Regulatory Education for Industry (REdI): PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

Bethesda Marriott | Pooks Hill, MD | November 3-4, 2015

Common Deficiencies in Container Labels and Carton Labeling for Biological Products

Jibril Abdus-Samad, PharmD, LT USPHS
Labeling Reviewer

Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ),
Center for Drug Evaluation and Research (CDER)

Objectives

- **Identify common deficiencies for container labels and carton labeling for biological products**
- **Discuss appropriate labeling with regard to proper name, dosage form, strength, route of administration, and manufacturer information**

Common Deficiencies

Common deficiencies observed in CDER during review of products regulated under the Public Health Service Act:

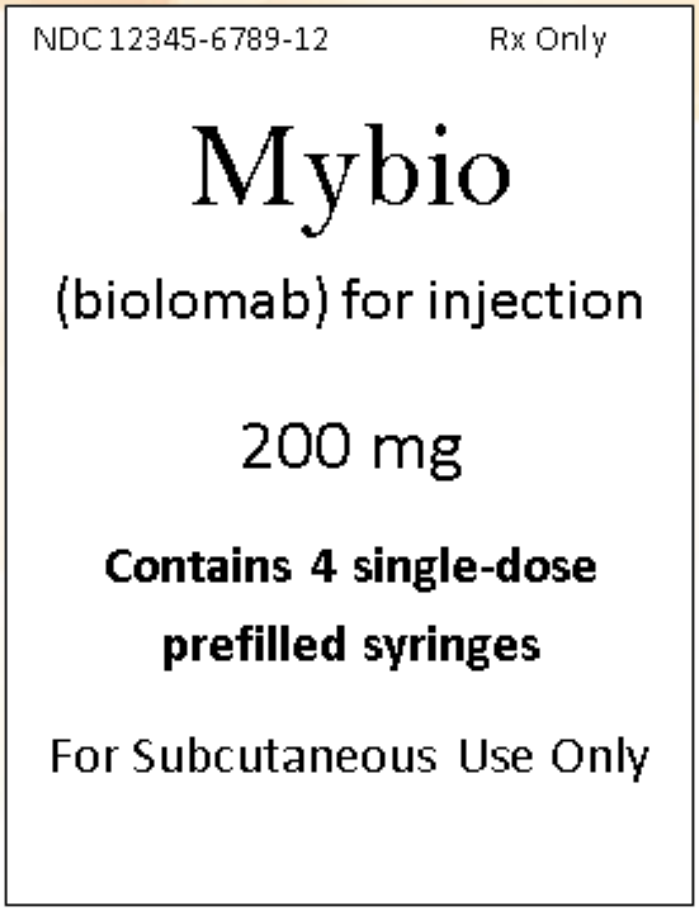
- **Dosage form**
- **Placement of dosage form alongside proper name**
- **Strength**
- **Route of Administration**
- **Manufacturer Information**

Example #1

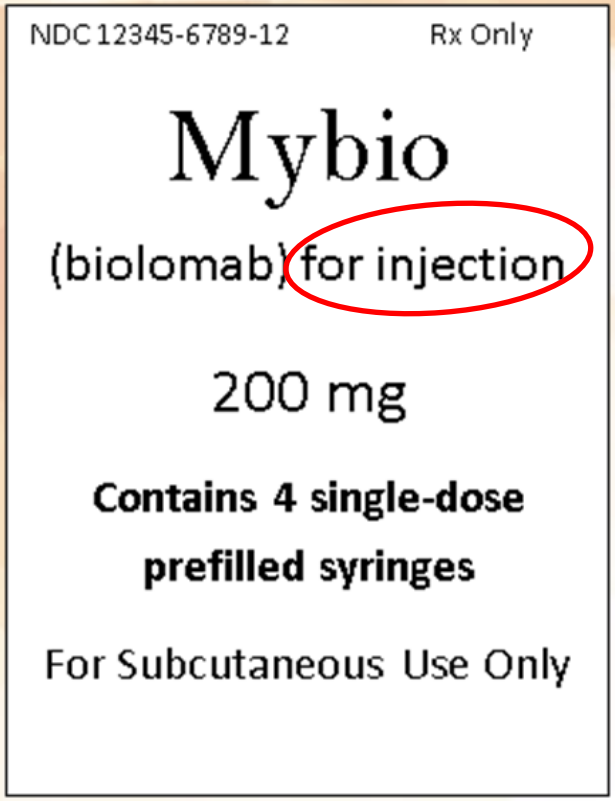
License Bio submits a BLA for Mybio (biolomab)

- **Injectable solution of 200 mg in 0.5 mL in a prefilled syringe**
- **Subcutaneous use**
- **Supplied in cartons containing 1, 2, and 4 prefilled syringes**

Proposed Carton Labeling #1



Deficiency: Dosage Form



- **[DRUG] *Injection*. Liquid preparations that are drug substances or solutions thereof.**
- **[DRUG] for *Injection*. Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for *Injections*.**

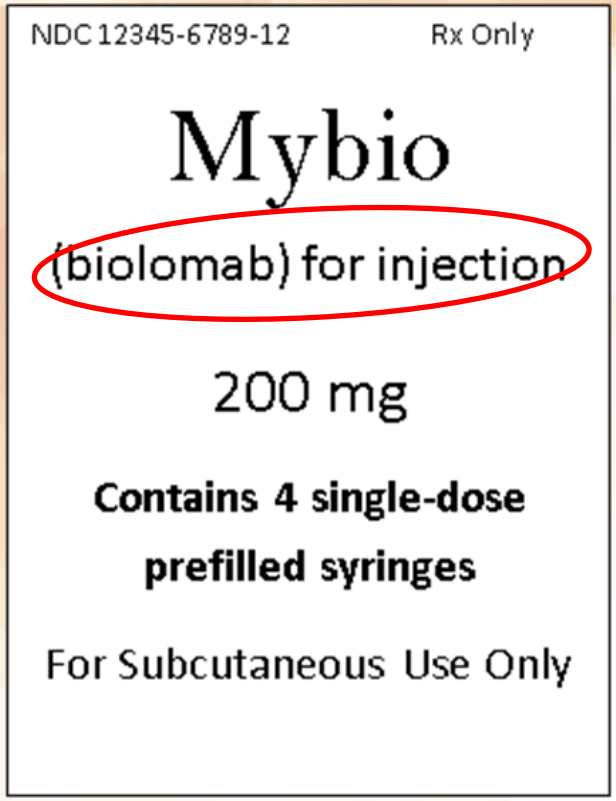
Note: these are the primary dosage forms applicable to OBP products. USP

USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature.

Proper Name Definition

- **Defined in 21 CFR 600.3(k) as applied to a product, means the name designated in the license for use upon each package of the product.**
- **Does not include a dosage form**

Deficiency: Placement of Proper Name & Dosage Form



- **The proper name should not include the dosage form.**
- **The dosage form can appear on the line below the proper name.**

Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Draft Guidance. April 2013
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Correct Proper Name & Dosage Form Placement Options

- **NDA**

Mydrug
(drugozide) injection

Mydrug
(drugozide injection)

Mydrug
(drugozide)
Injection

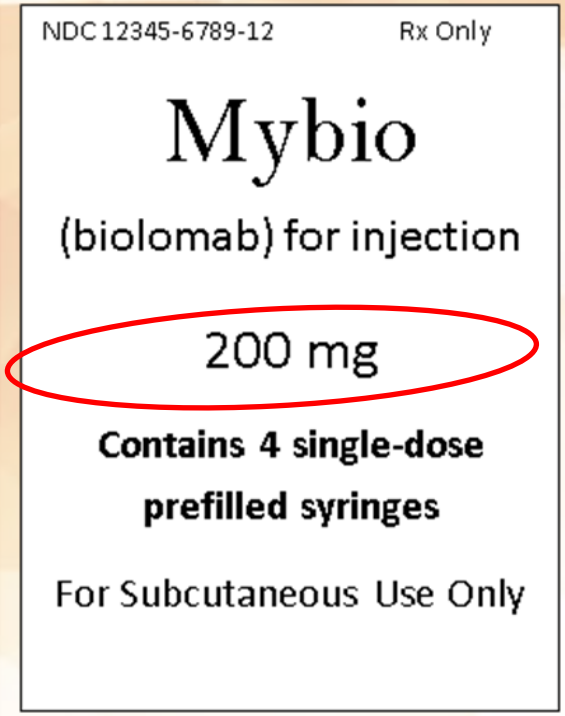
- **BLA**

Mydrug
(drugozide)
Injection

drugozide
Mydrug
Injection

Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Draft Guidance. April 2013
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

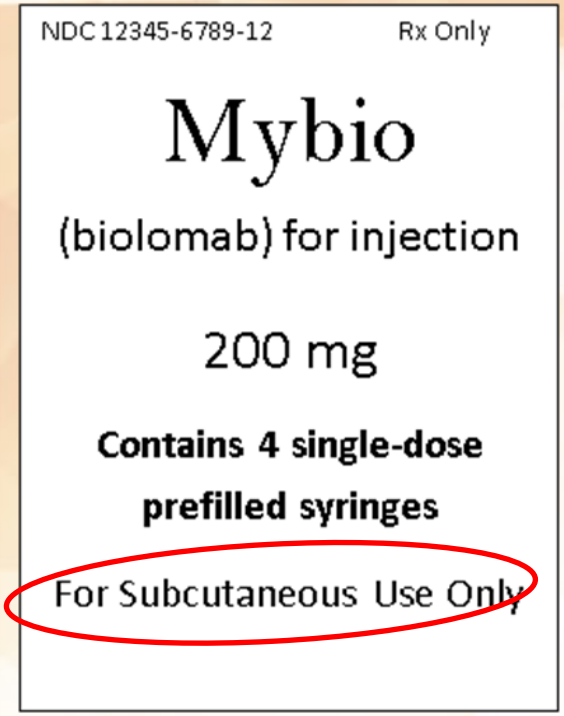
Deficiency: Strength Presentation



- **For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength.**

- USP General Chapters: <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multi-Dose Injectable Drug Products.
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Deficiency: Prominence of Route of Administration



- **Route of administration should appear more prominently than the quantity of prefilled syringes**

- 21 CFR 610.61(k) and 21 CFR 201.15
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Revised Carton Labeling #1

Before

NDC 12345-6789-12 Rx Only

Mybio

(biolomab) for injection

200 mg

Contains 4 single-dose prefilled syringes

For Subcutaneous Use Only

After

NDC 12345-6789-12 Rx Only

Mybio

(biolomab)

injection

200 mg/0.5 mL

For Subcutaneous Use Only

Single-Dose

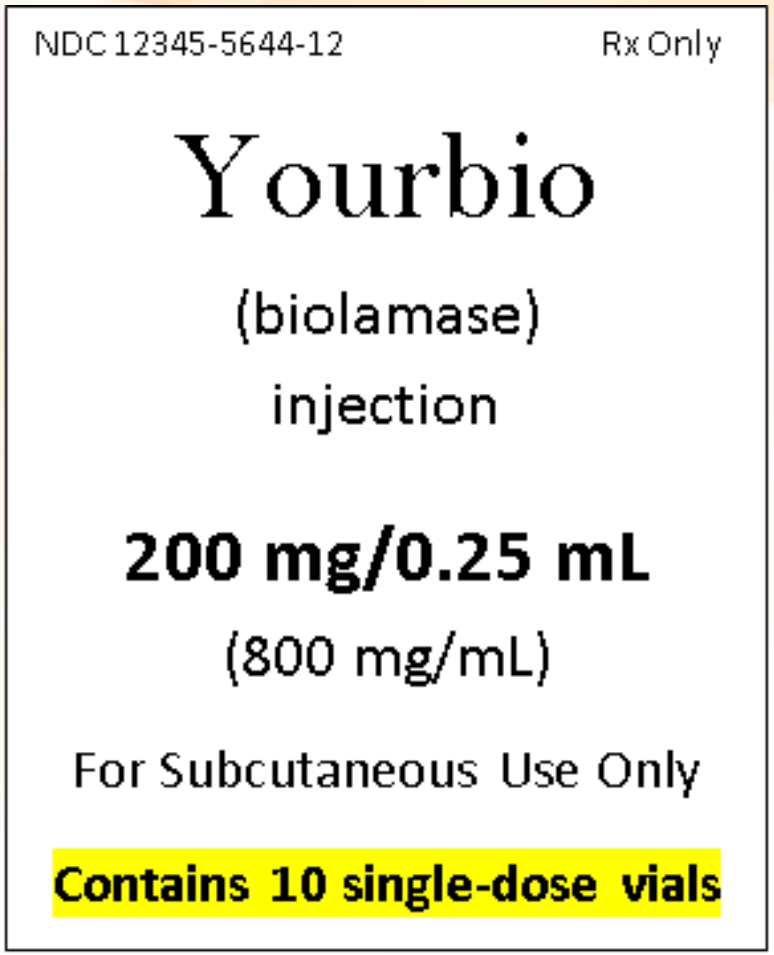
Contains 4 prefilled syringes

Example #2

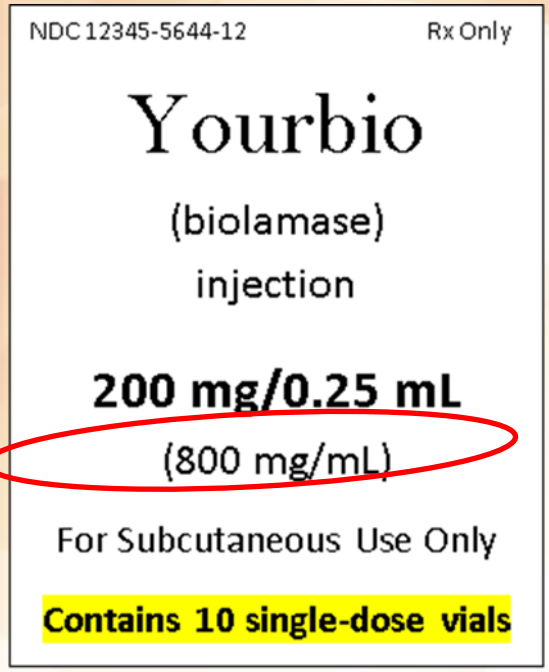
License Bio submits a BLA for Yourbio (biolamase)

- **200 mg/0.25 mL, 400 mg/0.5 mL, and 600 mg/0.75 mL solution**
- **Subcutaneous injection**
- **Single-dose vials**

Proposed Carton Labeling #2



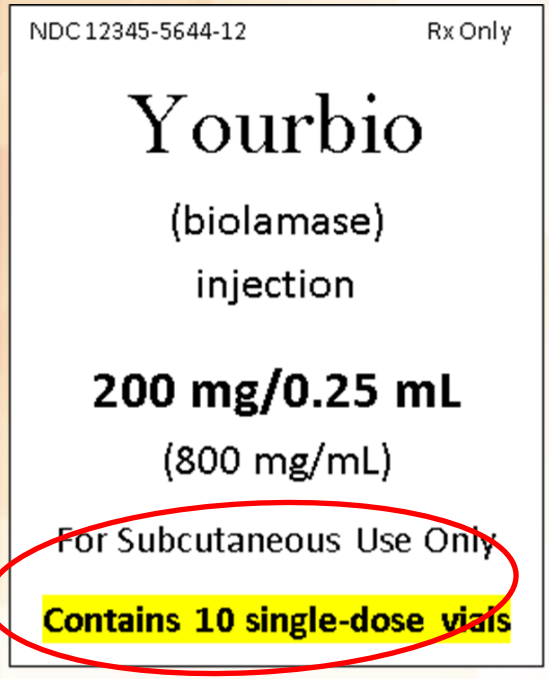
Deficiency: Strength Presentation



- **For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength.**

- USP General Chapters: <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multi-Dose Injectable Drug Products.
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Deficiency: Prominence of Route of Administration



- **Route of administration should appear more prominently than the quantity of prefilled syringes**
- **Color can be used for strength differentiation**
- **Consider other warnings and critical information**

Revised Carton Labeling #2

Before

NDC 12345-5644-12 Rx Only

Yourbio

(biolamase)

injection

200 mg/0.25 mL

(800 mg/mL)

For Subcutaneous Use Only

Contains 10 single-dose vials

After

NDC 12345-5644-12 Rx Only

Yourbio

(biolamase)

injection

200 mg/0.25 mL

For Subcutaneous Use Only

Single-Dose Vial. Discard Unused Portion

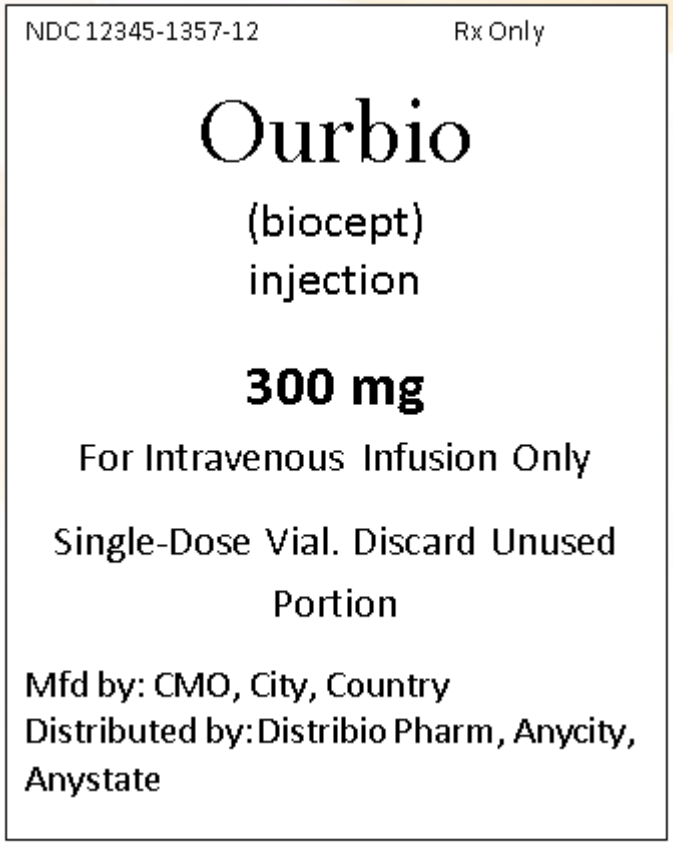
Contains 10 single-dose vials

Example #3

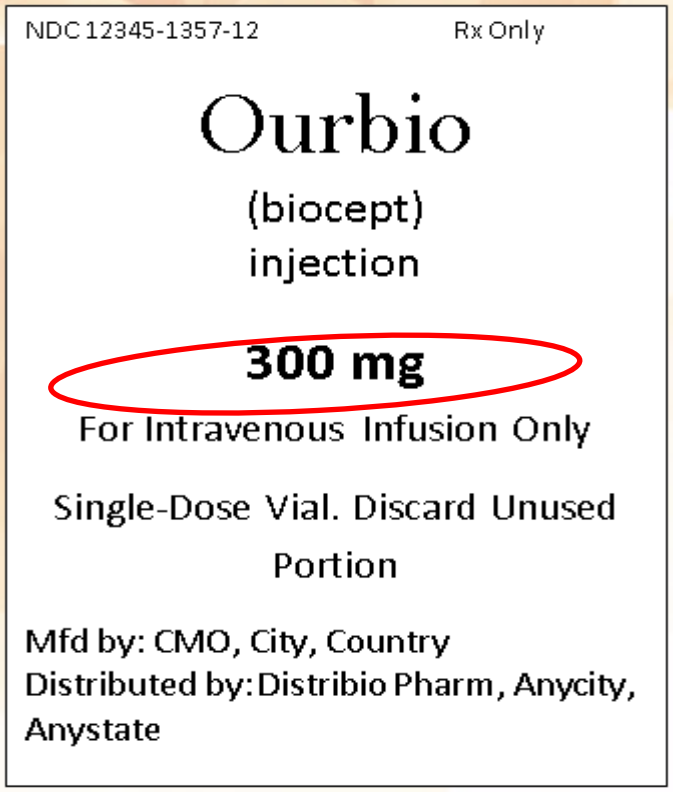
License Bio submits a BLA for Ourbio (biocept)

- **300 mg lyophilized powder in a single-dose vial**
- **Intravenous Infusion**
- **Contract manufacturer in CMO, Inc.**
- **Distributed by Distribio Pharm**

Proposed Carton Labeling #3



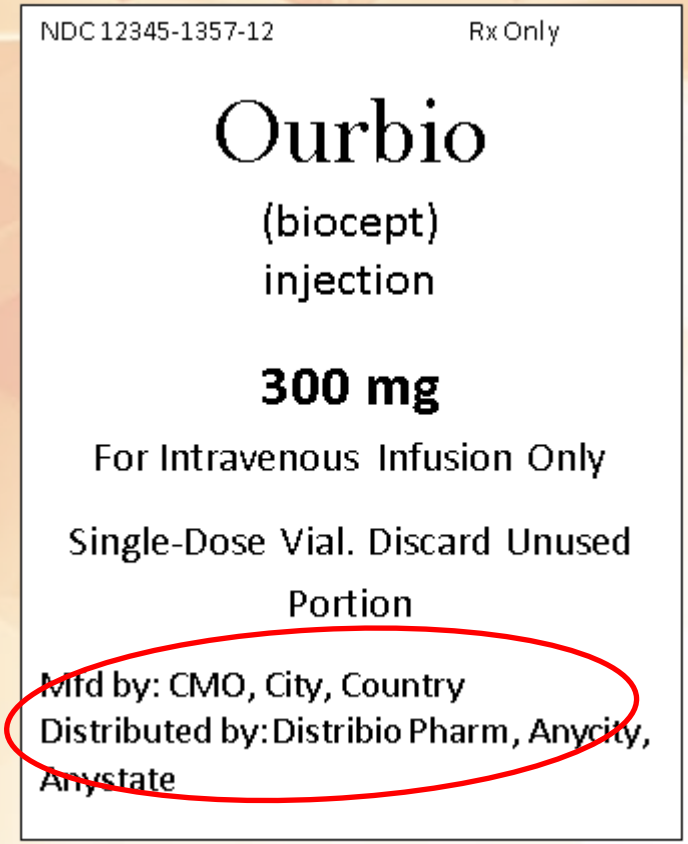
Deficiency: Strength Presentation



- **Dry powder products should express the strength in terms of the total amount of drug per vial**

- USP General Chapters: <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multi-Dose Injectable Drug Products.
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Deficiency: Manufacturer Information


NDC 12345-1357-12 Rx Only

Ourbio

(biocept)
injection

300 mg

For Intravenous Infusion Only

Single-Dose Vial. Discard Unused Portion

Mfd by: CMO, City, Country
Distributed by: Distribio Pharm, Anycity, Anystate

- **The Applicant or licensed manufacturer is considered the manufacturer**
- **Licensed manufacturer name, address, and license number**
- **Contract manufacturer is not required on labeling**
- **Distributor name and address can appear provided the licensed manufacturer name, address and license number appear**

- 21 CFR 600.3(t), 21 CFR 610.60(a)(2), 21 CFR 610.61(b), 21 CFR 610.64
- Guidance for Industry Cooperative Manufacturing Arrangements for Licensed Biologics http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm069908.pdf

Revised Carton Labeling #3

Before

NDC 12345-1357-12 Rx Only

Ourbio

(biocept)
injection

300 mg

For Intravenous Infusion Only

Single-Dose Vial. Discard Unused Portion

Mfd by: CMO, City, Country
Distributed by: Distribio Pharm, Anycity, Anystate

After

NDC 12345-1357-12 Rx Only

Ourbio

(biocept)
for Injection

300 mg/vial

For Intravenous Infusion Only

Reconstitute and Dilute Prior to Use

Single-Dose Vial. Discard Unused Portion

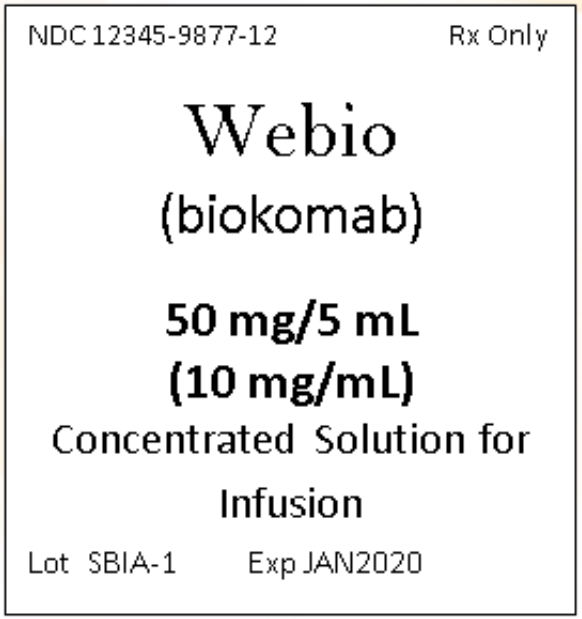
Mfd by: License Bio, Anytown, Anystate,
U.S. Lic. No 9999
Distributed by: Distribio Pharm, Anycity, Anystate

Example #4

License Bio submits a BLA for Webio (biokomab)

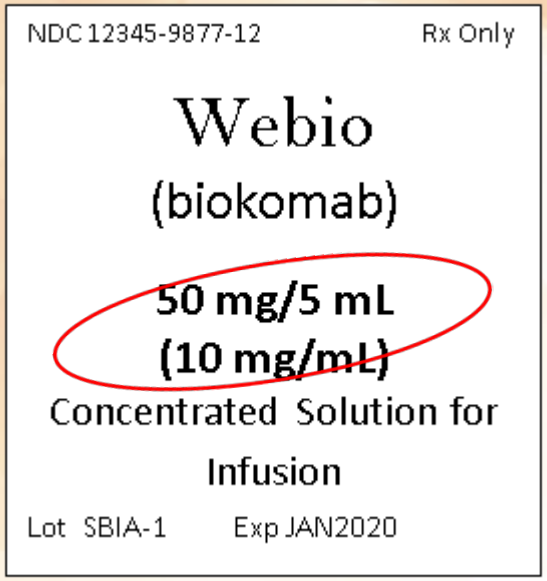
- **50 mg/5 mL injectable solution**
- **Must be diluted**
- **Intravenous infusion**
- **Single-dose vial**

Proposed Container Label #4



Note: Assume this container label is a partial label - 21 CFR 610.60(c).

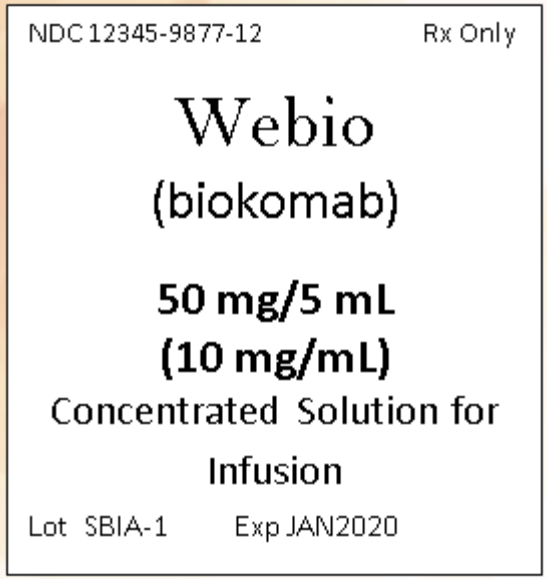
Deficiency: Strength Presentation



- **Strength per total volume expressed prominently, then strength per mL enclosed by parentheses.**

- USP General Chapters: <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multi-Dose Injectable Drug Products.
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

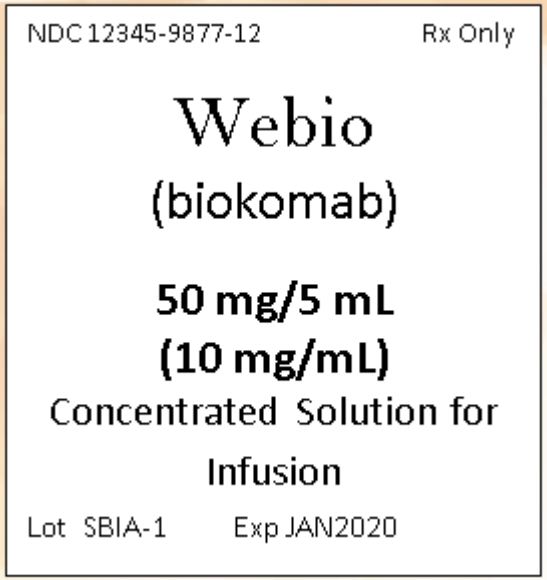
Partial Label Recommendations



- **Name (proprietary and <u>proper</u>)**
- **Strength**
- **Route of Administration**
- **Warnings or Cautionary Statements**
- **<u>Manufacturer</u>**
- **<u>Lot</u> and expiration**

- 21 CFR 610.60(c) and 21 CFR 201.10(i)
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Omissions from Partial Label

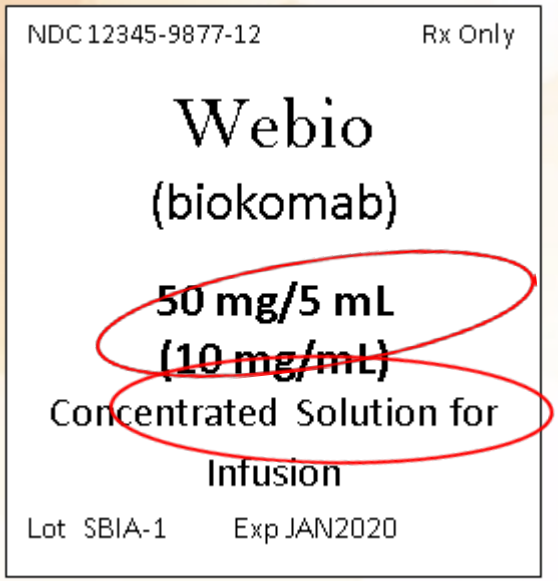


- **Dosage form, Rx only, NDC, & linear bar code**
- **Containers bearing partial labels shall be placed in a package which bears all the items required for a package label**

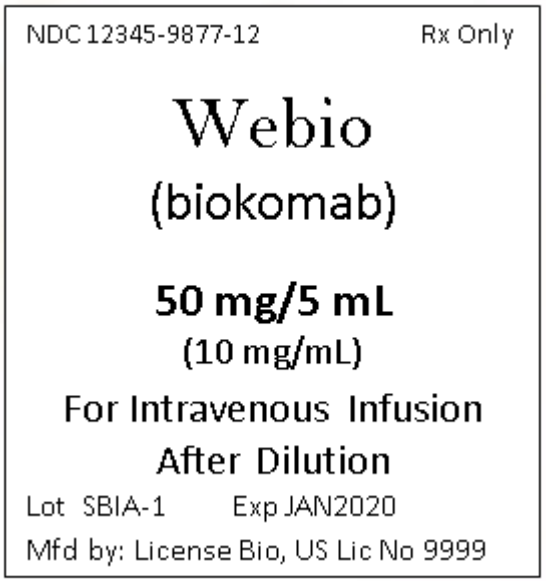
- USP General Chapters: <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multi-Dose Injectable Drug Products.
- Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Revised Container Label #4

Before



After



Summary

Common deficiencies observed in CDER during review of products regulated under the Public Health Service Act:

- **Dosage form**
- **Placement of dosage form alongside proper name**
- **Strength**
- **Route of Administration**
- **Manufacturer Information**

Questions?

References

Code of Federal Regulations

Biologic Labeling Regulations – Subpart G

- **21 CFR 610.60 – Container label**
- **21 CFR 610.61 – Package Label**
- **21 CFR 610.62 – Proper Name**
- **21 CFR 610.63 – Divided Manufacturing**
- **21 CFR 610.64 – Name and address of distributor**
- **21 CFR 610.67 – Bar Code label requirements**
- **21 CFR 610.68 – Exemptions or alternative to labeling requirements for biological products held by Strategic National Stockpile**

Code of Federal Regulations

General Labeling Provisions – Subpart A

- **21 CFR 201.2 – Drugs and devices; National Drug Code numbers**
- **21 CFR 201.5 – Drugs; adequate directions for use**
- **21 CFR 201.6 – Drugs; misleading statements**
- **21 CFR 201.10 – Drugs; statement of ingredients**
- **21 CFR 201.15 – Drugs; prominence of required label statements**
- **21 CFR 201.17 – Drugs; location of expiration date**
- **21 CFR 201.25 – Bar code**

Code of Federal Regulations

Labeling Requirements for Prescriptions Drugs and Insulin – Subpart B

- **21 CFR 201.50 – Statement of identity**
- **21 CFR 201.51 – Declaration of net quantity of contents**
- **21 CFR 201.55 – Statement of dosage**
- **21 CFR 201.100 – Prescription drugs for human use**

FDA Guidance

- **Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Draft Guidance.**
- **Cooperative Manufacturing Arrangements for Licensed Biologics**
- **Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products**
- **Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex**

USP General Chapters

USP General Chapters

- <1> Injections
- <7> Labeling
- <1091> Labeling of Inactive Ingredients
- <1151> Pharmaceutical Dosage Forms

Presentation of Names

- **Biologic**
  - **Proper Name above proprietary name**
  - **21 CFR 610.62**

- **Specified Biologic (21 CFR 601.2)**
  - **Exempt from 21 CFR 610.62**
  - **Proprietary Name above proper name**
  - **21 CFR 201.10(g)(2)**