Guidance for Industry

의약품 제조에 사용되는 단클론 항체

(Monoclonal Antibodies Used As Reagents in Drug Manufacturing)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
March 2001
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I. 서론(INTRODUCTION)

This guidance is intended to provide recommendations to sponsors and applicants on the use of monoclonal antibodies (mAbs) as reagents in the manufacture of drug substances\(^1\) that are regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The guidance focuses on the chemistry, manufacturing, and control (CMC) issues that should be addressed in new drug applications (NDAs), abbreviated new drug applications

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\(^{1}\) This guidance has been prepared by the Monoclonal Antibodies Working Group of the rDNA Reagent Technical Committee of the Complex Drug Substances Coordinating Committee (CDS CC) in the Center for Drug Evaluation and Research (CDER), with input from the Center for Biologics Evaluation and Research (CBER), at the FDA.

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\(^{2}\) The term drug substance, which is used throughout the text, is intended to include biological products as defined in 21 CFR 600.3(g).

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본문 전체에 나오는 "원료의약품"이라는 용어는, 21 CFR 600.3(g)에 정의된 생물학적 제품도 포함한다.
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(ANDAs), biologics license applications (BLAs), supplements to these applications, or investigational new drug applications (INDs).

This document presents issues associated with and recommendations on the documentation to support the use of mAb reagents generated by hybridoma technology or production of recombinant mAb or their fragments in bacteria, including phage display technology, fungi (yeasts and molds), and nonprimate animal-derived transfected cell lines. Monoclonal antibodies or their fragments generated by other methods can present additional concerns. The recommendations provided in this document should be considered when such materials are used; however, the guidance does not address the particular method of production of the mAbs or their fragments.

This document does not provide recommendations on mAbs that are used as diagnostics, radiolabeled imaging agents, or therapeutic products. For a discussion of mAb products for human therapeutic or diagnostic use please refer to the Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (PTC 1997). The recommendations for characterization and testing for mAbs used as parenteral pharmaceuticals are by necessity stringent, and not all of them are applicable to mAbs that are used as reagents in drug manufacturing.

3 This document is available on the Internet at http://www.fda.gov/cber/points.htm.
II. 배경 (BACKGROUND)

Monoclonal antibodies are immunoglobulin molecules secreted from a population of identical cells (i.e., cloned cells). They are homogeneous in structure and binding specificity. In the context of this guidance, mAb reagents refers to monoclonal antibodies used as reagents in a drug substance manufacturing process.

The issues related to mAbs used as reagents are somewhat different from those of mAbs used as parenteral therapeutic agents. For mAb reagents, the primary emphasis is on assessment of the following:

- Biological safety, in particular the assessment of contamination of the mAb reagent with adventitious agents and/or process-related impurities from the cell substrate or cell line sources.
- Performance characteristics of the mAb reagent during drug substance manufacture (e.g., avidity and specificity for the target molecule).
- Potential presence of residual amounts of the mAb reagent in the final drug substance and/or drug product.

mAb 시약으로 사용되는 mAb의 특성 분석 및 시험에 관한 권고 사항은 엄격하며, mAb 시약으로 사용되는 mAb에는 그 모든 것이 적용되지 않는다.
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The recommendations in this guidance apply to the use of mAb reagents in the drug substance manufacturing process where the mAb reagent is used to purify the drug substance. The extent of characterization required for the mAb reagent depends on the nature of the steps that follow use of the mAb, and thus will vary among submissions. While many CMC concerns regarding the use of mAb reagents are unique to biotechnology-produced reagents, the general concepts expressed in the FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (FDA 1987) also apply. An early and continued dialogue between the applicant and the Agency is encouraged to discuss the data that should be submitted to support the use of the mAb reagent.

III. Monoclonal Antibody Reagents (PRODUCTION OF MONOCLONAL ANTIBODY REAGENTS)

The sponsor or applicant should submit information (e.g., production process, specification) to support the use of the mAb reagent or a letter of authorization (LOA) to a drug master file (DMF) that contains this information. A description of the mAb manufacturing process should be provided. The description is used to assess the potential impact on the biological safety, quality, and purity of the drug substance and/or drug product. The mAb reagent should be adequately characterized and its identity, purity, and structural integrity should be assessed, as these factors are vital to its efficient and uninterrupted performance during production of drug substances (see section IV). Reagents that have not been fully characterized for viral safety should not be introduced into facilities where
biologics and drugs from mammalian cell culture are produced because of the potential for cross-contamination. Additional recommendations relating to mAb reagents are:

- For mAb reagents prepared using hybridoma propagation, serum additives in culture media should be free of contaminants and adventitious agents.
- Manufacturers should use bovine-derived materials only from cattle that were born, raised, and slaughtered in countries that are free of BSE (bovine spongiform encephalopathy).4

The predominant concern with the use of mAb reagents in drug substance manufacture is the introduction of adventitious agents (e.g., viruses, bacteria, fungi, mycoplasma) and/or process-related impurities (e.g., protein and DNA contaminants, column leachables, media components) into the drug substance. Of particular concern are those that are not removed during drug substance manufacture steps after the introduction of the mAb reagent. In many instances, the extent of the cell bank safety characterization and the clearance studies for

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4 A list of countries affected by BSE or those that have a substantial risk associated with BSE (due to a lack of implementation of an adequate surveillance program) can be found on the Internet at http://www.aphis.usda.gov/NCIE/country.htm

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adventitious agents and/or process-related impurities should follow the established standards for mAbs intended for human use (see PTC 1997, sections II.B and C). A reduced level (i.e., less than recommended in PTC 1997) of testing of cell banks and/or validation of the procedures used to remove or inactivate adventitious agents and/or process-related impurities during purification of the mAb may be appropriate under certain circumstances, with justification. Early dialogue with the Agency is encouraged when a reduced level of testing and/or validation is planned. A reduced level can be justified when, for example:

- The drug product is terminally sterilized.

- The use of the reagent is followed by adequate steps for the removal and/or inactivation of the adventitious agents and/or process-related impurities. In this instance, the overall assessment of the removal and/or inactivation process can take into account validation data from steps in the manufacture of the reagent and manufacture of the drug substance.

- Processing steps downstream of the reagent include extremes of pH.

원료의약품 제조에 mAb 시약을 사용하는 것과 관련하여 주로 우려되는 부분은, 외래성 인자(예, 바이러스, 세균, 진균, 마이코플라즈마) 및/또는 공정 관련 불순물(예, 단백질 및 DNA 오염물, 칼럼 유출물, 배지 성분)이 원료의약품에 유입될 가능성이다. mAb 시약 도입 이후의 원료의약품 제조 단계에서 제거되지 않는 것이 특히 우려 대상이다. 사람용 mAb에 대해 설정된 표준에 따라 세포 뱅크 안전성 평가와 외래성 인자 및/또는 공정 관련 불순물의 클리어런스 실험을 실시한다(PTC 1997, 섹션 II.B/C 참조). 세포 뱅크 실험 및/또는 mAb 제조 시의 공정 관련 불순물 및/또는 외래성 인자 제거 또는 불활화 절차에 대한 브리웨이션 수준을 축소(즉, PTC 1997에 권고된 수준 이하)하여 실시하는 것도 상황에 따라서는 적절할 수 있으나, 타당성을 증명해야 한다. 실험 및/또는 브리웨이션 수준의 축소를 계획할 때는 FDA와 미리 협의하는 것이 바람직하다. 예를 들어 다음과 같은 경우에 실험/브리웨이션 수준의 축소가 타당할 수 있다.

- The drug product is terminally sterilized.

  원제의약품을 사후 멸균하는 경우.

- The use of the reagent is followed by adequate steps for the removal and/or inactivation of the adventitious agents and/or process-related impurities. In this instance, the overall assessment of the removal and/or inactivation process can take into account validation data from steps in the manufacture of the reagent and manufacture of the drug substance.

  시약을 사용한 다음에, 외래성 인자 및/또는 공정 관련 불순물의 제거 및/또는 불활화 단계를 거치는 경우. 이러한 경우에는 시약 제조 및 원료의약품 제조 단계의 브리웨이션 데이터를 감안하여, 제거 및/또는 불활화 공정을 종합적으로 평가한다.

- Processing steps downstream of the reagent include extremes of pH.

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or organic solvents, and there are reliable data in the scientific literature that the extremes remove and/or inactivate adventitious agents and/or process-related impurities.

시약 투입 이후의 공정 단계에 극단적인 pH 조건이나 유기 용매 처리 단계가 포함되어 있으며, 이러한 극단적인 조건이 외래성 인자 및/or 공정 관련 불순물을 제거하거나 불활화한다는 믿을만한 데이터가 과학 문헌에 제시되어 있는 경우.

- The mAb reagent is produced in an expression system in which human infectious agents do not propagate (e.g., plants, bacteria, fungi, insect cultures).

사람 감염성 인자가 증식하지 않는 발현 시스템(예, 식물, 세균, 진균, 곤충 배양)으로 mAb 시약이 생산되는 경우.

IV. 의약품 제조 시의 단클론 항체 시약(MONOCLONAL ANTIBODY REAGENTS IN DRUG MANUFACTURING)

A major use of mAb reagents is in the purification of drug substance by mAbs attached to a solid support (e.g., immunoaffinity chromatography). Issues relating to and recommendations on the information to submit in support of the use of mAb reagents in the purification process are discussed below. The information that should be submitted to support other uses of mAb reagents in drug manufacture will depend on the use and are not discussed in this guidance. Sponsors or applicants with questions on documentation to support other uses of mAb reagents are encouraged to contact the Agency.

mAb는 주로 고체 지지물에 부착시켜(예, 면역친화성 크로마토그래피) 원료의약품을 정제하는데 사용된다. mAb를 사용한 정제 공정을 뒷받침하기 위해 제출하는 정보에 관한 권고 사항과 이에 관련된 이유를 아래에서 설명한다. mAb 시약은 의약품 제조 시에 다른 용도로 사용하는 경우, 이를 뒷받침하기 위해 제출해야 할 정보는 용도에 따라 달라지며, 이러한 부분은 이 문서에서 다루지 않는다. 다른 용도의 mAb 사용을 뒷받침하는 문서에 대하여 질의가 있는 스폰서나 신청업체는 FDA에 문의한다.

A. 원료의약품 정제(Purification of Drug Substance)

The drug substance purification processes should be described in the application.
The drug substance manufacturer should establish a specification for the incoming mAb reagent, and perform testing before using the reagents in the manufacturing process. In addition to identity testing for the incoming mAb reagent, drug substance manufacturers should carry out additional testing (e.g., binding activity, adventitious agents) to ensure that the reagent will perform as intended. Affinity and specificity studies are recommended to assess whether the characteristics of a mAb reagent are optimal for targeted binding to the appropriate substrate during the manufacture of the drug substance.

Leaching of mAb or impurities from the solid support into the final product should be considered when specifications are established for the drug substance. The amount of column leachables is not uniform over the column lifespan and depends on several factors (e.g., length of storage, solutions used in the regeneration and/or sanitization steps, column operating parameters). A variety of methods can be used to test for leachables such as sampling the buffer flow-through prior to the load of the drug substance intermediate, in-process testing of the intermediate bulk, or testing the final drug substance. Alternatively, if documentation is available that the production steps that follow the use of the reagent mAb reduce the maximum amount of column leachables to appropriate levels, this documentation can be provided in lieu of routine testing for leachables.

Data on the ability of the affinity column to achieve the intended purity under
specified working conditions should be submitted. The stability of the mAb reagent during use, the column performance, and the microbial contaminants should be monitored during production of drug substance and documented by the drug substance manufacturer. Tests and acceptance criteria for residual mAb should be included in the specifications for drug substances processed with mAb reagents. Residual mAb should be monitored by sensitive and specific assay (e.g., enzyme-linked immunosorbent assay (ELISA)).

Changes in the mAb supplier or changes in the manufacturing process of mAb or solid support are considered to be drug substance manufacturing process changes that can have an effect on the biological safety and effectiveness of the drug substance and, consequently, the final product. In cases where significant changes have been implemented in the mAb manufacturing process that may change the purity or the performance of the reagent (e.g., specificity, avidity, microbiological safety), appropriate product comparability testing should be performed. The guidance document entitled FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (1996) contains a discussion of comparability testing for mAbs used parenterally. Comparability testing for mAb reagents should focus mainly on the performance characteristics of the reagent and its purity and stability. This is particularly important when changes in the reagent manufacture are likely to have an impact on the biological safety, purity, quality, or stability of the drug substance and/or drug product.

mAb 공급업체가 변경되거나 mAb 제조 공정 또는 고체 지지물이 변경되는 경우에는, 원료의약품과 최종 제품의 생물학적 안전성과 유효성에 영향을 줄 수 있는 원료의약품 제조 공정 변경으로 간주된다. 시약의 순도나 성능(예, 특이성, 결합력, 미생물학적 안전성)을 변화시킬 수 있는 mAb 제조 공정의 중대한 변경을 추진하는 경우, 제품 동등성 실험을 적절하게 실시한다. 주재료로 사용되는 mAb의 동등성 실험에 관한 정보는, FDA 가이드
V. 단클론 항체 시약 규격(SPECIFICATIONS FOR MONOCLONAL ANTIBODY REAGENTS)

Specifications for the mAb reagents should be provided. A certificate of analysis (COA) should be available for each individual reagent lot. For monoclonal antibodies linked to a solid support, COAs should be provided for both forms, unconjugated and linked. A copy of a representative COA should be provided.

mAb 시약 규격을 제공해야 한다. 시약 로트별로 COA가 있어야 한다. 고체 지지물에 링크된 단클론 양체인 경우, 두 가지 형태(비접합 및 링크) 모두에 대한 COA를 제공한다. 대표 COA 사본을 제공한다.

The COA should provide the test results, including those for adventitious agents, expiration date, and a disclaimer statement in large bold lettering: REAGENT USE ONLY; NOT INTENDED FOR HUMAN USE.

COA에는 시험 결과(외래성 인자 시험 결과 포함), 유효일자, 굵은 글씨로 쓴 문구(시약용: 인체 투여 용도 아님)를 표기한다.

A. 비접합 단클론 항체 시약 시험(Testing of Unconjugated Monoclonal Antibody Reagents)

Tests to adequately characterize the unconjugated mAb reagent typically include:

- Identity (e.g., reducing and nonreducing sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) pattern, isoelectric focusing (IEF) profile)
- Purity (e.g., high performance liquid chromatography (HPLC), SDS-PAGE, capillary electrophoresis)
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순도(예, HPLC, SDS-PAGE, CE)

- Protein concentration
  단백 농도

- Binding to the target molecule
  표적 분자 결합

- pH

- Microbial and/or bacterial endotoxin limits, as appropriate
  적절한 경우에는 미생물 및/또는 세균 엔도톡신 한도

- Preservatives, as appropriate
  적절한 경우에는 보존제

B. 고체 지지물에 링크된 단클론 항체 시험(Testing of Monoclonal Antibody Reagents Linked to Solid Support)

Tests for mAb reagents linked to solid support should include, at minimum, the following:
고체 지지물에 링크된 mAb 시약의 시험 항목은 최소한 다음과 같다.

- Physical characteristics (e.g., mean particle size, matrix structure)
  물리적 특성(예, 평균 입자 크기, 매트릭스 구조)

- Concentration of mAb (e.g., milligrams of mAb per gram of resin)
  mAb 농도(예, mg/g 레신)

- Specific binding capacity at recommended temperature and buffer ranges
  권장 온도 및 완충액 범위에서, 특이적 결합 능력

- Amount of leaching of mAb
  mAb 유출량
VI. Stability of Monoclonal Antibody Reagents

The mAb manufacturer should perform real-time stability studies of unconjugated and conjugated mAb. Based on these studies, the mAb manufacturer should determine and provide an expiry date for each lot of mAb reagent. Stability indicating tests should focus on performance and physical integrity of the mAb reagent. Either the drug substance manufacturer or the reagent manufacturer should provide data supporting the in-use chemical stability of the column and mAb reagent using the recommended storage buffer, regeneration and/or cleaning solutions under specific time and temperatures.

mAb 제조업체는 비접합 및 접합 mAb의 실시간 안정성 시험을 실시해야 한다. 이 시험 결과에 근거하여, mAb 제조업체는 mAb 시약 로트별 유효 일자를 부여한다. 안정성 시험 항목은 mAb 시약의 성능과 물리적 완전성에 중점을 두어 정한다. 원료의약품 제조업체나 시약 제조업체는 권장 보관 완충액, 재생 및/또는 세척액(지정 시간, 온도 조건)을 사용해, mAb 시약과 칼럼의 사용 시 화학적 안정성을 뒷받침하는 데이터를 제공해야 한다.
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참고문헌(REFERENCES)


FDA guidance for industry on Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, FDA, 1996.