“So you think you have a drug” seminar series
inaugural event

“So You Think You Have a Drug
You Want to Develop”

Mark Klempner MD
Executive Vice Chancellor,
MassBiologics of UMMS
Professor of Medicine

Thursday, October 30, 2014
3:00-4:00 pm
AS7.2072 Conf. Room
Albert Sherman Center

Co-sponsored by the UMass Center for Clinical and Translational Science, MassDrugs, and MassBiologics of UMMS
MassBiologics of UMMS
Mark S. Klempner, MD  Executive Vice Chancellor
Discovery Research, Process Development, Administration  cGMP manufacturing, QA/QC
Vector Process Development And Manufacturing Center

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Outline

• MassBiologics- A Unique UMass Asset

• What Questions Do We Ask When Considering Developing A New Medicine

• How Do We Develop A Medicine

• How We Can Help You
MassBiologics

• Established in 1894 as collaboration between the Commonwealth’s Department of Public Health and Harvard University (became part of UMMS in 1997)
• During a 120 year history MassBiologics has discovered and manufactured over 100 million doses of life saving medicines for the citizens of the Commonwealth and the world.
• Product Discovery often addresses needs of populations where commercial market is limited.
• Is the only non-profit, FDA-licensed manufacturer of vaccines and biologics in the United States.
Mission

To discover, develop, and manufacture biological medicines that improve the lives of people around the world while educating and training a workforce that will perpetuate this public health mission.
Over 120 Years of Evolution in Discovery and Manufacturing Technologies

1894-1946
- The State Labs, part of the Massachusetts Department of Public Health, focused on Equine antitoxins.
- Issued License #64 for producing smallpox vaccine and diphtheria antitoxin

1946-1997
- The State Labs become the State Laboratory for Plasma Fractionation and continues as part of the Massachusetts Dept. of Public Health. Focus changes to producing therapeutics from human serum.

1997-Present
- In 1997 the State Legislature transfers oversight to University of Massachusetts Medical School.
- MassBiologics manufactures vaccines and human monoclonal antibodies.

2014-
- cGMP Vector Manufacturing Center (VMC) awarded by Commonwealth of Massachusetts
- MassBiologics manufactures viral/plasmid vectors with single use bioreactors
Evolution of Products

1894-1946
- Diphtheria Antitoxin - Equine
- Botulism Antitoxin - Equine
- Tetanus Antitoxin - Equine
- Rabies Immunoglobulin - Equine

1946-1997
- Human Serum Albumin
- Human Immune Globulin
- Human Hyper-Immune Globulin to:
  - Scarlet Fever
  - Pneumococcus
  - Meningococcus
  - Tetanus
  - Measles
  - CMV
  - RSV
  - Varicella-zoster
  - Rabies
  - Hepatitis A

1997-Present
- Td Vaccine
- Human Monoclonal Antibodies against
  - SARS
  - C diff Toxins A and B
  - Rabies
  - Hepatitis C
  - Tet and Diph Toxins
  - SOD1 for ALS
  - sFlt-1 for Pre-eclampsia

New Targets
Contract Manufacturing

2014-
- rAAV vectored huMabs and therapeutic biologicals
- Plasmids for transient vectoring of huMabs
Products in Clinical Trials

• **C. difficile anti toxin A/B Phase III Clinical Trial**
  – Prevent recurrent CDAD
  – Licensed to Merck

• **HCV Monoclonal Antibody (mAb) in Clinical Trials**
  – Ongoing Phase 2 mAb + DAA in Liver Transplant Patients
  – Granted orphan-drug designation by the FDA (Nov 2013)
    • “prevention of hepatitis C recurrence in patients receiving liver transplantation”

• **Phase 2/3 Rabies mAb Trial ongoing in India**
  – 185/200 patients with exposure to potentially rabid animal randomized to HRIG + vaccine or Rabies mAb + vaccine
  – Pivotal trial for registration (licensure) in India

• **Diphtheria anti-Toxin mAb in Preclinical Development**
  – MCB produced and released Sept 2013
  – mAb potency assignment finalized September, 2014
What Do You Need To Consider To Develop A Medicine

Drug R&D

1-2 years

Target ID & Validation
- Link disease and target biomarkers
- High-throughput screening
- Rational Design
- In silico screening

Hit Generation
- Hits Confirmation
- Potency & cytotoxicity
- Prelim animal efficacy
- Initial SAR

Lead Gen & Optimization
- Potency Studies
- Selectivity Studies
- PK/ADME-Tox properties
- SAR pharmacophore modeling

Pre Clinical Animal Studies
- Pharmacological profile
- Administration route
- Drug interactions

Clinical Trials

4.3 Years

Phase 1: Safety
- 20-100 people
- 1-2 years

Phase 2: Efficacy Safety
- 100-300 people
- 1-2 years

Phase 3: Efficacy Safety
- 1,000-3,000 people
- 2-3 years

FDA Review & Approval
- 1-2 years

Pre-Clinical

4.3 Years

Phase I

1.6 Years

Phase II

2.4 Years

Phase III

2.7 Years

11 Yrs
**Uniform New Medicine Evaluation Template**

**UNMET Need for Medicine for Better Lives**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Green = Well defined, well reasoned target</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amber = Pseudo-defined; reasoning not thoroughly thought out/presented</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red = Nebulous; no rationale for selection</td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic Indication</strong></td>
<td>Green = Clear therapeutic/prophylactic indication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amber = Poorly defined/debatable therapeutic/prophylactic indication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red = Diagnostic, imaging agent</td>
<td></td>
</tr>
</tbody>
</table>
### Uniform New Medicine Evaluation Template (cont.)

<table>
<thead>
<tr>
<th>FEASIBILITY OF GENERATING AND EVALUATING A mAb</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
</table>
| **Immunogen***                               | Green = Fully identified or minimal work needed to identify completely/specific  
Amber = Minimal work needed to identify completely/may be an issue with specificity; or identified/non-specific; or Early stage of identification; some data available  
Red = Unknown | | |
| **Availability of immunogen***                | Green = Readily available from a commercial source; or able to generate in-house easily  
Amber = Available from a commercial source but expensive; or able to generate in-house with difficulty or expensive  
Red = Not available; IP costs prohibitive or not available for licensing | | |
| **In vitro assays to assess functionality**   | Green = Assay(s) developed or assay(s) in development; body of data to support relevance  
Amber = Assay(s) in development; promising but not enough data to support relevance  
Red = No ability to develop a relevant model | | |
| **In vivo model for efficacy**                | Green = Small animal model(s) developed and accepted as standard  
Amber = Large animal model developed and accepted as standard but expensive; or small animal model with data to support relevance  
Red = No ability to develop a relevant model | | |

*If a MAb has already been generated by the respondent the section is N/A
**Uninform New Medicine Evaluation Template (cont.)**

<table>
<thead>
<tr>
<th>PRECLINIAL DATA</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
</table>
| Literature      | **Green** = Paper(s) indicate feasibility of MAb approach against the target; quality of research not in question  
**Amber** = Minimal information or quality of research paper questionable  
**Red** = Literature indicates MAb approach against target is not feasible | |
| In vitro data   | **Green** = Substantial data from a relevant model  
**Amber** = Minimal data from a relevant model  
N/A = No data as not at that stage of development | |
| In vivo data    | **Green** = Substantial data from a relevant model  
**Amber** = Minimal data from a relevant model  
N/A = No data as not at that stage of development | |
| Toxicology      | **Green** = Clean tox and/or cross-reactivity data  
**Red** = Tox and/or cross-reactivity data with issues  
N/A = No data as not at that stage of development | |
**Uniform New Medicine Evaluation Template (cont.)**

<table>
<thead>
<tr>
<th>CLINICAL TRIAL FEASIBILITY</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
</table>
| **Patient population and potential impact**    | **Green** = > 200,000/year in US; or > 200,000/year in US and ROW; or small patient population but large impact on morbidity/mortality  
**Amber** = 10,000 - 200,000 in US and/or ROW  
**Red** = < 10,000/year in either US or ROW or only in ROW; or large population but minimal impact on morbidity/mortality |                |
| **Ethics**                                     | **Green** = No ethical concerns; or ethical concerns; able to overcome by using animal effectiveness rule (21 CFR 601.90) - relevant model(s) readily available  
**Amber** = Ethical concerns; able to overcome by using animal effectiveness rule - relevant model(s) available on a limited basis or are in early stage of development/promising data  
**Red** = Ethical concerns/unable to use animal effectiveness rule - no animal model possible |                |
| **Risk of adverse effects**                    | **Green** = No known risk  
**Amber** = Risks theoretical or likely by dose  
**Red** = Likely risk for a serious outcome |                |
| **Study size/cost (Phase II) - based on measurable and clinically significant primary endpoint** | **Green** = ≤ 200 subjects; ≤ 2 years  
**Amber** = 200 - 500 subjects; 2 - 4 years  
**Red** = > 500 subjects or > 5 years |                |
**Uniform New Medicine Evaluation Template (cont.)**

<table>
<thead>
<tr>
<th>MARKET</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
</table>
| **Worldwide market**            | **Green** = > $1 billion  
**Amber** = $50 million to $1 billion  
**Red** = < $50 million            |                |
| **Alternate therapies (licensed)** | **Green** = None; or available but not highly effective  
**Amber** = One used on or off-label  
**Red** = > one; highly effective; no problems with supply |                |

<table>
<thead>
<tr>
<th>COMPETITION</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
</table>
| **In development**               | **Green** = None (drugs, MAbs, or biologics)  
**Amber** = MAbs or non-MAb(s) in early stages (Preclinical, Phase I/II)  
**Red** = MAA$^2$ (drugs/MAbs/biologics) in final stages of review |                |
| **IP Concerns**                  | **Green** = None; or patents pending - likely to have no issues with claims  
**Amber** = Patent(s) pending - claims could be restrictive  
**Red** = Freedom to operate and/or prior art issues; or patent applications not filed |                |
<table>
<thead>
<tr>
<th>BUSINESS AND COLLABORATION OPPORTUNITIES</th>
<th>EVALUATION CRITERIA</th>
<th>RATING (Color)</th>
</tr>
</thead>
</table>
| Ability to collaborate                  | **Green** = Part of UMass; no affiliations/agreements with outside entities re. target or one(s) that MBL could enter  
**Amber** = Inventor(s) are founder(s) of start-up company; or Potential collaborator negotiating with third party  
**Red** = Restrictive agreements/IP issues |                |
| Type of collaboration                   | **Green** = Full partnership  
**Amber** = Scientific and/or investment and/or clinical  
**Red** = In-licensing; cost prohibitive |                |
| UMass - collaboration would enhance scientific knowledge | **Green** = UMass Medical School  
**Amber** = UMass affiliated  
**N/A** = Not part of UMass; or collaboration would not enhance scientific knowledge |                |
| Scientific/clinical                     | **Green** = Respected leader in scientific or clinical field and/or unique models/assays/facility for performing or developing such assays  
**Amber** = Capable hands to share workload; or inventor(s) are founder(s) of a start-up  
**Red** = Nothing outside of target |                |

¹ROW - Rest of World

²MAA - Marketing Authorization Application (eg BLA, NDA in US)
**Unmet Need for Medicine to Prevent Lyme Disease**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EVALUATION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Borrelia burgdorferi</td>
</tr>
<tr>
<td><strong>Therapeutic Indication</strong></td>
<td>monoclonal antibody for passive immunization against Borrelia burgdorferi, the causative agent of Lyme disease</td>
</tr>
<tr>
<td></td>
<td>administered annually, prior to beginning of tick-exposure season</td>
</tr>
<tr>
<td></td>
<td>-- seek initial licensure in adult, then in pediatric population</td>
</tr>
</tbody>
</table>
### “UNMET” Evaluation for a mAb to prevent Lyme Disease

<table>
<thead>
<tr>
<th>Pre-Clinical feasibility</th>
<th>overall: for passive protection, OspA is a validated immunogen for human protection and provides a clear path</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogen:</td>
<td>OspA antibodies can provide passive protection (no treatment once disease acquired)</td>
</tr>
<tr>
<td>identified</td>
<td>can be recombinantly expressed</td>
</tr>
<tr>
<td>availability</td>
<td>possibly, if antigen is used for a recombinant vaccine</td>
</tr>
<tr>
<td>antigen IP</td>
<td>composition IP on antibody generated against antigen possible</td>
</tr>
<tr>
<td>functional assay(s)</td>
<td>yes, can perform a bactericidal assay with bacteria, antibody, complement and fluorescent stains</td>
</tr>
<tr>
<td>in-vivo model</td>
<td>yes, mouse model for acute disease and model of antibiotic refractory arthritis are available</td>
</tr>
<tr>
<td>toxicology</td>
<td>looking to dose subjects only once, but maintain protection sufficient for approximately 4 months - we would need to ask/confirm with agency about duration of tox monitoring (1 dose with 1 month study sufficient?)</td>
</tr>
<tr>
<td></td>
<td>if plan is to give a single dose to subject 1x/season but every year, would need to do tox studies with repeated doses in mice to maintain serum levels and again, need to ask/confirm with agency about duration of tox follow-up</td>
</tr>
<tr>
<td>execution of project:</td>
<td></td>
</tr>
<tr>
<td>biohazard level</td>
<td>biohazard level 2</td>
</tr>
<tr>
<td>facilities needed</td>
<td>standard lab facilities. If performing animal tick transfer experiment, may need to maintain a tick colony</td>
</tr>
<tr>
<td>collaborators</td>
<td>MBL Executive Vice Chancellor is a Lyme expert with many connections in the field</td>
</tr>
<tr>
<td>background literature</td>
<td>very clear animal work in several species to support passive protection. Crystal structure of target protein (OspA) with bound neutralizing antibody (LA-2)</td>
</tr>
</tbody>
</table>
“UNMET” Evaluation for a mAb to prevent Lyme Disease

<table>
<thead>
<tr>
<th>regulatory:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>animal rule</td>
<td>no</td>
</tr>
<tr>
<td>US or ROW</td>
<td>(guidelines to be aware of, including any relating to combination trials) path to licensure of vaccine straightforward</td>
</tr>
<tr>
<td>SOC</td>
<td>(trial design compatible with standard of care) SOC is antibiotic course after diagnosis or probable diagnosis - antibody drug should have no effect on the treatment</td>
</tr>
<tr>
<td>dose:</td>
<td>IM preferable over IV. Based on previous OspA LA-2 equivalent epitope competitive ELISAs to quantitate LA-2 Elisa titer - predictive protective levels estimate dose at around 20 mg dose for a 70 kg individual with an antibody with a 1 month half-life to have higher than 0.4 ug/ml at end of tick season --however, some data showing breakthrough with &lt;1000ng/ml level, so may need to confirm higher dose not required for complete protection</td>
</tr>
</tbody>
</table>
Making a mAb Medicine

Key Components

Drug Discovery

Clinical Studies

Process Development

Good Manufacturing Practice and Quality Controlled Drug Product

Preclinical Safety & Efficacy

Regulatory Affairs and Business Development

MassBiologics

Medicine for Better Lives
Product Discovery

• Responsible for identification and selection of Human Monoclonal Antibodies
  – Monoclonal antibody isolation, transgenic mice, B-cell cloning
  – Develop screening assays for binding and in-vitro potency
  – Characterize leads: Heavy and light chain sequence, affinity, epitope mapping
  – Develop/Test leads in animal models of disease
  – Manage and lead teams of Research Associates and Scientists
Process Development Activities

• **Upstream process development**
  – Cell line, medium, and bioreactor process

• **Downstream process development**
  – Purify proteins

• **Analytical method development**
  – Characterize proteins

• **Formulation development**
  – Safe and stable formulations

• Develop, optimize, scale-up manufacturing processes

• Preclinical material production and technology transfer to GMP manufacturing facility
Mammalian Cell Culture Development

- Full support from transfection to pilot production
- Cell line characterization
- Master & working cell bank creation
- 1L Bench top bioreactors (DasGip & Applikon)
- Wave disposable bioreactors (2-20L)
- Scale up bioreactors (10L & 60L Applikon)
Cell Culture Development

Benchtop Bioreactors
Pilot Scale Production

60L Scale up bioreactor
Analytical Method Development

- Purity/impurity profiles
- Peptide mapping
- Carbohydrate analysis
- Concentration
- ELISA
- Host cell protein
- Host cell DNA
- Activity
- Kinetic/binding assays
- Spent media analysis
Manufacturing Process for MAbs

1. **CIP/SIP**
2. **Vial**
3. **Preculture**
4. **20L Bioreactor**
5. **100L Bioreactor**
6. **500L Bioreactor**
7. **2,000L Bioreactor**
8. **10,000L Bioreactor**
9. **Cation Exchange**
10. **Anion Exchange**
11. **Virus Filter**
12. **Virus Inactivation**
13. **Capture Column**
14. **Diafiltration**
15. **Formulate**
16. **0.2 µm filter**
17. **Fill**
18. **Release**

**Final Steps:**
- **Medium**
- **Buffer**
- **Centrifugation**
GMP BDS Manufacturing

55L & 500L Bioreactors
GMP BDS Manufacturing

2500L Bioreactor & Harvest Tank
GMP Fill/Finish Manufacturing

Bosch Fill Line
Quality

• **Quality Assurance:**
  Responsible for assuring that appropriate procedures exist, are followed in a document manner and investigating and evaluating deviations from such procedures.
  – Independent of manufacturing [21 CFR §211.22]
  – Write what you do: Do what you write
  – SOPs, BRs, standard forms, verifications, reviews

• **Quality Control:**
  Responsible for checking quality of starting, intermediate and finished materials
  – Water, clean room environments, incoming chemical and consumables
  – Safety, Purity and Potency of drug intermediates, bulk and final vial product
  – Microbiology, Chemistry, Biochemistry, Bioassay (in vitro and in vivo)
Validation and Quality Systems

**Validation:**
- Responsible for proving that (engineering) systems perform consistently within specification:
  - sterilization, depyrogenation, temperature controlled units, HVAC etc..
  - written protocols, new systems/periodic reviews/change management
  - FDA mandated for licensed product and “safety” systems for CTMs

**Quality Systems:**
- Management of *Controlled Documents* – paper and virtual
- cGMP archive system (statutory record retention)
- Validation of cGMP computerized systems
- Operation of validated clinical data management systems
Regulatory

• Compile/file Investigational New Drug applications (INDs)
• Maintain Biologics License Application
• Write and file license and IND supplements
• Manage day-to-day and strategic relationship with FDA
• Participate in internal projects to gauge and manage regulatory impact

How do we communicate to the FDA that:
• our products/processes are safe & appropriate for clinical trial subjects

OR, for pivotal trials/licensed products,
• safe in patients
• effective for their intended/labeled indications
Business Development of New Medicines

• Overview of role:
  – Protection of asset: contracts, patents, disclosure review for inadvertent or premature disclosure of IP
  – Commercialization of asset: identify competitors and collaborators, strength/weakness of product, regulatory/reimbursement issues; source collaborators/funding for translational work; negotiate MTAs, research, and clinical trial agreements
  – Management of asset: maintain issued patents; manage collaborations to maximize benefits; re-negotiate/terminate contracts that no longer meet objectives; continued monitoring of competitive landscape related to products
Development of a High Cell Density Fed-batch Insect-cell Based Process Platform


*Process Development and **Product Discovery, MassBiologics of the University of Massachusetts Medical School, 460 Walk Hill Street, Mattapann MA 02126

Abstract
MassBiologics is currently developing a high cell density fed-batch insect-cell based process platform for the production of proteins, viral-like particles and virions for use as human therapeutics. In order to achieve this end, the impact of feeding three different types of nutrient pools on Sf9 cell culture growth was tested using a design-of-experiments (DOE) approach. In the ranges tested, yeastolate and MassBiologics' chemically defined feed (F-19), a protein-free mixture of amino acids, vitamins, trace minerals and other cell culture nutrients, both individually and combinatorially increased maximum culture cell densities while a chemically defined lipids mixture had no significant impact. A yeastolate feed rate was identified above which the maximum cell density obtained was reduced, putatively, due to toxic metabolic by-product accumulation. Maximum cell densities increased with increasing feed rates of MassBiologics' chemically defined feed. Spent medium analysis indicated depletion of several amino acids during the shake flask screen. The feed medium was supplemented with these amino acids and modified feed and feed rates based on the shake flask experiment were implemented in a 1 L scale bioreactor experiment. The highest cell densities obtained during this experiment were approximately 3-fold higher than those obtained in an unfed bioreactor culture.

Methods
Shake Flask Full-factorial Feed Development Experiment

Figure 1. (Top) 3-factor, 2 or 3 level full-factorial DOE designed to elucidate the impact of different feeds on maximum cell density in Sf9 shake flask culture. (Bottom) JMP leverage plots show that, in the ranges tested, yeastolate and MBL's chemically defined feed (F-19) significantly (p<0.05) impact culture maximum viable cell density.

Figure 2. (Top) In addition to increasing or decreasing maximum viable cell density in Sf9 cultures, different feed combinations impacted culture longevity. (Bottom) Results of spent medium analysis at Day 11 indicate that specific amino acids (Ser, Gln, Cys) were depleted from some cultures and, thus, subsequent media formulations should be enriched in these components.

Figure 3. Increased rates of lactate (Top) and ammonia (Bottom) appear to be associated with the higher rate of available feed used in this experiment. Because yeastolate addition is required for optimal growth using the current feed strategy (Figure 1 and Figure 2), it’s feed rate will require optimization in subsequent experiments.

Figure 4. Growth (Top) and culture viability (bottom) of 1 L bioreactor fed-batch and unfed cultures. The maximum VCD of cultures fed with MBL's chemically defined feed, yeastolate and a defined lipids mixture were about 3-fold higher than that of the unfed culture grown under otherwise identical conditions. These results further indicate that the correct combination of the three feeds is required for maximal growth.

Figure 5. Potentially toxic lactate (top) and ammonia (bottom) accumulation were minimized by feeding cultures properly. Higher rates of accumulation occurred, in some cases, after Day 9 when culture growth had ceased.

Figure 6. Growth (top) and percentage of cells expressing GFP (bottom) of infected and non-infected bioreactor (DS) and shake flask (SF) cultures. The bioreactor infected at about 8e6 cells/mL, and the shake flask derived from it infected more quickly (shake flask) and to a higher degree (bioreactor) than those infected at about 7e6 cells/mL. Optimization of this procedure will be subject of future experiments.

Conclusions & Future Work
Using a DOE approach and leveraging in-house analytical capabilities, MassBiologics has developed a high cell density fed-batch process for growing Sf9 insect cells. In bioreactors, the process resulted in a VCD increase of about 300% relative to unfed bioreactor cultures.

Initial infection (GFP-expressing baculovirus) and protein expression experiments indicate that cells can be efficiently infected in bioreactors at a VCD of about 8e6 cells/mL but that infection in this system at a VCD of about 17e6 was inefficient. Differences in infection rates between bioreactors and shake flasks seeded with post-infection cells from the bioreactors indicates that conditions inside the bioreactors are suboptimal for baculovirus infection in a yet-to-be defined way.

Subsequent work will focus on optimizing bioreactor conditions conducive to baculovirus infection and the associated protein expression. For example, high rates of CO2 gassing were required to maintain pH in the desired range (pH<6) in mid to late culture and, as a result, high rates of dissolved CO2 were observed (data not shown, previously demonstrated to be growth inhibitory); an alternative pH control strategy is currently being formulated. It is also anticipated that post-infection feed rates will require optimization since the current feed rates were appropriate for rapidly growing, rather than quiescent, infected cultures.
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