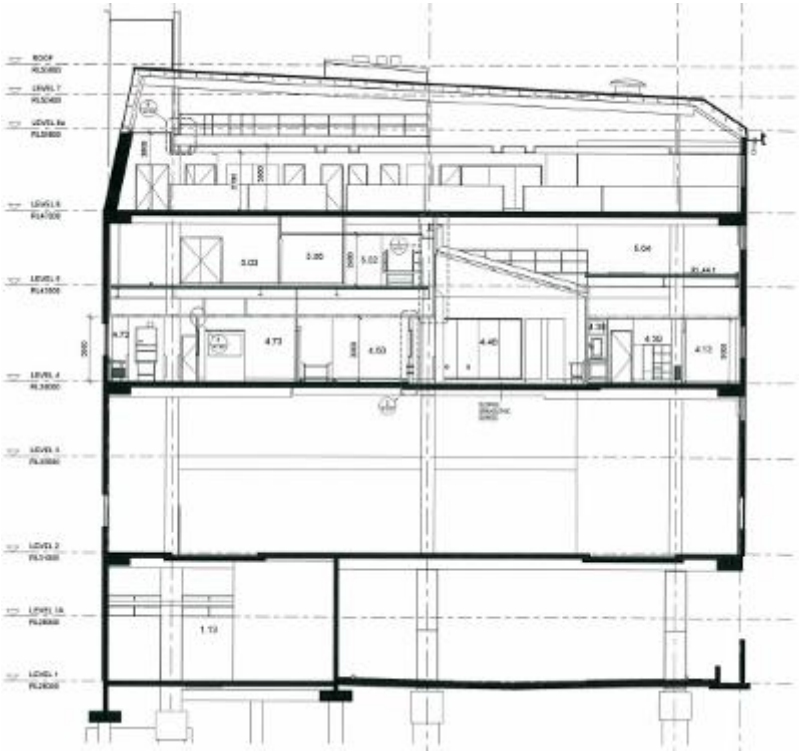


(Image courtesy of Google Maps)

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Facility - General

- Brownfield site
  - 24/7 manufacturing, 50 weeks/year
- 6 levels, (60x35m, 8000m^2 total space)
  - 285m^2 warehouse
  - 1200m^2 clean room (465m^2 CNC)
  - Future expansion to the west
    - Fit out of level 2/3 manufacturing
- Extending Groningen CMO capacity
  - USP: Fully Single-use Technology (SUT)
    - Up to 2000L fed batch
    - 50 - 500L XD®
  - DSP: Hybrid SUT/multiple use (10kg batch)
  - QA, QC, PD, Engineering, Sales/Admin

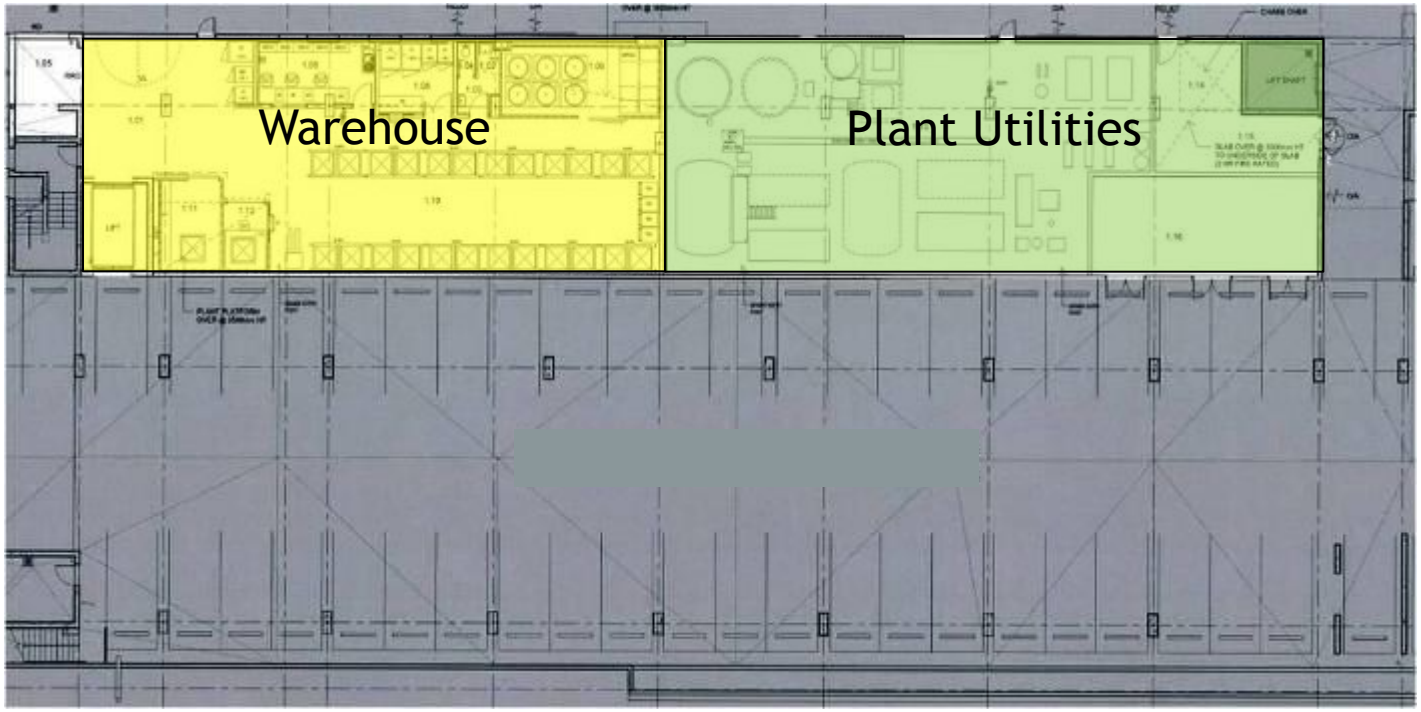


- Building Status
  - Shell currently to level 6 – (due to be complete April 2012)
    - Internal fit out & equipment procurement - 2012
    - Commissioning and validation – 1Q/2Q 2013
  - Open for GMP manufacture – Expected mid 2013

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Level 1 - Warehouse and Plant Utilities

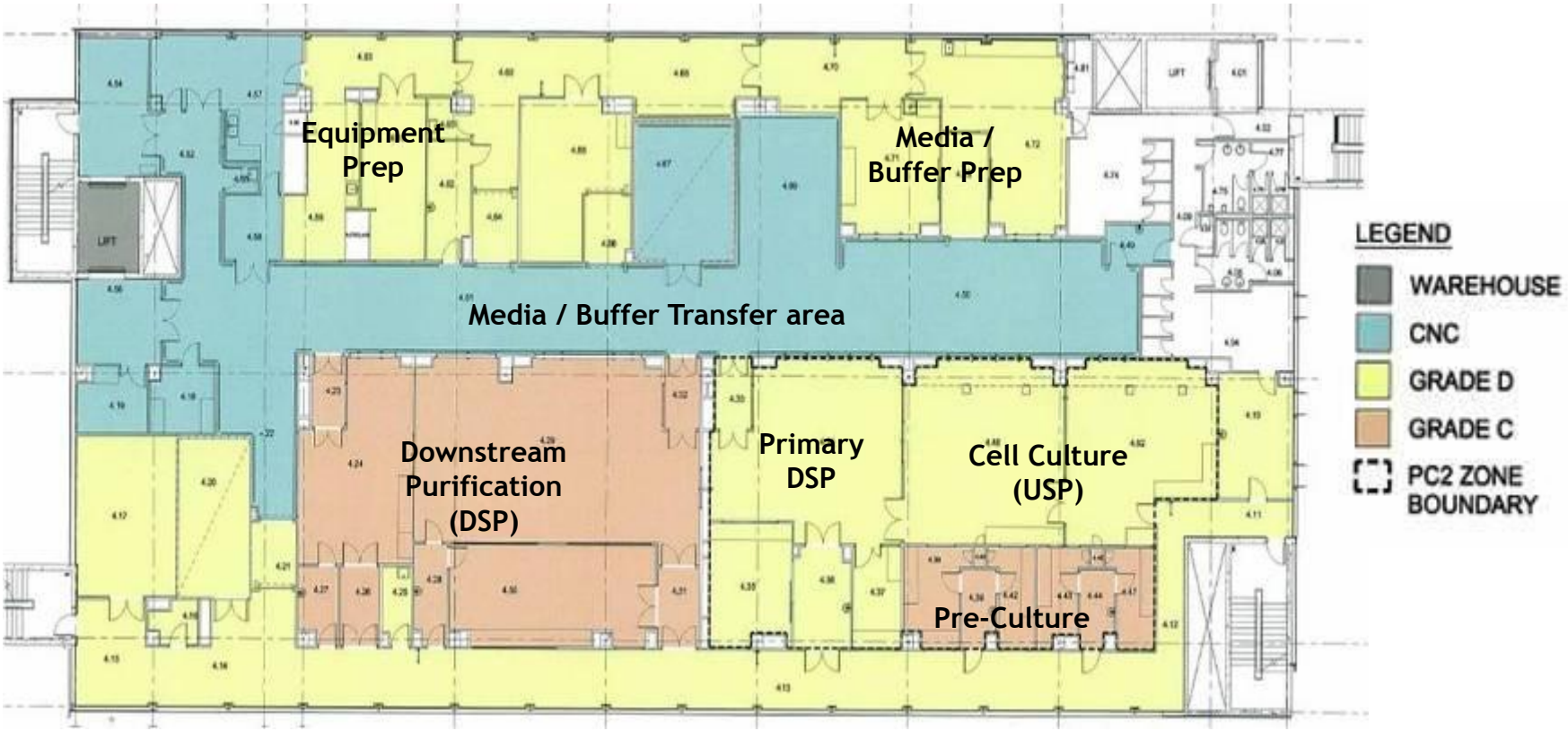
- Reduced WFI and overall energy footprint due to single-use systems
  - Significantly reduced stainless steel equipment scope
  - No SIP required
  - No CIP skids



DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Level 4 – Manufacturing Area

- "Ballroom" approach to clean room design – mobile equipment
  - Dedicated pre-culture rooms with multi-product upstream suites
  - Single downstream train and post viral clearance finishing suite



DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Single-Use Media/Buffer Approach

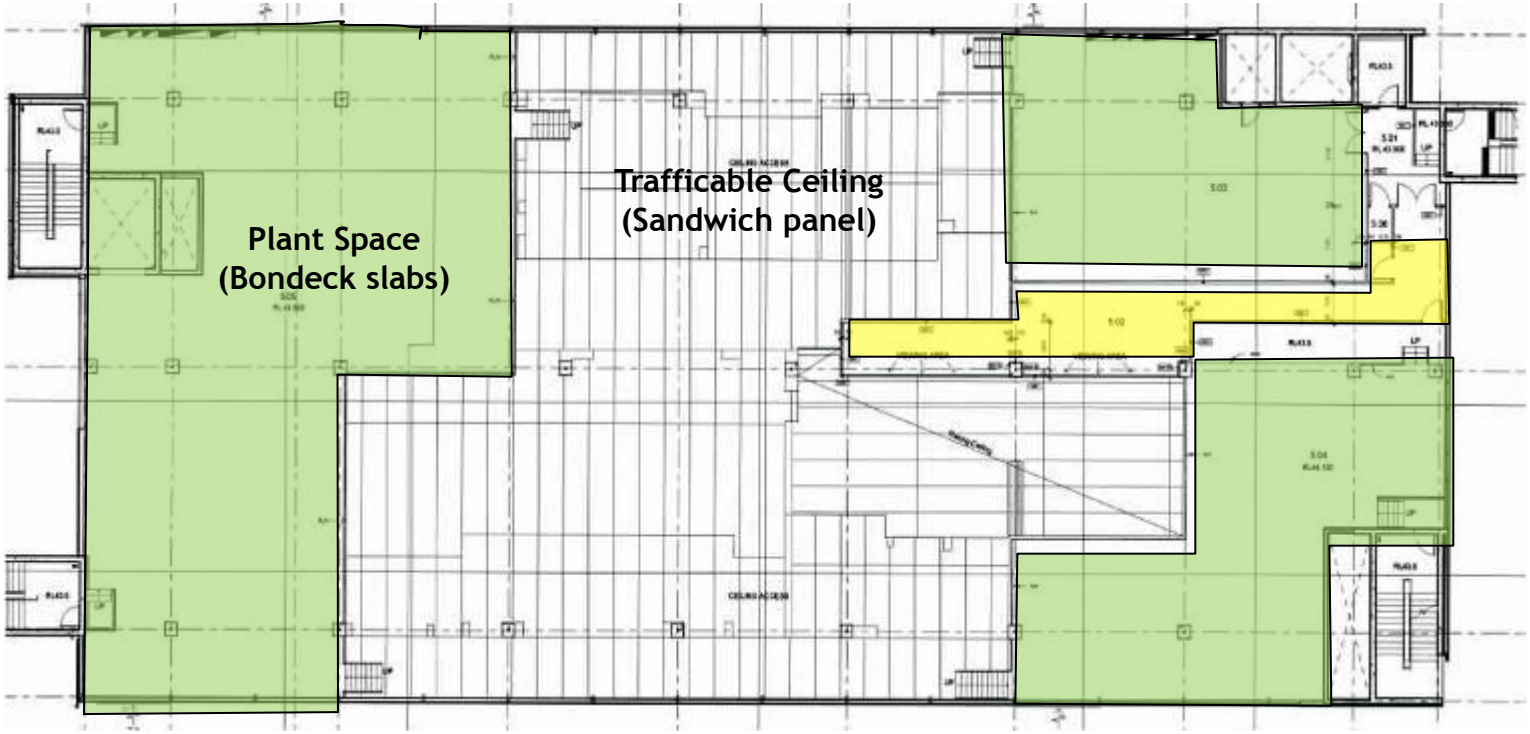
- Media and buffer supply and storage based on Bag-based technology
  - 500L bag-lined totes to be located outside of the clean room
  - Connected aseptically through the wall to process skids

(Images courtesy of Sartorius, Pall and Thermo)

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Level 5 - Mezzanine

- Utilities supporting level 4 manufacturing
- Client viewing corridor



DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

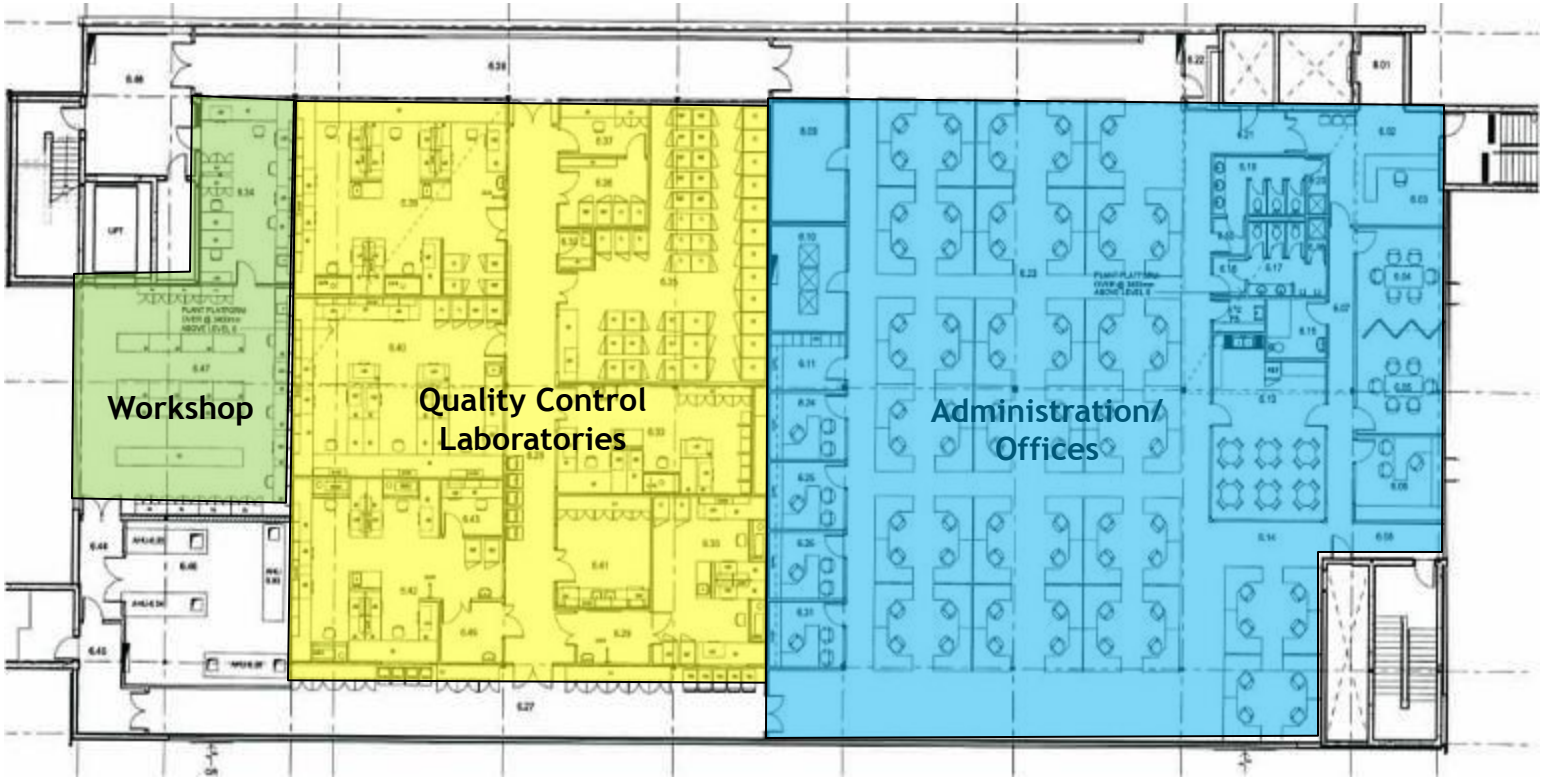
Level 5 – Client Viewing Corridor

- Example view into cell culture and Primary DSP suites
  - Less disturbance to operations
  - Reduced safety and environmental risk to production area cleanliness

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Level 6

- Workshop, QC Laboratories, Office/Admin



DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Presentation Overview

- DSM Biologics
- New Brisbane Facility
- Design philosophies
  - Single-use
  - Sustainability
- Conclusions

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Single-Use Technology Drivers

- Ideally suited to contract manufacturing operations
  - Reduced risk for cross contamination
  - Minimal cleaning / sterilisation validation
  - Focus operators on value-add activities
    - Very fast change-over (no cleaning or sterilising)
  - Enable flexible manufacture
    - Must be adaptable to suit the client's needs/process
    - "Future proof" for new innovations (skids easy to replace)

- Facility design implications
  - Smaller footprint (clean room area)
    - Increased use of non classified areas
  - No SS transfer piping
    - Use of pass throughs and pre-sterilised tubing
  - Faster implementation and reduced Cap Ex
    - Standard equipment delivery in 2-3 months
    - Reduced qualification (IOQ at supplier)

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

(Image courtesy of Wyeth)

Single-Use Implementation - Upstream

- Fully single-use envisioned for upstream:
  - Dispensing operations through to buffer and media make-up
  - Solution filtering, storage and transfer
  - Cell culture vessels
  - Cell Harvest (depth filtration)

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

(Images courtesy of Thermo, Sartorius, Pall and Millipore)

Single-use Implementation - Upstream

- Fully single-use envisioned for upstream:
  - Dispensing operations through to buffer and media make-up
  - Solution filtering, storage and transfer
  - Cell culture vessels
  - Cell Harvest (depth filtration)

(Images courtesy of Corning, GE and Xcellerex)

Single-use Implementation - Upstream

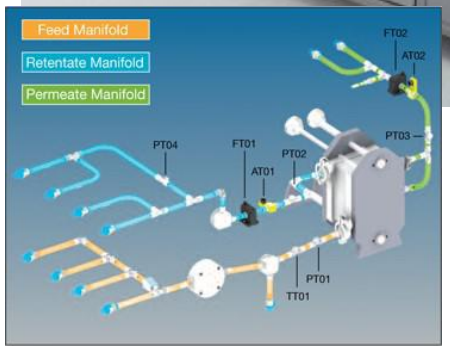
- Fully single-use envisioned for upstream:
  - Dispensing operations through to buffer and media make-up
  - Solution filtering, storage and transfer
  - Cell culture vessels
  - Cell Harvest (depth filtration)

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

(Image courtesy of Millipore and 3M CUNO)

Single-Use Implementation - Downstream

- Hybrid single-use / multi-use equipment:
  - Looking to utilise single-use where possible
    - Often limited by sensors or requirements for in-line dilution



(Images courtesy of Sartorius, Millipore, PALL and GE)

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Single-Use = Sustainability?

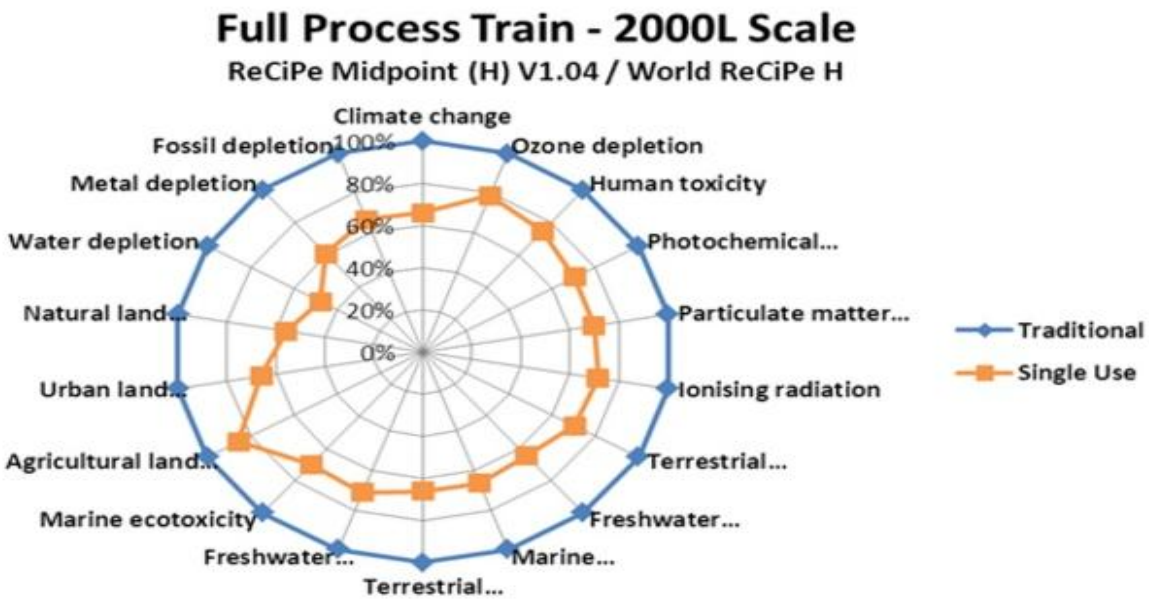
- While SU systems do produce additional solid waste, they can however provide a range of environmental benefits beyond traditional stainless steel (SS) systems
  - Reduced WFI needs (no CIP/SIP)
  - Reduced CO_2 footprint and resource conservation
  - Reduction of hazardous cleaning chemicals sent to sewer
    - Safety hazard reduction for not exposing operators to cleaning agents
  - Reduced sterilisation autoclave needs

- Multiple studies have looked to evaluate the environmental cost of using single-use systems
  - Most recently – a comprehensive Life Cycle Analysis by GE & BioPharm Services
    - "Cradle to grave" analysis of mAb process using entirely SUT at 100L, 500L and 2000L vs. a SS facility
    - **All** 18 environmental impacts studied returned measurably positive impacts with single use over SS!

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Single-Use = Sustainability?

Environmental impact assessment



ReCiPe Midpoint (H) V1.04 / World ReCiPe H	
Midpoint impact category	Unit
Climate change	kg CO2 eq
Ozone depletion	kg CFC-11 eq
Human toxicity	kg 1,4-DB eq
Photochemical oxidant formation	kg NMVOC
Particulate matter formation	kg PM10 eq
Ionising radiation	kg U235 eq
Terrestrial acidification	kg SO2 eq
Freshwater eutrophication	kg P eq
Marine eutrophication	kg N eq
Terrestrial ecotoxicity	kg 1,4-DB eq
Freshwater ecotoxicity	kg 1,4-DB eq
Marine ecotoxicity	kg 1,4-DB eq
Agricultural land occupation	m2a
Urban land occupation	m2a
Natural land transformation	m2
Water depletion	m3
Metal depletion	kg Fe eq
Fossil depletion	kg oil eq

Single Use approach exhibits lower environmental impact in all 18 categories studied

imagination at work

ecoassessment coe
GE Global Research

(Slide courtesy of GE)

The Future of Protein Manufacturing

Today

- Large stainless steel bioreactors
- DSP bottlenecks
- Large footprint/high CAPEX

Tomorrow

- Single-use systems
- Efficient processes
- Small footprint/low CAPEX
- Fast and flexible
- Meeting product quality demands

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Conclusions

- DSM expecting to begin GMP operations for our new Brisbane cGMP manufacturing facility by mid 2013
  - Mammalian-produced API production, up to 2000L bioreactors
  - Open-plan, flexible design incorporating single-use technology

- DSM Biologics is excited to expand into the Australasian market and partner with BPA
  - We see excellent opportunities for collaboration with BPA and the Australian biotech industry, and are looking forward to providing high-quality manufacturing services
  - Look for the up-coming April DSM Roadshows (major centres)

- We are interested in hiring
  - Please contact or send CVs to ben.hughes@dsm.com

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

BRIGHT SCIENCE. BRIGHTER LIVING.™