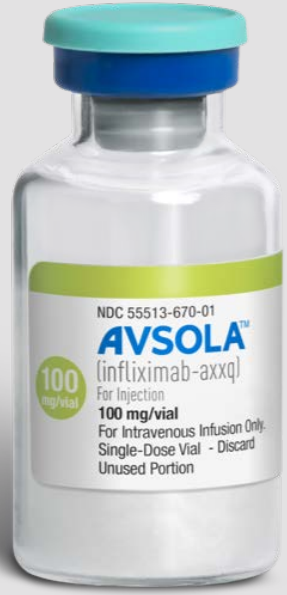
COMMERCIAL BIOSIMILAR DRUG SUBSTANCE TECHNOLOGY TRANSFER: APPROVAL ACCELERATED BY CLINICAL MANUFACTURING SITE EXPERIENCE AND CLOSE & EFFECTIVE COMMUNICATION BETWEEN SPONSOR & HEALTH AUTHORITY

JOCELYN MCQUEEN
GLOBAL REGULATORY AFFAIRS (CMC)
AMGEN, INC.

AMGEN®

PRODUCT INTRODUCTION



- **Product Name: AVSOLA®** (biosimilar to Remicade® (infliximab))
- **Modality:** Monoclonal antibody
- **Mechanism of Action:** Tumor necrosis factor (TNF) blocker [a]
- **Dosage Form and Strength: 100 mg lyophilized power** for in a 20 mL single-dose vial for reconstitution and dilution
- **Administration: Intravenous infusion** at different mg per kg depending on indication
- **Indications:** Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis

[a] Infliximab products neutralize the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit binding of TNFα with its receptors. Infliximab products do not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα.

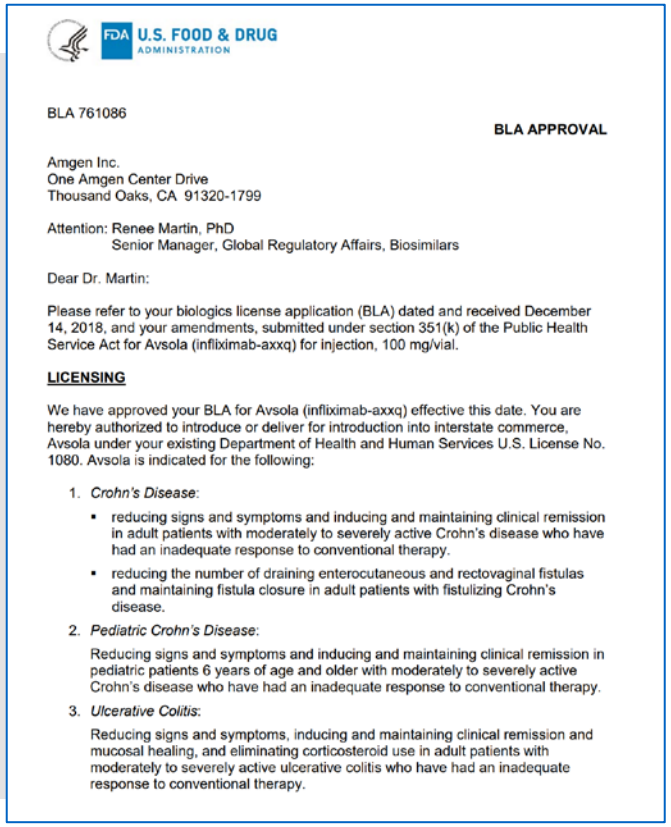
AVSOLA BACKGROUND IN USA

AVSOLA (infliximab-axxq) BLA Approved by US FDA:

Dec 2019

Drug Substance Manufacturing Site at US Launch = Sending Site

BLA = Biological License Application, FDA = Food and Drug Administration



U.S. FOOD & DRUG ADMINISTRATION

BLA 761086

BLA APPROVAL

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Attention: Renee Martin, PhD
Senior Manager, Global Regulatory Affairs, Biosimilars

Dear Dr. Martin:

Please refer to your biologics license application (BLA) dated and received December 14, 2018, and your amendments, submitted under section 351(k) of the Public Health Service Act for Avsola (infliximab-axxq) for injection, 100 mg/vial.

LICENSING

We have approved your BLA for Avsola (infliximab-axxq) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Avsola under your existing Department of Health and Human Services U.S. License No. 1080. Avsola is indicated for the following:

1. *Crohn's Disease*:
   - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
   - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
2. *Pediatric Crohn's Disease*:

   Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
3. *Ulcerative Colitis*:

   Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

COVID-19 HITS GLOBALLY

Coronavirus SARS-CoV-2 sparks COVID-19 pandemic:

early 2020

To enable COVID-19 therapy manufacturing, capacity needed across the Amgen network, AVSOLA drug substance required expedited transfer to Receiving Site

DR_MICROBE/ISTOCK/GETTY IMAGES PLUS

ACCELERATED DRUG SUBSTANCE TECHNOLOGY TRANSFER

Required Innovative Regulatory Strategy

- **Concepts from ICH Q12 and PDA Technical Report 56 employed**

1) **Amgen requested Biosimilar BPD Type 2 Meeting with US FDA (CDER)**
   - **Key points in Regulatory Messaging:**
     - **AVSOLA drug substance previously manufactured for clinical supply at Receiving Site**
     - **Amgen assessed as a low-risk change**
     - Based on following, included in briefing materials:
       - **Process comparisons: clinical [Receiving Site] to commercial [Sending Site] to commercial [Receiving Site]**
       - **Equipment, raw material, and control strategy comparisons**
       - **No change in scale from clinical process to commercial process at Receiving Site**
       - **Reference to robust data set(s) from Receiving Site included in Original BLA (ex. analytical comparability)**
       - **Reference to established commercial manufacturing history & successful inspection history at Receiving Site**

ICH = International Council on Harmonization, PDA = Parenteral Drug Association, BPD = Biological Product Development, CDER = Center for Drug Evaluation and Research

ACCELERATED DRUG SUBSTANCE TECHNOLOGY TRANSFER

Required Innovative Regulatory Strategy

1) **Amgen proposed regulatory flexibility on submission content & accelerated review and approval**
   - **Key Components of Proposal:**
     - **Submit in CMC PAS comprehensive risk-based assessment of expected manufacturing performance at Receiving Site**
     - **Submit in CMC PAS process validation protocol for AVSOLA drug substance manufacturing at Receiving Site**
     - **Commit* to place the first 3 drug substance batches on stability**
     - **Commit* to submit the results of the process validation, including lot release data, following completion**
     - **Commit* to immediately report any process validation or stability out of specification results to the Agency**
     - **Requesting FDA expedite review of CMC PAS based on the current public health concern (COVID-19)**
     - **Requesting FDA waive PAI, and if FDA deemed PAI necessary, consideration of alternatives to on-site inspection**

CMC PAS= Chemistry, Manufacturing, and Controls Prior Approval Supplement (standard review duration 4 to 6 months); PAI = Prior Approval Inspection
* Committed data would be submitted to FDA via submission categories on Slide 9, including Annual Report of Minor Changes (implement, then notify)

ACCELERATED DRUG SUBSTANCE TECHNOLOGY TRANSFER

Required Close & Effective Communication between Sponsor & Health Authority

2) **FDA Written Response in 10 days!** (standard timeline is 90 days)

– **Agreement with Modifications:**

- **Conduct selected extended physiochemical and/or biological characterization on attributes including: primary structure, disulfide integrity, FcRn binding, ADCC, and CDC**
- **Commit to submit lot release data from the first drug product lot filled with drug substance from Receiving Site**
- **Establish a protocol to assess release and/or characterization results against pre-established comparability acceptance criteria or compared to corresponding results from Sending Site**
- **Commit to report the results of the transfer upon successful execution of the protocol as a CBE-30 supplement**
- **Propose expedited review timeline in the upcoming CMC PAS**
- **No comment on final determination of need for PAI, but given pandemic, being flexible. Would assess Receiving Site compliance history upon receipt of CMC PAS to determine if PAI required.**

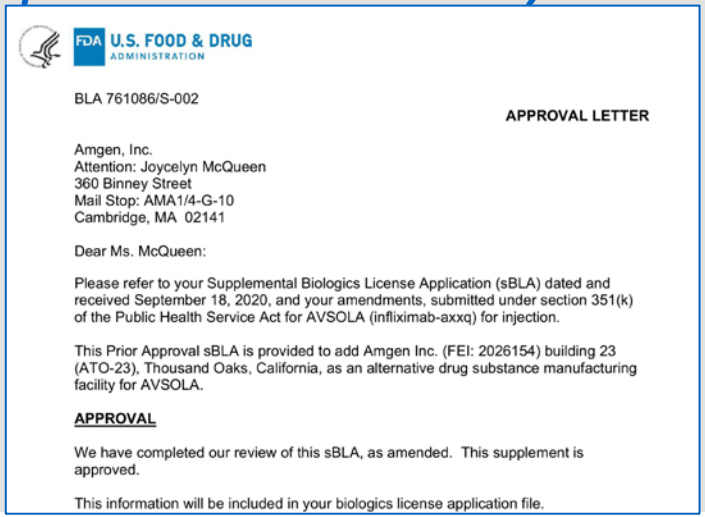
FcRn = neonatal Fc receptor, ADCC = anti-body cell-mediated cytotoxicity, CDC = compliment-dependent cytotoxicity, CBE-30 = Changes Being Effective in 30 Days Supplement

ACCELERATED DRUG SUBSTANCE TECHNOLOGY TRANSFER

Required Close & Effective Communication between Sponsor & Health Authority

3) **Amgen expeditiously submits PACMP as CMC PAS**
   - Submission occurred in parallel to process validation
   - Included status update to FDA on process validation
   - 6 fast rounds of FDA Information Requests & Amgen responses
4) **FDA approves in 2 months!**
   (standard review duration is 4 to 6 months)

   FDA waives PAI!



U.S. FOOD & DRUG ADMINISTRATION

BLA 761086/S-002

APPROVAL LETTER

Amgen, Inc.
Attention: Joycelyn McQueen
360 Binney Street
Mail Stop: AMA1/4-G-10
Cambridge, MA 02141

Dear Ms. McQueen:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received September 18, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for AVSOLA (infliximab-axxq) for injection.

This Prior Approval sBLA is provided to add Amgen Inc. (FEI: 2026154) building 23 (ATO-23), Thousand Oaks, California, as an alternative drug substance manufacturing facility for AVSOLA.

APPROVAL

We have completed our review of this sBLA, as amended. This supplement is approved.

This information will be included in your biologics license application file.

Approval Achieved in Under Half Standard Timeline without PAI!

AVSOLA® (infliximab-axxq) For Injection 100mg/vial

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SUBSEQUENT SUBMISSIONS (LOWER REPORTABILITY), AS COMMITTED

5) CBE-30 containing Receiving Site established conditions & committed data:

- 3.2.S.2.1 (Manufacturer(s)) replaced to add Receiving Site as drug substance manufacturing site
- Description of Manufacturing Process and Process Controls [Receiving Site]
- Raw Materials [Receiving Site]
- Control of Critical Steps and Intermediates [Receiving Site]
- Process Validation data [Receiving Site]
- Process Development History, including process comparisons
- Analytical Comparability, including select characterization data
- Batch Analyses data [Receiving Site]
- Facilities & Equipment [Receiving Site]
- Adventitious Agents Safety Evaluation [Receiving Site]

CBE-30 = Changes Being Effective in 30 Days Supplement (may distribute after 30 days)

6) Annual Report of Minor Changes (ARMC) containing stability data:

- Stability data from drug substance process validation lots [Receiving Site]
- Stability data from commercial drug product lot filled with drug substance manufactured at Receiving Site

ARMC = Implement, then submit notification (no product restriction)

SUMMARY


https://www.nutcache.com/blog

- **Problem Statement:**

  accelerated commercial drug substance technology transfer necessary to open-up manufacturing network capacity for investigational COVID-19 therapy

- **Acceleration & Communication:**

  unique regulatory strategy developed using concepts from ICH Q12 and PDA Technical Report No. 65: Technology Transfer (Agency Meeting and PACMP)

  close and effective communication between Amgen & FDA

- **Solution:**

  commercial drug substance available for distribution earlier than standard timeline, ensuring capacity for investigational COVID-19 therapy, without compromising supply of commercial drug product to patients

AVSOLA (infliximab-axxq) For Injection 100mg/vial

AMGEN

PUBLIC INFORMATION / REFERENCES

- Amgen - AVSOLA website
- AVSOLA US Prescribing Information
- AVSOLA US FDA Approval Letter
- FDA Draft Guidance for Industry: Comparability Protocols for Human Drugs and Biologics (Rev 1, April 2016)
- FDA Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018)
- ICH Q12 Guideline Step 4 (2019)
- **PDA Technical Report No. 65 (Revised 2022): Technology Transfer**