

## Off-Label Use of FDA-Approved Drugs and Biologicals

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**Note: This guideline applies to biologics or drugs for which no specific Plan guideline exists**

### Definitions

**Indication:** An indication is defined as a diagnosis, illness, injury, syndrome, condition or other clinical parameter for which a drug may be given.

**FDA approval:** Approval for marketing by the Food and Drug Administration (FDA) of drugs/biologics that are considered safe and effective.

**FDA-approved indication:** An indication depicted on the drug/biologic's official label with prescribing instructions, which includes, but is not necessarily limited to, dosage, route of administration, duration and frequency of administration and population to whom the drug would be administered.

**Medically accepted indication;** any:

1. Usage consistent with FDA-approved indication (labeled indication).
2. Articles or Local Coverage Determinations (LCDs) published by National Government Services.
3. Usage supported by  $\geq 1$  citations in at least 1 of the following drug compendia:
  - American Hospital Formulary Service Drug Information (AHFS-DI) — indication is supportive.
  - Clinical Pharmacology — indication is supportive.
  - NCCN Drugs and Biologics Compendium — indication is a Category 1 or 2A.
  - Micromedex<sup>®</sup> DrugDex<sup>®</sup> — indication is Class I, Class IIa, or Class IIb.
  - Lexi-Drugs<sup>®</sup> — indication is Evidence Level A

**Off-label (also referred to as unlabeled or non-FDA-approved) usage:** Drug/biologic usage for an indication that is not listed on the official label; further defined as administration of the drug/biologic in a way that deviates

significantly from the prescribing information on the official label for a particular indication. This includes, but is not necessarily limited to, dosage, route of administration, duration and frequency of administration and population to whom the drug would be administered.

**Phase II trials:** Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

**Phase III trials:** Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.

### Guideline

*Note: for chemotherapeutic drugs see [Appendix](#) page 5.*

Providers may request coverage of off-label usage. Supportive data substantiating usage must be submitted to the Plan (see pp. 3–4 for documentation requirements); the data must include:

1. A use supported by clinical research that appears in at least 2 randomized controlled trials on large patient groups (e.g., 300–3,000 or more depending upon the disease/medical condition studied) that definitively demonstrate safety and effectiveness.

**OR**

2. If no evidence is available (per # 1), at least 2 trials with reasonably large patient samples (e.g., 20-300) showing consistent results of safety and efficacy. Greater consideration will be given to higher powered studies with levels of evidence in the following descending order: Randomized or nonrandomized controlled trials, prospective cohort studies, retrospective case control studies, cross sectional studies, surveillance studies, consecutive case series, single case series.

Studies submitted for Plan review must come from different centers and be published in national or international peer-reviewed journals (with editorial committees comprised of physicians).

*Note: Peer-reviewed medical literature includes scientific and medical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).*

**OR**

3. A use that is an accepted standard of medical practice. “Are there published recommendations from specialty societies or in other authoritative evidence-based guidelines” (e.g., a state-of-the-art review article published in a recognized textbook or a reputable publication)?

*Note: Acceptance by individual health care practitioners, or even a limited group of health care practitioners, does not typically indicate general acceptance by the medical community. Testimonials indicating such limited acceptance and limited case studies, distributed by sponsors with potential financial conflict of interest in the outcome, are not sufficient evidence of general acceptance by the medical community.*

The broad range of available evidence must be considered and its quality must be evaluated before a conclusion is reached. After such evidence is received, the Plan will, with the appropriate guidance of specialty-specific consultants, as indicated, make a coverage determination for the off-label use of the drug or biological. The Plan may determine usage to be reasonable and necessary for the treatment of illness or injury if, on the basis of available or presented evidence, it is shown to be safe and effective and does not violate national (or in the case of Medicare members) local Medicare determinations and regulations. The approval will include, but is not limited to, diagnosis, dosage, route of administration, duration and frequency of administration and appropriate patient population.

### **Published Evidence Guidance**

In principle, rankings of research design have been based on the ability of each study design category to minimize bias. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

1. Randomized controlled trials
2. Nonrandomized controlled trials
3. Prospective cohort studies
4. Retrospective case control studies
5. Cross-sectional studies
6. Surveillance studies (e.g., using registries or surveys)
7. Consecutive case series
8. Single case reports

The design, conduct and analysis of trials are important factors as well (e.g., a well-designed, well-conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size).

In determining whether there is supportive clinical evidence for a particular use of a drug or biologic, the quality of the published evidence must be considered. Such consideration involves the assessment of all the following study characteristics:

1. Adequate number of subjects.
2. Response rate.
3. The effect on key status and survival indications; that is, the effect on the patient's well-being and other responses to therapy that indicate effectiveness (e.g., reduction in mortality, morbidity, signs and symptoms).
4. The appropriateness of the study design; that is, whether the experimental design (in light of the drugs and conditions under investigation) is appropriate to address the investigative question (e.g., in some clinical studies, it may be unnecessary or not feasible to use randomization, double-blind trials, placebos or crossover).
5. The prevalence and life history of the disease when evaluating the adequacy of the number of subjects and the response rate.



## Appendix

The following sections of the New York State insurance law mandate coverage for chemotherapy. The specific provisions (A) and (B) are also included below.

1. New York Insurance Law § 3216. Individual accident and health insurance policy provisions.
2. New York Insurance Law § 3221. Group or blanket accident and health insurance policies; standard provisions.
3. New York Insurance Law § 4303. Definition of benefits under non-profit medical and dental indemnity or health and hospital service corporations.
  - A. Every policy which provides coverage for prescribed drugs approved by the Food and Drug Administration of the United States government for the treatment of certain types of cancer shall not exclude coverage of any such drug on the basis that such drug has been prescribed for the treatment of a type of cancer for which the drug has not been approved by the Food and Drug Administration. Provided, however, that such drug must be recognized for treatment of the specific type of cancer for which the drug has been prescribed in one of the following established reference compendia:
    - i. National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium™; or
    - ii. United States Pharmacopeia Drug Information; or recommended by review article or editorial comment in a major peer-reviewed professional journal.
  - B. Notwithstanding the provisions of this paragraph, coverage shall not be required for any experimental or investigational drugs or any drug which the Food and Drug Administration has determined to be contraindicated for treatment of the specific type of cancer for which the drug has been prescribed. The provisions of this paragraph shall apply to cancer drugs only and nothing herein shall be construed to create, impair, alter, limit, modify, enlarge, abrogate or prohibit reimbursement for drugs used in the treatment of any other disease or condition.