Single Trial Approval Pathway in the US FDA

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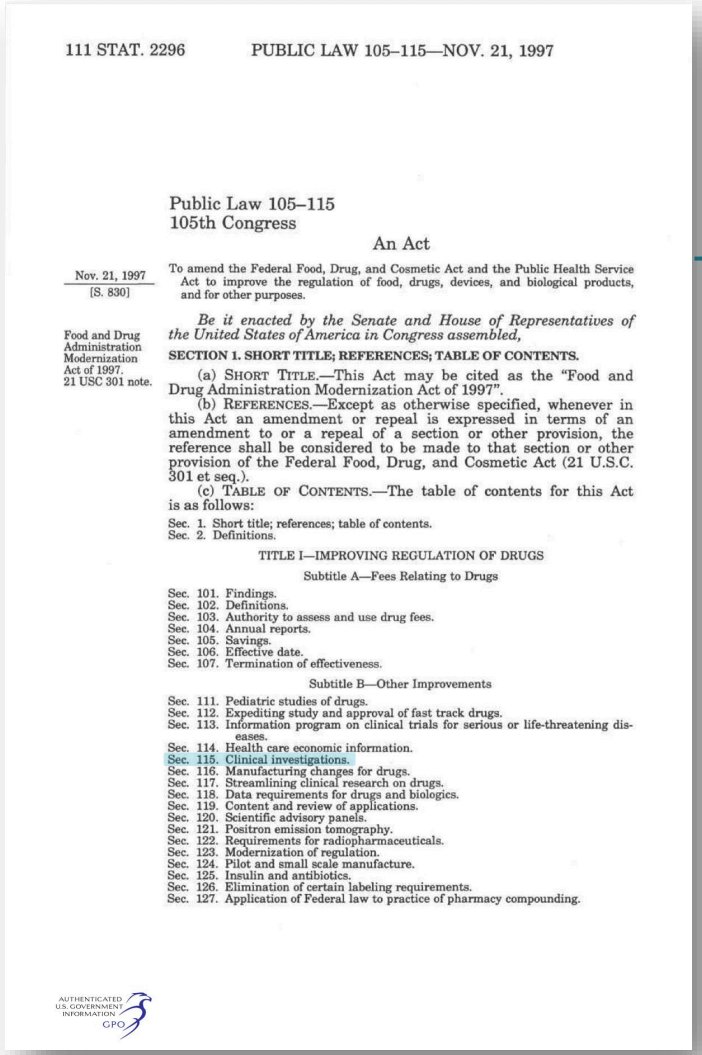
OCULAR THERAPEUTIX
Retina experience redefined™

Substantial Evidence of Effectiveness with a Single Trial is Well-Established



111 STAT. 2296 PUBLIC LAW 105–115—NOV. 21, 1997

Public Law 105–115
105th Congress

An Act

Nov. 21, 1997
[S. 830]

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Food and Drug Administration Modernization Act of 1997.
21 USC 301 note.

SECTION 1. SHORT TITLE; REFERENCES; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Food and Drug Administration Modernization Act of 1997".

(b) REFERENCES.—Except as otherwise specified, whenever in this Act an amendment or repeal is expressed in terms of an amendment to or a repeal of a section or other provision, the reference shall be considered to be made to that section or other provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

(c) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

Sec. 1. Short title; references; table of contents.
Sec. 2. Definitions.

TITLE I—IMPROVING REGULATION OF DRUGS

Subtitle A—Fees Relating to Drugs

Sec. 101. Findings.
Sec. 102. Definitions.
Sec. 103. Authority to assess and use drug fees.
Sec. 104. Annual reports.
Sec. 105. Savings.
Sec. 106. Effective date.
Sec. 107. Termination of effectiveness.

Subtitle B—Other Improvements

Sec. 111. Pediatric studies of drugs.
Sec. 112. Expediting study and approval of fast track drugs.
Sec. 113. Information program on clinical trials for serious or life-threatening diseases.
Sec. 114. Health care economic information.
Sec. 115. Clinical investigations.
Sec. 116. Manufacturing changes for drugs.
Sec. 117. Streamlining clinical research on drugs.
Sec. 118. Data requirements for drugs and biologics.
Sec. 119. Content and review of applications.
Sec. 120. Scientific advisory panels.
Sec. 121. Positron emission tomography.
Sec. 122. Requirements for radiopharmaceuticals.
Sec. 123. Modernization of regulation.
Sec. 124. Pilot and small scale manufacture.
Sec. 125. Insulin and antibiotics.
Sec. 126. Elimination of certain labeling requirements.
Sec. 127. Application of Federal law to practice of pharmacy compounding.

AUTHENTICATED U.S. GOVERNMENT INFORMATION GPO

Precedent is Well-Established

Section 115 of the **FDA Modernization Act of 1997** amended and clarified FD&C Act § 505(d) to define **"substantial evidence"** and **explicitly allow one adequate and well-controlled trial plus confirmatory evidence**[1]

The **1998 FDA Guidance** reiterated that the **"substantial evidence" requirement** for effectiveness…**could be met by a single trial plus confirmatory evidence**[2]

The **2023 FDA Guidance** explained even more clearly how **one trial plus confirmatory evidence** can meet the statutory **"substantial evidence"** standard[3]

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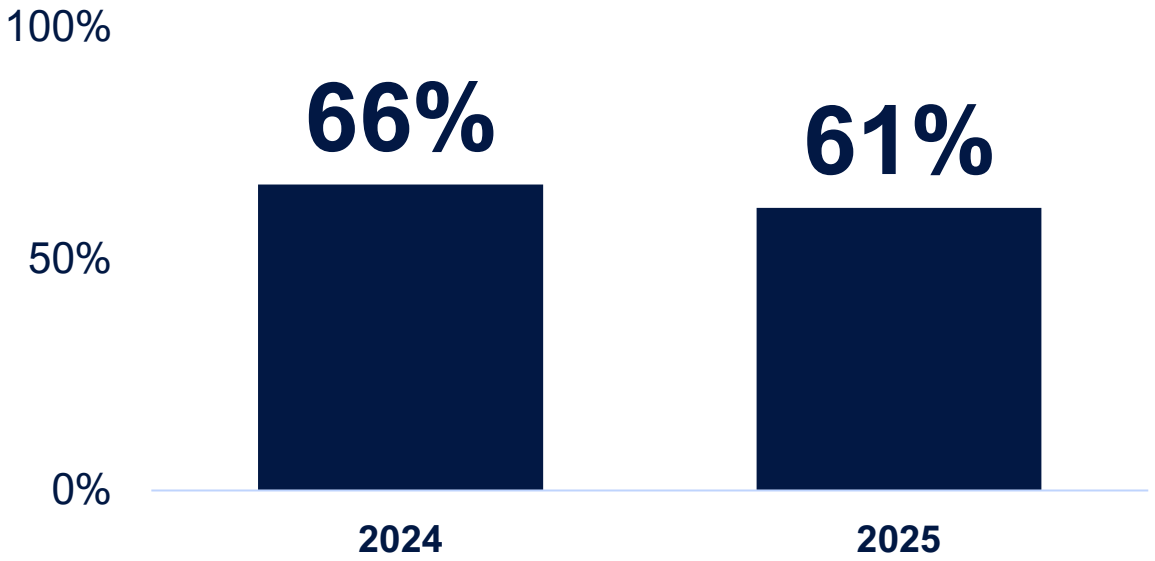
1. FDAMA § 115, Pub. L. No. 105-115, amending Federal Food, Drug, and Cosmetic Act § 505(d), 21 U.S.C. § 355(d). 2. FDA, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry (May 1998). 3. FDA, Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Draft Guidance for Industry (Sept. 2023).

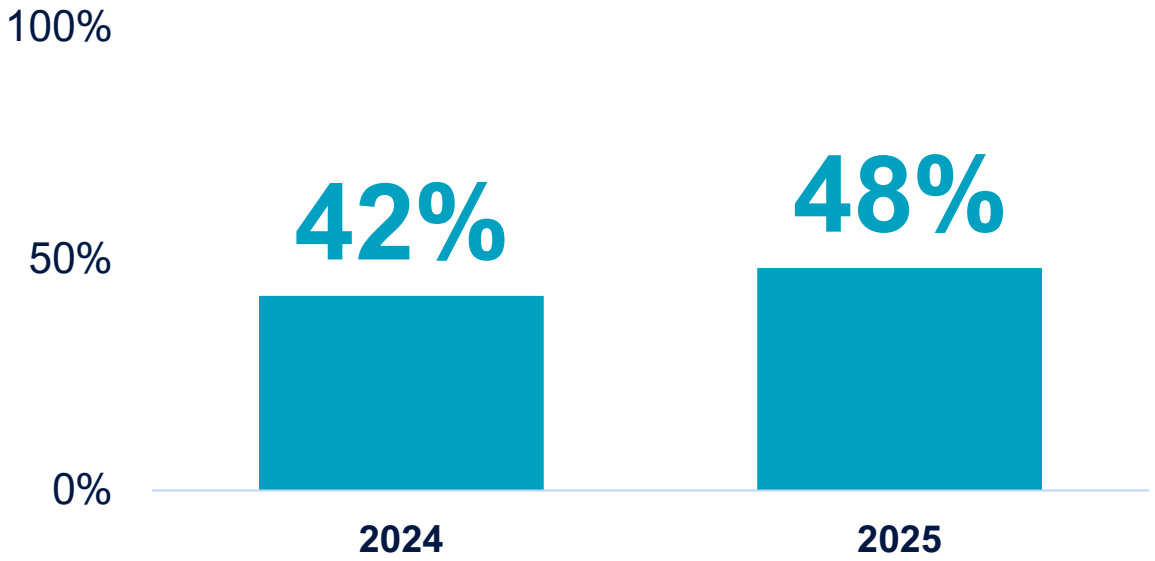
Approvals based on a Single Trial are Common and Increasingly Frequent

Percent of All CDER NDAs Approved with a Single Trial[1]



Majority of **recent CDER approvals** based on **single pivotal trial**[1]

Percent of Non-Orphan CDER NDAs Approved with a Single Trial[1]



Over 40% of recent non-orphan CDER approvals based on a single-trial[1]

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1. Ocular internal analysis of CDER's novel drugs approvals for 2024 and 2025 CDER, Center for Drug Evaluation and Research.

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

Pre-Data

- ☐ **Adequate & Well-Controlled Trial**
- ☐ Protocol Aligned with FDA

Post-Data

- ☐ Superiority Primary Endpoint Met
- ☐ Clinically Meaningful Results
- ☐ Safety Dataset Meeting FDA Submission Requirements
- ☐ Supporting Confirmatory Evidence

Code of Federal Regulation
21 CFR § Part 314 defined what qualifies as an **"adequate and well-controlled" study**

Evidence from clinical trials that are **not adequate and well-controlled** (eg. sham introduces bias) can be corroborative, but **cannot stand alone**

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1. 21 C.F.R. § 314.126 — Adequate and well-controlled studies.

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Pre-Data

- [x] **Adequate & Well-Controlled Trial**
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Post-Data

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SOL-1 was prospectively designed to meet the standards of an **adequate and well-controlled clinical trial** under 21 CFR § 314

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1. 21 C.F.R. § 314.126 — Adequate and well-controlled studies.

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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Post-Data

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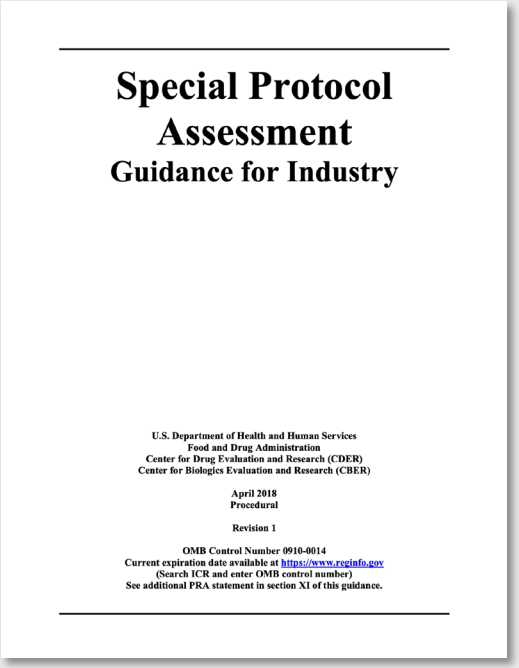
A SPA means the FDA has agreed that the **study design, endpoints, study size, and analysis plan** are adequate to address the scientific and regulatory requirements for a study that could support approval[1]



Special Protocol Assessment
Guidance for Industry

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)

April 2018
Procedural

Revision 1

OMB Control Number 0910-0014
Current expiration date available at https://www.reginfo.gov
(Search ICR and enter OMB control number)
See additional PRA statement in section XI of this guidance.

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1. Special Protocol Assessment; Guidance for Industry; Availability, 83 Fed. Reg. 16356, Apr. 16, 2018.; "An SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design (e.g., entry criteria, dose selection, endpoints, and planned analyses) for a study intended to support a future marketing application... However, an SPA agreement does not indicate FDA concurrence on every protocol detail."

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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SOL-1 conducted under SPA

Only active wet AMD trial conducted under SPA

"The special protocol assessment is an official agreement between a sponsor & the agency that we will accept a certain trial design… **If you successfully complete that protocol, that will be highly supportive of approval of the product."**

W. Boyd – FDA Deputy Division Director of Ophthalmology | Retina World Congress, May 2026

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SPA, Special Protocol Assessment; AMD, age-related macular degeneration

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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FDA Division of Ophthalmology considers p values ≤ 0.001 to be **potentially supportive** for **single trial approval**

"Single adequate and well-controlled trials can support approval…often with very strong p-values (e.g., <0.001)"

W. Boyd – FDA Deputy Division Director of Ophthalmology | Retina World Congress, May 2026

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Xipere approved for UME on single trial (PEACHTREE) with **p value <0.001** (trial included 96 subjects, safety package with 296 subjects incl. patients from open-label AZALEA)(Oct 2021)

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1. Godoy CB et al Ramachandran R, Sapre P, Ross JS. Confirmatory evidence supporting single pivotal trial new drug approvals by the Food and Drug Administration, 2015 through 2023. *Clin Trials*. 2026;23(1):109-112.

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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FDA Division of Ophthalmology considers p values ≤ 0.001 to be **potentially supportive** for **single trial approval**

SOL-1 reported highly statistically significant (p value = 0.0006) risk difference of **17.5%** for patients treated with AXPAXLI vs control in maintenance of vision at week 36

All six pre-specified sensitivity analyses also statistically significant

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1. Puthumana J, Wallach JD, Ross JS. Single pivotal trial evidence supporting FDA approval of original drug and biologic indications, 2015–2023. Clinical Trials. 2025. doi:10.1177/17407745251376620.

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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- First trial to show **superiority** in preventing vision loss against an active anti-VEGF control, aflibercept 2mg
- **69% of AXPAXLI Subjects Rescue-Free** at 12 months
- **Time to first rescue injection** ~6 months difference with aflibercept
- **3 hierarchically controlled key secondary** endpoints **met with statistical significance**

SOL-1 demonstrated superiority on the prespecified primary endpoint, strengthening effect size over time, consistent visual outcomes, and supportive anatomic benefit creating a highly persuasive efficacy statement

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Hierarchical testing: endpoints are tested in a prespecified order and significance is claimed only if prior endpoints are met.
VEGF, vascular endothelial growth factor

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- ☐ **Safety Dataset Meeting FDA Submission Requirements**
- ☐ Supporting Confirmatory Evidence

- FDA notes one trial may establish effectiveness, but FDA still requires adequate safety exposure
- The **2023 nAMD Guidance** defines a **minimum of 300 patients with at least 9 months follow up**

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nAMD, neovascular age-related macular degeneration; NDA, New Drug Application

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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AXPAXLI safety dataset will include **>300 patients on AXPAXLI for 12 months** at time of planned NDA submission

- SOL-1 52-week safety (n=170 at 52 weeks) plus
- SOL-R Interim 52-week safety (n >130 patients)
  - 0.0001 alpha penalty, no additional SOL-R analysis
- SOL-1 masking maintained through Year 2 for labeling
- At 120-day safety update, Year 2 SOL-1 safety data submission intended to support repeat dosing

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- ☐ **Supporting Confirmatory Evidence**

2023 FDA Guidance[1] defined "confirmatory evidence"

1. Clinical Evidence from a Related Indication
2. Mechanistic or Pharmacodynamic Evidence
3. Evidence from a Relevant Animal Model
4. Evidence from Other Members of the Same Pharmacological Class
5. Natural History Evidence
6. Real-World Data/Evidence
7. Evidence from Expanded Access Use

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1. FDA, Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Draft Guidance for Industry (Sept. 2023).

Meeting The Evidentiary Standard for Effectiveness with a Single Pivotal Trial

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AXPAXLI's Substantial Evidence of Effectiveness supported by broad confirmatory evidence

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1. FDA, Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Draft Guidance for Industry (Sept. 2023).

AXPAXLI NDA Package Designed to Meet FDA "Substantial Evidence of Effectiveness" and Safety Requirements

Highly Positive SOL-1 Trial Aligned with FDA through SPA + **Safety** + **Confirmatory Evidence** =

Positive, Adequate, Well-Controlled Trial	Highly Stat Sig Results	Clinical Coherence & Consistency	Sufficient Safety Package	Broad Confirmatory Evidence
SOL-1 has SPA Agreement w/ FDA	**SOL-1 superiority trial is highly stat sig**	**3 of 5 key secondaries met in hierarchical fashion w/ stat sig**	**>300 patients for one year at NDA submission**	**Strong confirmatory evidence as part of NDA**
Design, endpoints, study size, and SAP aligned in advance	17.5% risk dif. for AXPAXLI vs control at Week 36 (p=0.0006)	Superiority in maintaining vision, anatomic results, rescue-free all supportive	Will include 170 from SOL-1 and >130 from SOL-R	Mechanistic, PD, PK, class consistency, animal model, natural history, and real-world evidence

AXPAXLI NDA Submission in 4Q 2026 Following Interim SOL-R Safety Analysis

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wAMD, wet age-related macular degeneration; SPA, Special Protocol Assessment; SAP, statistical analysis plan; NDA, New Drug Application