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FDA-Approved Drugs, Biologicals, Cellular and Gene Therapies

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
RX501.063 Compounded Drug Products
RX503.001 Off-Label Use of Drugs Without a Medical Policy

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

When the requested chemotherapeutic agent is being utilized in a regimen in combination with other chemotherapeutic agents, the entire regimen (including dose, frequency, and duration) must be consistent with recommendations in at least one authoritative source including, but not limited to, FDA labeling and nationally recognized compendia or clinical Guidelines such as National Comprehensive Cancer Network (NCCN) and CMS coverage policy. HCSC may require a provider to submit documentation from nationally recognized compendia, clinical Guidelines, or active Phase III clinical trials supporting the requested regimen.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically

diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Louisiana, R.S. 22:999 prohibits excluding coverage for a drug prescribed for the treatment of cancer even where the FDA has not approved the product for that indication so long as that drug is recognized for treatment of the covered indication in a standard reference compendia or in substantially accepted peer reviewed medical literature. Coverage requirement also includes all medically necessary services related to the administration of the product. Coverage is not required where use of the product for the prescribed indication is contraindicated. "Medical literature" means scientific studies published in a journal specified by the United States Department of Health and Human Services pursuant to Section 1861(t)(2)(B) of the Social Security Action, 107 Stat. 591 (1993), 42 U.S.C. 1395x(t)(2)(B), as amended. "Standard reference compendia" means authoritative compendia as identified by the secretary of the United States Department of Health and Human Services.

EXCEPTION: For HCSC members residing in the state of Louisiana, R.S. 22:1054.1 requires coverage for a minimum initial treatment period of not less than three months for medically necessary drugs prescribed for the treatment of metastatic or unresectable tumors or other advanced cancers even where the drug is not FDA approved to treat the specific tumor type or a cancer of the location of the body afflicted so long as the drug is FDA approved for the treatment of cancer with the specific genetic mutation. Continued coverage of the prescribed drug shall be provided after the initial treatment period if the treating physician certifies the prescribed drug is medically necessary for the treatment of the patient's cancer based on documented improvement of the patient. Coverage may be denied only if an alternative treatment has proven to be more effective in published randomized clinical trials and is not contraindicated in the patient.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: This policy is **only** applicable to those drugs, biologicals, cellular, and gene therapies that are processed under the Medical Benefit (non self-administered drugs, biologicals, cellular,

and gene therapies). Refer to the applicable pharmacy benefit plan for self-administered drugs, biologicals, cellular, and gene therapies approved by the FDA (Food and Drug Administration).

NOTE 2: This policy document will apply **only** when there is no current, active drug, biological, cellular, or gene therapy-specific Medical Policy in place. Upon development of a drug, biological, cellular, or gene therapy-specific policy, the coverage in this policy document will no longer be applicable.

Non-FDA Approved
Drugs, biologicals, cellular or gene therapies without FDA approval for any indication **are considered experimental, investigational and/or unproven**.

Safety, Efficacy and Clinical Benefit
FDA-approved drugs, biologicals, cellular or gene therapies **are considered medically necessary** based on the FDA-labeled indications **only** when the safety, efficacy and established clinical benefit have been identified.
In the event the FDA labeling indicates that clinical benefit has **NOT** been established, the drug, biological, cellular or gene therapy **will be considered not medically necessary**.

The need for genetic testing, scans or other services that might be included in the FDA label as being part of the criteria as a prerequisite to utilize the drug, biological, cellular or gene therapy **may be considered medically necessary** providing that the clinical benefit of the drug, biological, cellular or gene therapy has been established. In the event the FDA labeling indicates that clinical benefit has **NOT** been established, genetic testing, scans or other related services for the drug, biological, cellular or gene therapy **will be considered not medically necessary**.

FDA Approved
Coverage of a drug, biological, cellular or gene therapy that meets the coverage criteria shall also include medically necessary services associated with the administration of the drug.

HCSC reserves the right to request clinical documentation pertaining to the requested therapy or treatment in question, including but not limited to progress notes, laboratory tests and/or diagnostic studies. A request may be considered medically necessary based on the inclusion and exclusion criteria utilized in pivotal clinical trials that subsequently lead to the FDA approval of the product.

FDA-approved drugs, biologicals, cellular or gene therapies **are considered medically necessary** for an indication when any of the following apply:

- The drug, biological, cellular or gene therapy is listed in one of the following standard reference compendia as safe and effective for the prescribed indication:
    - Micromedex DrugDex Compendium (DrugDex);
    - American Hospital Formulary Service Drug Information (AHFS-DI);
    - Clinical Pharmacology (Elsevier/Gold Standard, Inc.);
    - Lexi-Drugs (Wolters Kluwer);

- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium.

OR:

- The drug, biological, cellular or gene therapy is supported by clinical research that appears in peer-reviewed scientific literature specific for the indication in question. **NOTE 3:** Peer-reviewed literature means a published scientific study including a trial that is preferably large, multi-centered and prospective, double blinded and randomized. Peer-reviewed medical literature does not include publications or research studies that are sponsored to a significant extent by a pharmaceutical company or financially interested parties.

Orphan Drugs

Use of an orphan drug **may be considered medically necessary** when used to treat rare diseases and disorders as defined by the Orphan Drug Act of the U.S. Food and Drug Administration.

Clinical Benefit

In the event the FDA labeling for an orphan drug indicates that clinical benefit has **NOT** been established, the drug, biological, cellular or gene therapy will be considered **not medically necessary**.

The need for any genetic testing, scans or other services that might be included in the FDA label as being part of the criteria as a prerequisite to utilize the orphan drug may be **considered medically necessary** providing that the clinical benefit of the drug, biological, cellular or gene therapy has been established.

In the event the FDA labeling indicates that clinical benefit has **NOT** been established, any genetic testing, scans or other related services for the orphan drug, biological, cellular or gene therapy will be **considered not medically necessary**.

Coverage of a drug, biological, cellular or gene therapy that meets the coverage criteria shall also include medically necessary services associated with the administration of the drug, biological, cellular or gene therapy.

NOTE 4: An Orphan Drug is defined in the 1984 amendments of the Orphan Drug Act as "a drug intended to treat a condition affecting fewer than 200,000 persons in the United States or will not recover development cost, plus a reasonable profit, within seven years following FDA approval. The Orphan Drug Act was signed into law on January 4, 1983."

NOTE 5: This policy does not address the use of a drug off-label. Refer to **RX503.001 Off-Label Use of Drugs without a Medical Policy** for coverage on drugs used off-label and no current Medical Policy is in place.

NOTE 6: This policy does not address compounded drugs. Refer to **RX501.063 Compounded Drug Products.**

Policy Guidelines

None.

Description

Food and Drug Administration (FDA)
The FDA is a U.S. (Federal) government agency that regulates the following items:

- Food (human and animal, other than meat and poultry);
- Dietary Supplements (human and animal);
- Drugs (human and animal);
- Cosmetics;
- Medical and/or Occupational Devices, Equipment, Supplies (human and animal);
- Radiation Emitting Products (human and animal);
- Biologics; and
- Blood Products.

The FDA is responsible for:

- Protecting the public health by assuring that foods (except for meat from livestock, poultry and some egg products which are regulated by the U.S. Department of Agriculture) are safe, wholesome, sanitary and properly labeled; ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective;
- Protecting the public from electronic product radiation;
- Assuring cosmetics and dietary supplements are safe and properly labeled;
- Regulating tobacco products; and
- Advancing the public health by helping to speed product innovations.

The FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions.

The mandate of the FDA is to regulate, by approving, labeling, and monitoring, the numerous medical products in an expeditious, yet thorough evaluation of the product's safety and effectiveness in meeting the labeling claims. The process is handled by FDA review teams to recommend approval of a product. Following approval, safety teams determine whether the product is hurting an individual. Under current law, the FDA must approve all drugs and devices before they can be marketed. Although the process may be known as the FDA testing program, the FDA does very little of the testing. The developer of a new drug or device uses its own lab or hires another private company to conduct animal tests on the product for safety before proceeding to clinical trials. Generally these tests are often conducted by a medical school department or consulting firm. When each phase of the testing is completed, the developer submits details of the testing process, evidence of adherence to FDA protocols, and the test results to the FDA.

The FDA requires clinical testing for most products, such as drugs, devices, biologics, and blood products. However, dietary products are not pre-approved for safety and efficacy. Only after the dietary supplement has been marketed, the FDA monitor for unsafe products. Certain foods, such as infant formulas or medical foods are regulated more strictly than other dietary supplements as they are consumed by highly vulnerable individuals.

Neither the FDA nor the federal government regulates the practice of medicine. The FDA's role is to mandate that products should be labeled with their ingredients, be safe, and be effective. A licensed provider may choose to use an FDA approved product for other indications than those stated on the product label. Off-label use is not illegal. (Refer to Off-Label Use of FDA Approved Drugs policy for coverage criteria.) There is an obligation by providers to report any adverse events, including events resulting in hospitalization or death of a patient, especially those not previously described on the product label.

Authority for the FDA comes from laws from the Legislative branch, and regulations, which are the interpretations of laws, from the Executive branch of the Federal government. The basic law is found in the FD&C Act, and the regulations are found in the Code of Federal regulations.

It is important to recognize that it is never a drug or other product, such as a device, that is approved or not approved, but a claim about the use of the drug or other product. The claim is granted a marketing license, which is, in effect, a product label.

FDA Approval Process For Drugs Or Biologicals

The drug approval process from a laboratory to the market shelves is usually long with varied routes of exploration. Often a drug is developed to target a specific disease, while others are discovered by accident. Most drugs undergo pre-clinical animal laboratory testing or trials, never advancing to human clinical trials or review by the FDA. If a drug does advance to the FDA, a rigorous evaluation begins by scrutinizing the clinical trial design, the severity of adverse effects, the manufacturing conditions, the labeling instructions, and the drug distribution and regulations. The following stages list the process to drug approval:

- Stage One – Drug manufacturer or sponsor applies to the FDA by submitting an Investigational New Drug (IND) Application. The FDA must be shown the results of pre-clinical testing and the proposals for human testing. The FDA determines whether it is safe to move forward with drug testing on humans.
- Stage Two – Clinical trials begin once the IND is reviewed by the FDA and a local institutional review board (IRB). The IRB is responsible for approving the clinical trial protocols, to mandate the participants have given consent and are fully informed of the risks, and to direct researchers take appropriate steps to protect participants from harm.
- Stage Three – The formal step is for the drug sponsor to request the FDA's consideration in approving a new drug for marketing in the U.S., via a New Drug Application (NDA). The NDA includes all the animal and human testing data and analysis of data as well as information about the drug's behavior in the participant's body, and how the drug will be manufactured. A review team of physicians, chemists, statisticians, microbiologists, pharmacologists, and

other experts evaluates the studies the sponsor submitted showing the drug is safe and effective for its proposed use. The FDA may call on an advisory committee of outside experts to review the NDA and make their recommendations. Traditional approval requires that clinical benefit be shown before approval can be granted. Accelerated approval is given to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments. This allows an NDA to be approved before the required measures of effectiveness are available.

There are a number of reasons the FDA may not approve a product claim, including:

- Insufficient evidence to support the claim,
- The risks are considered unacceptable, or
- The FDA and the sponsor cannot come to an agreement about the scope or wording of the claim.

For example, the majority of oncology drugs that are not approved on the basis of the first initial application are subsequently approved upon resubmission of study data or revision of the claim.

510(k) Clearance Process

From 1976 going forward, any product that was found to be essentially similar to one that was marketed prior to May 28, 1976 was basically "grandfathered in." This is known as the 510(k) clearance process, and the manufacturer is only required to demonstrate the new product is essentially similar to a product that was marketed prior to 1976. When a product passes through the 510(k) clearance process, the FDA states that it has "cleared" the product for marketing, not approved it, but this distinction is not always made in everyday practice.

For example, the common over-the-counter (OTC) drug, Aspirin, originated in Germany prior to World War I. After the war, the U.S. and other countries did not officially recognize the patent held by the German manufacturer on Aspirin; therefore, this allowed U.S. manufacturers to make Aspirin under various brand names. Any drug marketed before 1938 received "grandfather" status as the manufacturers did not have to show efficacy. Then again, prior to 1976, any drug that was similar did not require testing and was cleared by the FDA under the 501(k) clearance process and "grandfathered". Of note, there is not one true "brand" of Aspirin. If any manufacturer had applied to market Aspirin for use with new indications in 1976 or after, it may have been designated as a prescription only drug.

Premarket Approval (PMA) Process

In the PMA process, the manufacturer is required to provide the FDA with clinical data regarding the safety and effectiveness of the product. Typically, this data is generated through an investigational device exemption (IDE) trial that has been reviewed by the FDA. The manufacturer presents the data to an FDA advisory committee. The committee votes on a recommendation for further action to the FDA. If the advisory committee recommends for approval, the FDA takes the recommendation under advisement and issues their final determination sometime after the advisory committee meeting. The time frame is

unpredictable, ranging from a month to over a year. Frequently, there is publicity when the advisory committee recommends approval, but final FDA approval, if given, occurs later.

Orphan Product Designation (OPD)
An Orphan Drug is defined in the 1984 amendments of the Orphan Drug Act as "a drug intended to treat a condition affecting fewer than 200,000 persons in the United States or will not recover development cost, plus a reasonable profit, within seven years following FDA approval. The Orphan Drug Act was signed into law on January 4, 1983."

Rationale

While there may be exceptions, most benefit plans or health contracts specifically exclude coverage for the patient's use of drug(s) when used:

- During a clinical trial or study, and/or
- For purposes or in a manner other than the service was intended, and/or
- For cosmetic or not medically necessary indications or conditions, and/or
- In instances considered to be experimental, investigational and/or unproven.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J1302, J1747, J3490, J3590, J9376, J9999, [Deleted 10/2022: C9094]

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. FDA.gov – Is It Really FDA Approved? U.S. Food and Drug Administration. Available at <http://www. fda.gov> (accessed December 7, 2022).
2. FDA.gov – The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective. U.S. Food and Drug Administration. Available at <http://www.fda.gov> (accessed December 7, 2022).
3. Novitas Solutions, Inc. Local Coverage Article: Approved DRUGS and Biologicals; Includes Cancer Chemotherapeutic Agents (A53049). (Eff 06/06/2022). Available at <http://www.cms.gov> (accessed December 7, 2022).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
07/15/2024	Reviewed. No changes.
01/15/2024	Coverage revised to include cellular or gene therapies throughout the medical necessity and experimental, investigational and/or unproven coverage positions. Title changed from FDA-Approved Drugs and Biologicals.
06/01/2023	Reviewed. No changes.
1/15/2023	Document updated with literature review. The following change was made to Coverage: Updated list of standard reference compendia. No new references added; reference 3 updated.
8/1/2021	Reviewed. No changes.
9/15/2020	Document updated with literature review. Coverage unchanged. Added references 2, 3, 5-18.
4/1/2019	Added the following as an editorial clarification for denial reason when stated criteria are not met: Drugs and biologicals without FDA approval for any indication are considered experimental, investigational and/or unproven.
6/15/2018	Reviewed. No changes.
8/9/2017	New Medical Policy document. Coverage addresses FDA-approved drugs and biologicals when no specific drug/biological policy is available.