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1.0 Purpose

This SOP describes the procedure for the generation and approval of product labels, supplementary package labeling, and product information sheets.

2.0 Scope

This procedure applies to labeling used for Current Good Manufacturing Practices (CGMP) and Good Laboratory Practices (GLP) final products and cell/virus banks manufactured in the Biopharmaceutical Development Program (BDP). This SOP applies to bulk and final products and product intermediates that will be released to other institutions for “further manufacturing use only”. This procedure does not apply to labels used for research and development products. Contract manufacturers who produce labels may use their labeling system provided that the labels produced are reviewed and approved by the BDP prior to use.

3.0 Overview of the Process

Label requestors, working with appropriate staff, complete a Request for Label Formatting form (**Form 21403-01**) that collects specific information about the product that is needed for the formatting of product labels. Manufacturing departments select the appropriate label stock and format the label according to a standardized format. A sample of the formatted label (label proof) with appropriate forms (**Form 21403-02**) is routed for review and approval. Final drug product labels, labels for active pharmaceutical ingredients (APIs), and labels and products intended for external distribution receive a higher level of review than labels for products intended for internal use.

When a label’s format has been approved, the label may be produced in quantities sufficient for product labeling according to ***SOP 21411 – Printing, Inspection, and Reconciliation of Product Labels***.

4.0 Authority and Responsibility

4.1 BDP Manufacturing

4.1.1 BDP Manufacturing is responsible for working with appropriate personnel to obtain the required label content elements for the product label, and to initiate the Request for Label Formatting Form.

4.1.2 BDP Manufacturing is responsible for formatting a label proof according to the information described in this SOP and using label stock appropriate for the labeling application.

4.1.3 BDP Manufacturing is responsible for maintaining label proofs (hard copy and electronic) and printed labels in a secure manner until use.

4.2 BDP Project Scientist

4.2.1 The Project Scientist is responsible for providing information on label content and for review and approval, if appropriate, of the label proof.

4.2.2 The Project Scientist is responsible for assisting in determining the appropriate reviewers for the label proof.

4.3 NCI/Pharmacist

4.3.1 The NCI CTEP Pharmacist, or designee, is responsible for the review and approval of the label proof for GMP final products used in CTEP IND's. The BDP may request the pharmacist to review other labels on a case-by-case basis. The NCI Pharmacist does not approve labels for internal use, such as labels for cell/virus banks, product intermediates, or for research and development purposes.

4.4 NCI/Biological Resources Branch

4.4.1 The NCI Project Director is responsible for the review (and approval, if appropriate) of GLP toxicological and GMP final product labels.

4.4.2 The Chief, Biological Resources Branch, NCI, may approve labels for external use on behalf of, or in addition to, the NCI Project Directors.

4.4.3 NCI/BRB personnel may be asked to review other labels on a case-by-case basis.

4.4.4 NCI/BRB Project Director may be asked to assist in determining whether an NCI Pharmacist is required to review the label should the product to be labeled not be part of a CTEP sponsored IND.

4.5 Biopharmaceutical Quality Assurance/Regulatory Affairs

4.5.1 Quality Assurance is responsible for the review and approval of labels according to this SOP.

4.5.2 Regulatory Affairs may be requested to assist in determining the applicable reviewers for the label.

5.0 Requesting Label Formatting (Form 21403-01)

5.1 Manufacturing works with the Project Scientist, NCI CTEP Pharmacist and Principal Investigator (as necessary) to complete **Form 21403-01** "Request for Label Formatting".

5.1.1 The completion of **Form 21403-01** is not required for departments that are formatting product labels for products manufactured within the department and intended for internal use.

5.2 **Form 21403-01** is completed by following the prompts for information on the form.

5.2.1 "TBD" (to be determined) may be used to hold a place for label information that is not yet available (for example: date, titer or concentration).

5.2.2 "XXX" may be used to hold a place for a lot number, date of manufacture or cell count.

6.0 Generation of Label Proof

6.1 Once the appropriate information for label content is obtained on the Request for Label Formatting Form, Manufacturing formats a label to create a label proof for review and approval.

6.2 Select a label stock appropriate to the size of the product container and (for vials) that allows an unobstructed area on the vial for the visual observation of vial contents.

NOTE: This requirement does not apply to labels to be applied to cryovials.

6.2.1 The label substrate and adhesive must be selected to withstand any expected conditions of cold, heat, or dampness to which the vials may potentially be exposed.

6.2.2 Color-coding of label stock can be used to help with differentiating products. Once an alternate color is used, use the same color for any additional requests for the same type of product label.

6.2.3 Commonly used label/vial combinations are provided in the following table. Other combinations may be used as appropriate.

Vial Size	Label Size	Label Part Number
1.5 mL cryovial	0.625 "x 1.625"	22125
2 mL cryovial	0.625 "x 1.625"	22125
2 mL	0.625 "x 1.625"	22125
3 mL	¾" x 1 7/8"	22106
5 mL	¾" x 1 7/8"	22106
10 mL	1" x 2 ¾"	22103
Mini grip Bag for Final Packaging	Cut to Size (~ 1" x 2 ¾")	22103
Box Labels	2" x 4"	Avery

6.3 Product Label and Box Label Formatting

6.3.1 Maintain the placement of label content information in a manner similar to the placement of the information on the Request for Label Formatting form (to the extent possible) so that BDP product labels have a consistent format. See Section 6.3.6 for sample labels.

NOTE: Cell/Virus bank labels have more limited requirements for information. The information on the "Request for Label Formatting" form that is NOT applicable to cell/virus banks is indicated (and therefore, can be deleted from the label).

6.3.2 Use Arial font and attempt to use at least 5-point type. A small font size may cause the label to be unreadable and will not be approved for use. If the necessary information cannot be made readable on the label due to size or font issues, other fonts may be used if approved by all parties signing **Form 21403-01**.

6.3.3 The product name must be distinctive and larger than the rest of the type. Use bold type for the product name. If the name is similar to another product, use a format that emphasizes the difference, when possible.

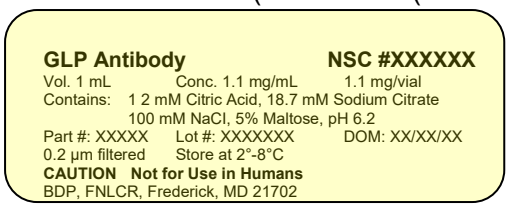
6.3.4 To conserve space, and when available, use scientifically recognized symbols (for example, "#", "μ", "β", "Δ", "≤", etc.).

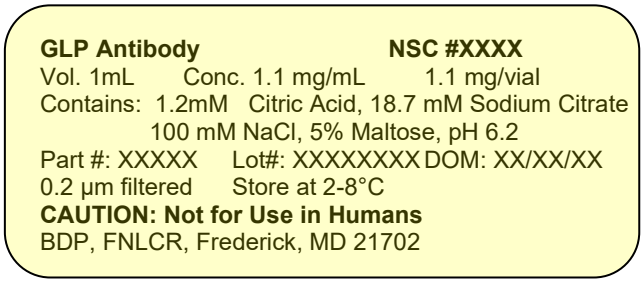
6.3.5 Information that normally would be included on the product label may be deleted from the label if the information will not be available in time for final label printing (for example, concentration of viral particles/mL). Information deleted from the product label must be provided on a supplementary label or an accompanying product information sheet. See table at Section 6.3.8.1, "Label Information – Order of Relevance".

6.3.6 Example Labels

(Shaded areas on labels show the area available for formatting. Enlarged labels are doubled in size.)

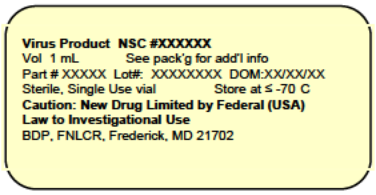
6.3.6.1 Standard Format (Actual size (1 7/8" x ¾")

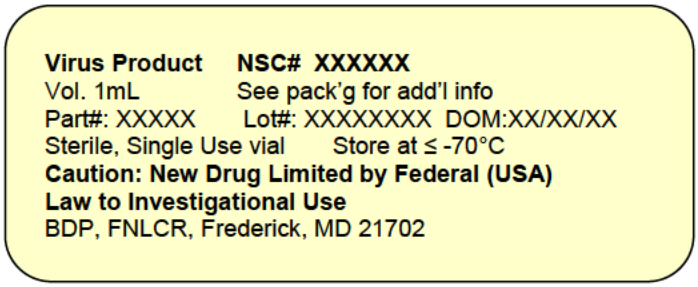




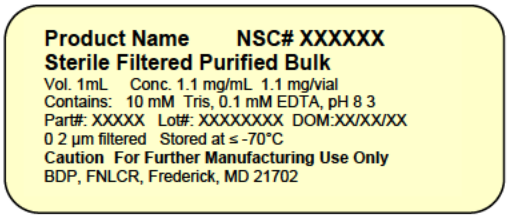
6.3.6.2 Virus Product (Actual size 1 7/8" x ¾")

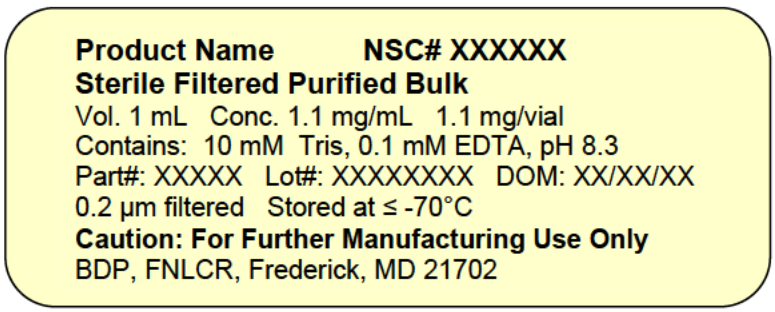
NOTE: When used for labeling of cryovials, this label wraps over itself by about ½". Therefore, only slightly more than 1 ¼" of the label is available for formatting.





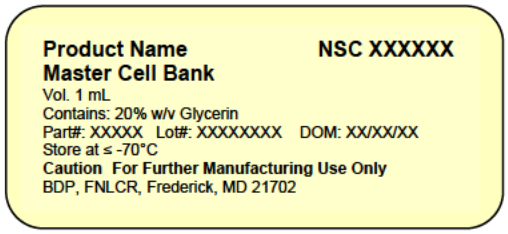
6.3.6.3 Bulk Product (Actual size 1 7/8" x ¾")

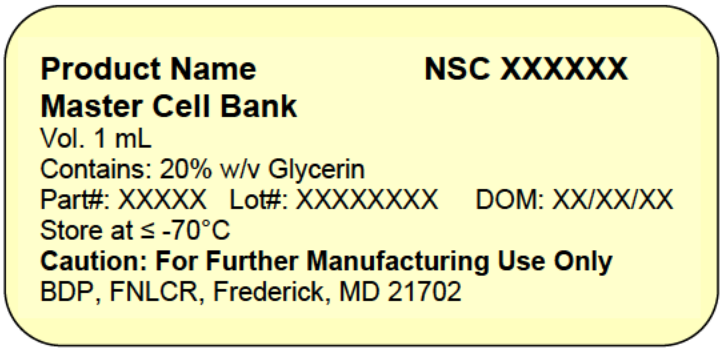




6.3.6.4 Cell/Virus Bank (Actual size 2 ¾" x 1")

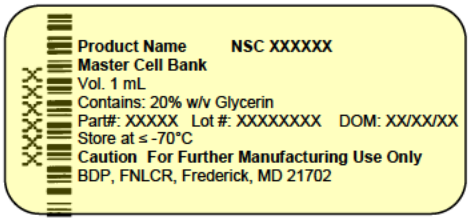
NOTE: When used for labeling of 1 mL vials, this label wraps over itself by about 1". Therefore, less than 1 3/4" of the label width is available for formatting.)

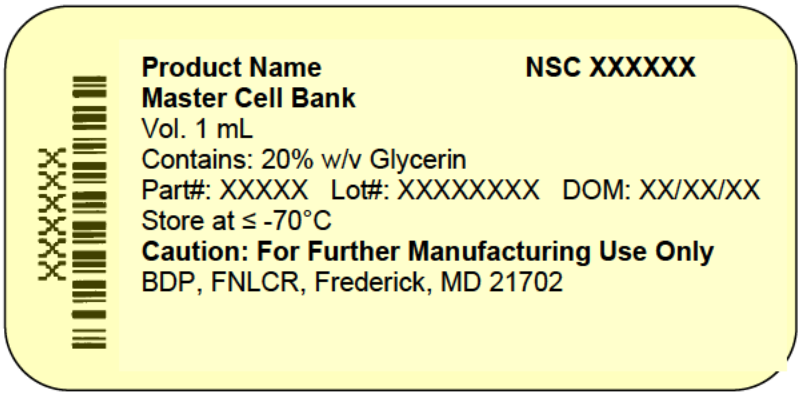




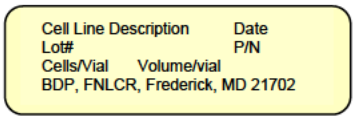
6.3.6.5 Cell/Virus Bank with Bar Code

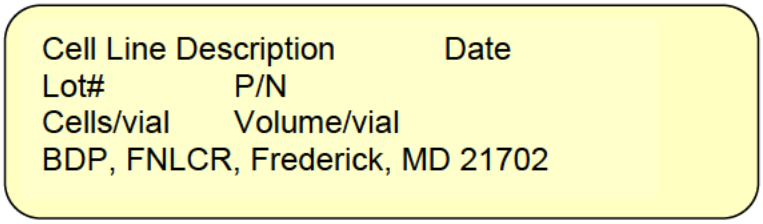
NOTE: When used for labeling of 1 mL vials, this label wraps over itself by about 1". Therefore, less than 1 3/4" of the label width is available for formatting.



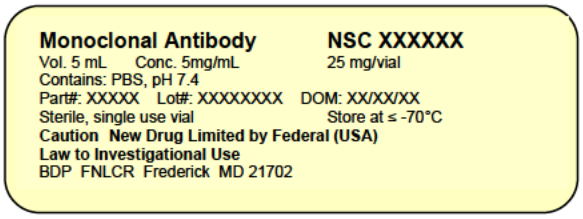


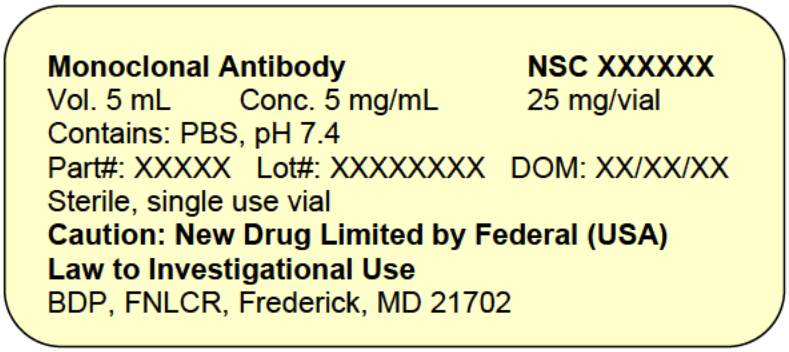
6.3.6.6 Cell Bank Label (Actual size 0.5" x 1.75"), (internal use)





6.3.6.7 Monoclonal Antibody (Actual size 2 ¾" x 1")





6.3.7 Box Labels

6.3.7.1 Box labels are formatted in the same manner as product labels. They may contain more information than will fit on a product label if larger label stock is available for the box label. The standard size for a box label is 2" x 4".

6.3.7.2 Box labels contain the product's BDP part number.

6.3.7.3 Box labels may also contain the number of boxes (for example "Box 1 of 2").

6.3.8 Guidance for Formatting Small Labels

Products with labels that are too small to accommodate all needed information must be accompanied by a supplementary information sheet or supplementary label that completes the presentation of required information. The product label must be formatted to present the most critical information.

6.3.8.1 As general guidance, the order of relevance for label information is presented below, listed from most critical information to least critical information. Specific products may have special requirements. Formatters should involve BQA to assist in the development of the format of small labels. The FDA may be contacted through BDP Regulatory Affairs in the event that immediate product labels cannot accommodate the minimum required information.

LABEL INFORMATION – ORDER OF RELEVANCE

Priority	Content	Required on Primary Label	May be Moved to Supplementary Label
1	Product Lot Number	Yes	No
2	Product Name / Description	Yes	No
3	Manufacturer Identification	Yes	No
4	Caution Statement	Yes	No
5	NSC Number	Yes	No
6	Storage Information (including reconstituted storage information)	Yes	No
7	Concentration & Volume	Yes (when available)	Yes (when information was not available at time of labeling)
8	Date of Manufacture	Yes	No
9	Total Content/Vial	Yes (when available)	Yes (when information was not available at time of labeling)
10	Other Information (for example, “Sterile”, “Single Use Vial”, “Contains no preservatives” or “route of administration” (if exclusive)	Preferred	Yes
11	Special Instructions (for example, “Do Not Shake”, “Protect from Light”, “Filtration required prior to administration”, etc.)	Preferred	Yes
12	Contains: (excipients and formulation components)	Optional	Yes
13	Reconstitution Instructions	If applicable	Yes
14	Route of administration	Optional	Yes

6.3.8.2 The statement “Caution: New Drug Limited by Federal (USA) Law for Investigational Use” must be added to the immediate package of an investigational new drug intended for human use per 21 CFR 312.6. Other caution statements can be added when the product is not intended for human administration such as “For Further Manufacturing Use” (such as for cell banks or bulk material) or “Not for Use in Humans” (for GLP lots).

6.3.8.3 Labels for cell banks intended for internal use, on 0.625" x 1.625" labels, are required to contain only product name, description, cell count/ vial, part number, lot number, and manufacturer's ID (see example); otherwise, if a label is so small that the "required or minimum" information (Items 1 - 9) cannot be accommodated on the label, then written approval from the BRB Project Director and BDP Quality Assurance is required to use smaller fonts, or move "required" items to the supplementary label or information sheet.

6.3.8.4 The label for products that will be accompanied by a supplementary label or information sheet should, when possible, also contain a phrase to indicate where more information is provided (for example, "See accompanying information sheet," "See packaging for additional information," or "See accompanying information for reconstitution instructions," etc.).

Vial Label (limited information)

Ad-D24-RGD **NSC#723256**
3.76E11 vp/mL 0.25 mL Volume
See pckg for add'l info Lot L0506019
Caution New Drug-Limited by Federal (USA) Law to Investigational Use
BDP, FNLCR, Frederick, MD 21702

Bag/Box Label (with additional information)

Ad-D24-RGD **NSC 723256**
9.4E10 vp/vial 3.76E11 vp/mL 0.25 mL volume
Excipients: Glycerol, NaCl, and Tris
Part No 50158 Lot L0506019 DOM 08/03/05
Sterile, single use vial Store at ≤ -70°C
Caution: New Drug Limited by Federal (USA) Law to Investigational Use
BDP, FNLCR, Frederick, MD 21702

6.3.9 When labels have been completely formatted, electronically save the label format on the S drive (S:\,within a folder for the project number and name the file "project number, part number, lot number, label type (product, box, supplementary), version number (starting with 00) ,and date (YYMMDD)." Reference **Form 21403-02**.

For example: the second version of the box label for Project #500, Final Vialed Product (Product Number 50227), Lot L1234567, formatted on February 5, 2016, would have a file name of:

500 50227 L1234567 box Ver02 160205

7.0 Label Proof Review and Approval Form (Form 21403-02)

When the vial, supplementary (if any), and box label have been fully formatted, they are circulated for review and approval to authorize them for use. Label proofs must be approved before labels are produced for product labeling.

7.1 Print a copy of each label format using the label stocks that will be used for the product, and affix each to its own **Form 21403-02**, "Label Proof Review, and Approval."

7.1.1 Input the information prompted for on the form (project number, part number, lot number, label version, etc.).

7.1.2 Include the file name for the electronic file format.

7.2 Circulate the Review and Approval of Label Proofs with the Request for Label Formatting forms to reviewers.

7.2.1 Final drug product labels, labels for APIs (active pharmaceutical ingredients), and labels and products intended for external distribution receive a higher level of review than labels for products intended for internal use. GMP/GLP final drug product, API bulks, and cell or vial banks intended for outside distribution as a final product require review from all applicable reviewers. Cell/viral banks not intended for outside distribution as a final product may have a limited review including the originator, formatter, manufacturing, and QA.

7.2.2 Manufacturing and the Project Scientist will assist in determining the appropriate BDP reviewers of **Form 21403-02** "Label Proof Review and Approval." BQA will review all labels.

7.2.3 Quality Assurance and Regulatory Affairs will determine if an NCI Pharmacist is required to review the label if it is a non-CTEP sponsored IND. Contacting the NCI/BRB Project Officer may be needed. BQA /RA will line out and initial any un-needed reviewers on **Form 21403-02**.

7.2.4 QA has the authority to request additional reviewers at any time to assure a complete review.

7.3 Reviewers will review all label information, paying specific attention to the information they are responsible for (see below).

NOTE: Two people are accountable for the accuracy of each informational item.

REVIEW RESPONSIBILITIES FOR LABEL PROOFS

Reviewers are expected to review ALL label information.

Priority	Content	Accountable Reviewers
1	Product Name/Description	Project Scientist, Pharmacist (if CTEP-sponsored), BRB (if not CTEP-sponsored)
2	Product Lot Number	Manufacturing, Quality Assurance
3	Manufacturer Identification	Manufacturing, Quality Assurance
4	Caution Statement	Quality Assurance, Manufacturing
5	NSC Number	BRB, Pharmacist (if CTEP-sponsored), Quality Assurance (if not CTEP-sponsored)
6	Storage Information (including reconstituted storage information)	Project Scientist, Manufacturing
7	Concentration & Volume	Manufacturing, Project Scientist
8	Date of Manufacture	Manufacturing, Quality Assurance
9	Total Content/Vial	Manufacturing, Project Scientist
10	Other Information (for example, “Sterile”, “Single Use Vial”, “Contains no preservatives” or “route of administration” (if exclusive)	Manufacturing, Project Scientist
11	Special Instructions (for example, “Do Not Shake”, “Protect from Light”, “Filtration required prior to administration”, etc.)	Manufacturing, Project Scientist
12	Contains: (excipients and formulation components)	Manufacturing, Project Scientist
13	Reconstitution Instructions	Project Scientist, Manufacturing

7.3.1 Reviewers document their review as “accept,” or “reject” by checking the appropriate box on **Form 21403-02**.

7.3.1.1 “Accept” indicates that the information was found acceptable, and except for supplying any “TBD” (to be determined) information, the label is fully accurate.

7.3.1.2 “Reject” indicates that the information is incorrect or inappropriate. The label review and approval process will be stopped, and the documentation returned to BDP Manufacturing for label reformatting of a new revision. Reasons for rejection of labels should be listed in the comment section of **Form 21403-02**.

7.3.1.3 Label formats that have been rejected will be updated to correct deficiencies and the revised label proof will be circulated for review and approval again to all reviewers using a new Label Proof Review and Approval form. The earlier "revised" or "rejected" label proof will be circulated attached to the updated label proof for comparison.

7.3.1.4 Once the **Form 21403-02** has been completed with all the required review signatures, the form is signed and dated by BQA (BQA reviews for overall completeness of the form).

8.0 Printing for Labels of Product

8.1 Once a label proof has been approved, labels may be printed for product labeling, see ***SOP 21411 - Printing, Inspection, and Reconciliation of Product Labels***.

9.0 Definitions

9.1 **Active Pharmaceutical Ingredient (API) –** Any substance or mixture of substances intended for use in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

9.2 **Cut Labels –** These are sheet labels or individual labels.

9.3 **Date of Manufacture (DOM) –** For products that are sterile filtered, the DOM is defined as the date that the bulk drug was sterile-filtered directly prior to dispensing into the final product container. For products that are not sterile filtered, the DOM is the date of the last processing step of the bulk preparation. For cell/virus banks, the DOM is the date of dispensing of the cells into vials.

9.4 **Fill Date –** The date the product is to be filled. This date is only used for cell/virus bank labels.

9.5 **Label –** A display of written, printed, or graphic matter upon the immediate container of any article. [FD&C Act sec 201(k)].

9.6 **Labeling –** All labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article. [FD&C Act sec 201(m)].

9.7 **Label Proof –** The proof of the label is an actual label printed on the label stock and used for the purpose of label approval.

9.8 **Nominal –** Target value acceptable to a certain tolerance.

9.9 **Roll Stock Labels –** These labels are on a roll and are printed with a single die.

9.10 **To Deliver –** The usable volume that can be extracted from a vial.

10.0 References and Related Documents

SOP 21411 *Printing, Inspection, and Reconciliation of Product Labels*

Form 21403-01 *Request for Label Formatting*

Form 21403-02 *Label Proof Review and Approval*

21 CFR 312.6 – Labeling of Investigational New Drug

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

21 CFR 58.105 (c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

21 CFR 610.60 (c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer, in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package, which bears all the items required for a package label.

21 CFR 610.60 (e) Visual inspections. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.