

The FDA Boxed Warning: Regulatory Strategy & Negotiation

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Executive Summary

Boxed (or “black-box”) warnings are the FDA’s strongest safety advisories on drug labels. They alert prescribers and patients to **life-threatening or serious risks** of a medication. Because a boxed warning can dramatically reduce usage, drugmakers often debate their scope and language. However, by law, the FDA has ultimate authority to require or remove boxed warnings based on evidence. Sponsors may *propose* alternative wording or present new data, but any changes proceed through formal FDA review (often including expert panels and public comment) (^[1] www.fda.gov) (^[2] www.fda.gov). In practice, companies and regulators do “negotiate” label text in the sense of back-and-forth discussion, but neither side simply “bargains away” a box warning. Post-approval labeling changes are governed by strict statutes and regulations (e.g. 21 USC 355(o)(4), 21 CFR 201.57, 314.70) that outline a formal process for supplements and safety labeling change orders (^[3] www.fda.gov) (^[2] www.fda.gov).

This report examines the strategy of handling FDA boxed warnings through multiple lenses: regulatory law, risk communication, market impact data, and **case studies** of recent actions. We survey the legal framework for labeling changes, analyze evidence on how warnings affect drug use, and detail varied examples—from pediatric antidepressants to menopause hormone therapy—where FDA and stakeholders interacted over boxed warnings. Expert interviews, law review guidance, and official FDA communications are cited throughout. The report also discusses future directions, including how new FDA panels and policies might influence how warnings are negotiated. In summary, while drug sponsors cannot simply veto FDA warnings, there is room for scientific dialogue. The FDA’s process—illustrated by real-world examples—allows a company to present evidence and propose wording, but ultimately the agency decides if a boxed warning is warranted and what it says (^[4] www.law.cornell.edu) (^[5] www.fda.gov).

Introduction and Background

The FDA introduced **boxed warnings** (often called “black-box warnings”) in the mid-20th century to highlight the most serious known drug risks. These warnings appear in a bold box at the top of a drug’s prescribing information. By regulation, boxed warnings are reserved for adverse effects that are so dangerous that extra emphasis is needed (^[4] www.law.cornell.edu). Over time, hundreds of drugs have received boxed warnings for risks ranging from suicide or cardiac events to fetal harm. Physician societies and patient groups rely on boxes to flag dangers, and courts often view a boxed warning as proof that the label adequately cautions users (^[6] www.jdsupra.com) (^[5] www.fda.gov).

Regulatory Basis. The [legal framework for prescription drug labeling](#) traces to the Federal Food, Drug, and Cosmetic Act. Most key rules are in 21 CFR §201.56–.57 and §314.70, plus FDA guidances. In particular:

- **21 CFR 201.57©(1)** specifies that *Fully [FDA] approved” drugs may require a boxed warning (the regulation uses “boxed warning”) for certain contraindications or serious warnings, particularly those that may cause death or serious injury. The rule mandates that a boxed warning must have an uppercase heading containing **“WARNING”**, briefly explain the risk, and refer to more detailed sections (e.g. “Contraindications” or “Warnings/Precautions”) (^[4] www.law.cornell.edu). Importantly, it states a box is ordinarily **based on clinical data** (human studies), but unusually *serious animal toxicity* can also suffice if no human data exist. In short, 21 CFR 201.57©(1) codifies the format and threshold for box warnings (^[4] www.law.cornell.edu).
- **21 CFR 314.70** governs *post-marketing labeling changes*. It requires a **Prior Approval Supplement** for substantial label modifications (^[7] www.law.cornell.edu). In practice, adding or modifying a boxed warning is treated as a major change: sponsors must submit a supplement to FDA for review before marketing the new

label. Thus, any change to the boxed warning triggers negotiations via that supplement. FDA evaluates the sponsor's proposed text and may counter-propose changes.

- **Section 505(o)(4) of the FD&C Act (21 USC 355(o)(4))** was added by the 2007 FDAAA. It explicitly authorizes the FDA to *mandate* labeling changes—including boxed warnings—when **new safety information** emerges post-approval (^[3] www.fda.gov). Under this law, FDA can order a "Safety Labeling Change" (SLC) without the sponsor's consent. The common procedure is: FDA issues an SLC letter citing the new risk; the drug sponsor then *must* submit either a labeling supplement (with proposed revisions) or a written rebuttal arguing no change is needed (^[2] www.fda.gov). A 30-day discussion follows; if no agreement is reached, FDA can issue a binding SLC Order requiring immediate label changes (^[5] www.fda.gov). In this way, 505(o)(4) formalized the "err on the side of safety" power of FDA, while still allowing the sponsor to present its arguments.

Scope and Trends. Boxed warnings appear on a growing but still small share of drugs. Between 1975 and 1999, only about **8.2%** of new molecular entities had any box warning (^[8] www.aafp.org). That proportion has risen in recent decades, partly because FDA has become more proactive about **post-marketing safety surveillance** (^[8] www.aafp.org). For context, Black box warnings are far rarer than "me-too" approvals: of 548 new drugs approved by 2000, only 45 ever got a box (^[8] www.aafp.org). Nonetheless, once applied, boxed warnings carry *very high visibility*. They appear on the FDA website, in the Physician's Desk Reference, and in promotional labeling. For manufacturers, a boxed warning is often viewed as a major commercial setback, associated with steep drops in prescriptions or even product withdrawal.

A key question for industry is whether a boxed warning can ever be negotiated or removed. While FDA has ultimate authority, drugmakers can petition for label changes if new data emerge. Historically, **rare instances** of warning removal have occurred (see Case Studies). More often, companies receive warnings they argue are too broad or can be softened. Below we examine how such label disputes are resolved in practice: Is it a negotiation between equals, or a one-sided mandate? We draw on sources ranging from FDA regulations and guidance to peer-reviewed studies and news reports.

Regulatory Mechanisms for Label Changes

NDA Review and Label Negotiation

Before marketing a new drug, the sponsor submits a New Drug Application (NDA) to the FDA with proposed labeling. This initial label includes all promised indications, dosing, and safety information. From here, **negotiation is part of the standard review process**. The FDA reviewer typically issues requests for clarification or additional studies (CRLs or Information Requests) that can include demands to narrow the indication or add warnings. At this stage, the sponsor and FDA correspond on acceptable **wording**. As one regulatory training module notes, *"the final approved label is not a submission; it is a negotiated legal contract"* (^[9] pharmacystandards.org). In that negotiation, the company usually argues for broad use and minimal cautions based on its clinical trials, while FDA (mandated to protect public health) often seeks to narrow use to subpopulations where benefits clearly outweigh risks (^[10] pharmacystandards.org). The compromise might define the indication tightly (e.g. "patients who have failed prior therapies") or add risk-related precautions.

For example, during NDA review the FDA may insist that comparative data only support treating severe cases of a disease, not mild ones. The guidebook analogy explains: the sponsor's "*Truth*" is its 5,000-patient study showing efficacy in all comers, so it wants the label "for Disease X." The FDA's "*Truth*" might be that efficacy was only clearly demonstrated in severe cases, so it pushes to limit to "severe Disease X." The final label (often a compromise) states something like "for treatment of Disease X in patients not controlled by standard therapy," which mixes both perspectives (^[10] pharmacystandards.org). Throughout NDA review, sponsors cite their own

data and literature, and FDA may request advisory committee input when the benefit-risk is unclear. If the sponsor and FDA cannot agree on a label change needed for initial approval, the application can be put on hold or issued a complete response letter. But once approval is at hand, the label textual decisions (including any boxed warning) usually rest in the NDA you negotiated to approval.

Post-Approval Label Changes (Section 505(o)(4) and Supplements)

Even after approval, the labeling negotiation continues, but under stricter procedures. If new safety concerns arise, FDA can require changes **in the label** via a formal route (especially after FDAAA 2007). In practice, when concerning safety data come in, FDA uses **Section 505(o)(4)** to issue a *Safety Labeling Change (SLC) request*. The sponsor then faces two choices: (1) submit a supplement with proposed wording changes, or (2) submit a rebuttal stating why changes are unwarranted (^[2] www.fda.gov). If the sponsor chooses a supplement, it usually includes language it believes addresses the safety issue. If the sponsor rebuts, it must support its case with data or analysis.

Once the sponsor responds, a **30-day discussion period** follows. During this period, agency and sponsor can exchange views and refine text. If an agreement is reached, the label changes are incorporated. If not, FDA can default to authority and *order* the labeling change via an official SLC Order. At that point, the sponsor has no option but to comply with FDA's final labeling language (^[5] www.fda.gov). Notably, these steps show that "negotiation" is built in: the sponsor has the chance to submit alternative language and justify positions, but only temporarily. The final decision always goes to FDA if consensus fails.

Regulations reinforce that route: under **21 CFR 314.70(b)(2)(v)** any change in labeling (except very minor editorial fixes) must go through a supplement for FDA approval (^[7] www.law.cornell.edu). In particular, changing or adding content to the boxed warning section (part of 201.57(a)) is a major change requiring FDA review (^[7] www.law.cornell.edu). Under this rule, once FDA says "we need a warning change," the sponsor cannot independently alter the box wording and distribute an unreviewed label – it must wait for FDA's blessing. Thus every substantive boxing or unboxing is vetted and "negotiated" through official submissions.

FDA has also issued guidance on implementing 505(o)(4). The guidance reiterates that FDA can **mandate** labeling updates when serious new risks are identified (^[3] www.fda.gov). It describes the SLC process formally: the FDA notifies the sponsor of the required content; the sponsor then either concurs (submits revised labeling) or challenges it (rebuttal). If the sponsor's proposed supplement is "approvable," FDA will promptly accept it; if not, FDA may enter a discussion period (^[11] www.fda.gov). Likewise, if the sponsor's rebuttal is unconvincing, FDA can request meeting or discussion. After 30 days, if no consensus is met, FDA issues an SLC order requiring exactly the label changes it initially demanded (^[5] www.fda.gov). This process shows that, even in post-market circumstances, modification of a boxed warning involves back-and-forth, but always within a narrow "safety first" framework.

Labeling Removal or Softening

Can a company proactively propose removal of a black box? Yes, especially if new evidence suggests the risk may not apply or is overstated. A sponsor may petition FDA to update labeling. For safety-driven boxes, FDA normally requires removal to be supported by substantial new data or consensus that the old risk no longer materializes. The hormone therapy example (below) is one case where, after new analysis, FDA initiated removal of a long-standing box (^[1] www.fda.gov). The process was similar to adding one: companies were asked to submit updated language and evidence; expert panels and public comment were utilized. In general, however,

removing an existing warning is **rare**. It requires high-level review of all evidence and often a Washington DC-level decision (as in this recent case).

Whether negotiating to *narrow* a warning is permissible depends on context. In reviewing new-box proposals, FDA sometimes agrees to limit their scope. For instance, if a risk is age-specific, the box may mention only that subgroup. But this is not a contractual negotiation – it’s FDA tweaking its requirement. The statutory power (505(o)(4)) works both ways: the sponsor, after receiving an SLC letter, may argue convincingly that the evidence actually shows lesser risk or a narrower at-risk population. If FDA accepts this during the 30-day discussion, the final labeling could be more limited. But again, if disagreement remains, FDA’s final language prevails. Thus companies can **influence** how a box is phrased or which patients it targets, but they cannot unilaterally refuse it if FDA deems it necessary.

Impact of Boxed Warnings on Drug Use and Perception

Multiple studies show that boxed warnings strongly affect prescribing, insurer coverage, and patient use. In general, issuing a new boxed warning drastically reduces use of the drug. A systematic review found that **drug-specific warnings** (especially boxed warnings) lead to *“particularly large decreases in utilization”* across multiple cases (^[12] [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). For example, when antidepressants received a black box for pediatric suicidality, prescribing in that age group plummeted and some doctors treated depression without medication (^[13] [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)) (^[12] [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)).

Table 1 below summarizes representative outcomes:

- **New Black Box ⇒ Usage Drop:** One study of nine drugs with new 2007–2013 box warnings (for death or cardiovascular risk) found that Medicare formulary restrictions (e.g. step therapy) increased for 40–50% of those drugs within 1–2 years (^[14] pubmed.ncbi.nlm.nih.gov). Another analysis noted that black-box communications in practice often spilled over into reduced prescribing even beyond the targeted subgroup (^[12] [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)).
- **Marketing and Legal Impact:** Boxed warnings frequently lead to updated medication guides and “Dear Doctor” letters. They also raise medicolegal stakes. For example, an article by pharmaceutical attorneys notes that promotion of drugs with boxed warnings is highly scrutinized – even a friendly social media post claiming “no drama” can trigger FDA enforcement (^[6] www.jdsupra.com). In sum, a box warning shifts the entire risk–benefit discussion: insurers push less coverage, physicians reconsider.

Selected FDA Labeling Actions (Case Study Examples)	Label Change	Year	Key Reason / Risk	Sources
SSRIs (e.g. Paxil, Zoloft) – treatment for pediatric depression/anxiety	Added Black Box Warning	2004	Increased risk of suicidal thoughts/behavior in children and adolescents (^[15] pmc.ncbi.nlm.nih.gov)	Remove ND
Droperidol (Post-op nausea/sedation)	Added Black Box Warning	2001	Risk of QT prolongation and fatal cardiac arrhythmias (^[16] www.medscape.com)	Remove ND
Montelukast (Singulair, asthma/allergy)	Added Black Box Warning	2020	Neuropsychiatric side effects – depression, suicidality (^[17] www.fda.gov) (^[18] www.fda.gov)	Add+ FDA Safety Comm.
Telithromycin (Ketek, pneumonia)	Added Black Box Warning	2007	Contraindications: fatal respiratory failure in myasthenia gravis patients (^[19] pmc.ncbi.nlm.nih.gov)	IMPACT ND

Selected FDA Labeling Actions (Case Study Examples)	Label Change	Year	Key Reason / Risk	Sources
			pmc.ncbi.nlm.nih.gov)	
Carvykti (ciltacabtagene, multiple myeloma CAR-T)	Added Black Box Warning	2025	Immune effector cell-associated enterocolitis (severe GI toxicity leading to bowel perforation) ([20] www.reuters.com)	Add FDA action
Elevidys (eteplirsen, DMD gene therapy)	Added "Strongest" Warning	2025	Acute liver failure (two pediatric deaths) ([21] www.reuters.com); use restricted to milder patients	Add FDA action
Hormone Replacement Therapies	Removed Black Box Warning	2025	Reanalysis showed long-term risks (heart attack, stroke, dementia) had been overstated (data from WHI) ([1] www.fda.gov)	Remove+ HHS/FDA PR
Depo-Provera (injectable contraception)	Added Black Box Warning	2004	Significant bone mineral density loss with long-term use ([22] pmc.ncbi.nlm.nih.gov)	Add FDA rule

Table 1: Examples of FDA boxed warning and label changes in recent history, with rationale and sources. (Each case illustrates how new evidence or policy led FDA to add or remove boxed warnings. Sources: FDA communications and published reviews ([15] pmc.ncbi.nlm.nih.gov) ([17] www.fda.gov) ([16] www.medscape.com) ([19] pmc.ncbi.nlm.nih.gov) ([20] www.reuters.com) ([21] www.reuters.com) ([1] www.fda.gov).)

These cases highlight that once a safety signal is deemed significant, FDA acts decisively, either by **imposing** a box (SSRI, montelukast, CAR-T, etc.) or **removing** one (HRT) after review. In each scenario, the label change followed a formal process, typically after data review and often with external advisories. However, sponsors do have a role in that process. For example, when FDA decided to place a box on montelukast, it “convened a panel of outside experts” and then **required** the boxed warning, indicating that company physicians or manufacturers cannot unilaterally reject the panel’s recommendation ([17] www.fda.gov) ([18] www.fda.gov). Likewise, after cases of liver toxicity in Elevidys, Sarepta itself paused distribution and worked with FDA on label revisions ([21] www.reuters.com). In all cases, successful negotiation by a company meant submitting new data and proposed wording during the 505(o)(4) process; failure to convince FDA led to the warning going in largely as FDA had planned.

Clinical and Commercial Implications

Prescribing Behavior. Black box warnings strongly influence medical practice. After the 2004 SSRI warning, physician surveys and prescription data showed steep declines in youth antidepressant therapy ([23] pmc.ncbi.nlm.nih.gov) ([12] pmc.ncbi.nlm.nih.gov). Some psychiatrists even reported caring for depressed teens without medications at all, for fear of legal liability. In contrast, removing a box can encourage re-evaluation. For instance, after HRT’s box is removed, clinicians may feel freer to prescribe hormone therapy for early menopause. However, the removal itself was politically contentious: some advisers resigned in protest, warning patients not to be “gaslit” by discarding caution ([24] apnews.com) ([25] apnews.com). This case shows how trust in labels can hinge on perceived transparency of the decision.

Market Access. Payers often hesitate to cover boxed-warning drugs. The Medicare formulary study ([14] pubmed.ncbi.nlm.nih.gov) found that 50% of such drugs became *more* restricted (via prior auth or step therapy) after a box was added. We can infer that commercial insurers behave similarly. Restricted access penalizes older or riskier drugs whose patents have ended, since generics cannot easily remove a black box without FDA-consensus. Thus, a box can accelerate generic substitution or even product withdrawal (as happened for some

already marginal drugs). Conversely, removal of a box can improve marketability: the HRT companies expect new generics (e.g. Premarin) to gain traction once fears subside (^[26] www.fda.gov).

Marketing and Communication. Drugmakers must handle a black-box product carefully in promotion. The FDA's Office of Prescription Drug Promotion (OPDP) strictly enforces that marketing cannot minimize or obscure boxed warnings (^[6] www.jdsupra.com). The recent admonitions to pharma on social media illustrate this point: even a Facebook claim of "no drama" for a high-risk drug resulted in FDA warning letters, because it implied "no safety concerns" about a boxed-warning drug (^[6] www.jdsupra.com). This means companies have limited "social contract" to adjust how they present such drugs; negotiation in practice means negotiating entire promotional strategy within FDA guidelines, not altering the warning itself.

Case Studies: FDA Interaction on Boxed Warnings

We now examine concrete examples where drug sponsors and the FDA **interacted** over boxed warnings. These cases illustrate the range from outright FDA mandates to collaborative label revisions.

SSRIs and Antidepressants (2004–2006)

In 2004 the FDA conducted an extended review of pediatric antidepressant use, prompted by reports of increased suicidal ideation in children on SSRIs. A *blue-ribbon advisory panel* unanimously recommended adding a black box warning about suicidality in pediatric patients (^[15] pmc.ncbi.nlm.nih.gov). The manufacturers had initially opposed broad pediatric labels for SSRIs but ultimately complied. The panel's advice was not binding, but the FDA "enhanced" the labels accordingly (^[27] pmc.ncbi.nlm.nih.gov). By October 2004, all SSRI antidepressants received a boxed warning about possible suicide risk in children (^[23] pmc.ncbi.nlm.nih.gov). A later 2006 rule extended the warning to all ages (see [41] references). In this case, negotiation was minimal: the sponsor companies participated in the FDA process and submitted analyses, but the final outcome (the warning text) reflected the panel's strong conclusion. Companies had the opportunity to suggest wording during the FDA's deliberations, but the decisive data (meta-analyses of pediatric trials) won the day.

Impact: The warning markedly reduced pediatric antidepressant prescribing. A variety of studies found dramatic drops in use among children and adolescents in 2004–05, illustrating the power of an FDA-mandated communication (^[12] pmc.ncbi.nlm.nih.gov) (^[23] pmc.ncbi.nlm.nih.gov).

Montelukast (Singulair) Warning (2020)

In March 2020, after reports linking montelukast to neuropsychiatric symptoms, FDA **required** a new boxed warning for serious behavior and mood changes (^[17] www.fda.gov) (^[18] www.fda.gov). Prior to this, montelukast labels had only general psychiatric precautions, but FDA convened an external expert panel to re-evaluate the risk. That panel's input, along with FDA's internal review, led to the boxed warning and also a recommendation to restrict montelukast to patients without safer alternatives (^[17] www.fda.gov) (^[18] www.fda.gov). The communication states FDA "decided a stronger warning is needed" after reviewing the information (^[17] www.fda.gov). Here again, the process was largely FDA-directed: the industry (Merck, generics) would have been involved during the panel or have received the new requirements, but the final content was set by FDA's expert consensus. Manufacturers then updated their labels per FDA's instructions (as required by law).

This case also shows stakeholder pressure: even after the 2020 box was added, in 2024 the New York Attorney General publicly urged FDA to strengthen the warning further, citing ongoing reports of youth suicidality (^[28] www.reuters.com). That illustrates external influence (state officials) *demanding* more action, but the FDA had already acted under 505(o)(4) to impose the box.

Menopausal Hormone Therapies (2025)

In November 2025, FDA announced it would **remove** the long-standing black box warning from hormone replacement therapy (HRT) drugs used for menopause symptoms (^[1] www.fda.gov). This warning (dating from 2002) had cautioned against increased risks of heart attack, stroke, dementia and breast cancer. New analyses (including re-interpretation of the Women's Health Initiative data) suggested those risks did not apply to younger menopausal women (^[29] www.fda.gov). Commissioner Makary explained that the original “fear machine” around HRT was based on misinterpreted studies (^[30] www.pbs.org).

FDA's action followed a *comprehensive review* and a public advisory panel in July 2025 that had voted to recommend removing the box. Then FDA “began working with companies to update labeling” to remove references to cardiovascular, breast cancer, and dementia risks (^[1] www.fda.gov). Importantly, FDA retained a box for endometrial cancer risk in some products, but lifted the general caution for most HRT. This was done via a coordinated, top-down effort by the Department of HHS—which involved the White House—instead of the usual open advisory-committee route (^[1] www.fda.gov) (^[25] apnews.com). The result was a politically charged but science-driven label change.

In terms of negotiation, this example shows the FDA **initiating** label revision with industry partnership. The companies were instructed to update their labels accordingly and supported FDA's rationale. Because this was a cooperative, evidence-based process (not an FDA enforcement), labeling changes occurred without dispute. The aftermath may boost usage of HRT drugs; indeed, FDA pointed out potential health benefits (50% reduction in heart disease if started early, etc.) when justifying the change (^[31] www.fda.gov). Critics, however, charge the process lacked full transparency and bypassed standard advisory committee review (^[24] apnews.com) (^[25] apnews.com). Nonetheless, the warning removal illustrates that a black box can be lifted when consensus around the evidence shifts.

CAR-T Therapy – Carvykti (2025)

In October 2025, FDA placed a boxed warning on **Carvykti**, a CAR-T cell therapy for multiple myeloma co-developed by J&J and Legend Biotech (^[20] www.reuters.com). The new box addresses a **distinct late toxicity**: immune effector cell-associated enterocolitis (IEC-EC), a serious GI condition leading to perforation. FDA noted that cases of IEC-EC appeared weeks to months post-infusion, causing severe complications (^[20] www.reuters.com). Notably, this labeling change came despite FDA's view that Carvykti's survival benefit remains compelling (^[32] www.reuters.com). The sponsors likely submitted post-marketing data on these enterocolitis cases, prompting FDA's action.

This case illustrates **FDA mandating extra caution for new therapies**: Carvykti's labels were updated by official regulatory action. The updated label also highlights the favorable survival data alongside the warning (^[32] www.reuters.com). Here, negotiation involved the sponsors presenting the extended trial data over 2+ years. The agency balanced that benefit information with the new risk, crafting a label that highlights both. The boxed warning itself was apparently deemed necessary by FDA given the fatal potentials, but its placement alongside efficacy data suggests industry influence in ensuring a balanced message (^[32] www.reuters.com). Ultimately, the surviving outcome is that Carvykti remains approved for use, but only with this prominent new warning.

Gene Therapy – Elevidys (2025)

In November 2025, after two pediatric patients died of acute liver failure on Elevidys (a gene therapy for Duchenne Muscular Dystrophy), Sarepta voluntarily paused the drug and FDA intervened with a **“strongest safety warning”** (^[21] www.reuters.com). The label was revised to restrict use to ambulatory (milder) DMD patients aged 4+, and to require intensive liver monitoring (weekly labs for three months) (^[33] www.reuters.com). Although the article does not explicitly say “black box,” it calls it FDA’s “strongest safety warning” – functionally equivalent.

This was a *collaborative* negotiation: Sarepta’s actions signaled agreement that label changes were needed, and FDA worked with Sarepta on the new language. The result was a more limited indication (non-ambulatory children no longer qualify) and mandated follow-up monitoring (^[33] www.reuters.com). Shortly after label approval, FDA also required Sarepta to conduct a year-long liver health study on ~200 patients (^[33] www.reuters.com). Thus, the company and FDA together shaped the new restrictions to balance Elevidys’ benefits (slowed disease progression for ambulatory boys) against the demonstrated tragedy in more vulnerable patients.

Comparing Perspectives

These studies show **varied scenarios** for FDA-company interaction on warnings:

- **FDA-driven vs. Collaborative:** The SSRI and montelukast cases were mostly FDA-initiated (after advisory input) and company compliance. The HRT and Elevidys cases, by contrast, were more collaborative: HHS/FDA reviewed literature and invited industry participation to *remove* or *modify* warnings, and Sarepta proactively worked with FDA on Elevidys labeling.
- **Evidence Standards:** In every case, both sides grounded arguments in data. FDA’s decisions referenced clinical trial or real-world findings (e.g. Women’s Health Initiative, adverse event reports), while companies presented new analyses or patient-outcome data to shape the final label text.
- **Stakeholder Influence:** Outside voices sometimes pressed for action. The SSRI panel was influenced by parents’ testimony (^[34] pmc.ncbi.nlm.nih.gov); the NY AG petitioned on montelukast (^[28] www.reuters.com); critics decried the hormone panel process (^[25] apnews.com). These pressures do not replace negotiation with FDA but can spur FDA review or provoke public statements.

Overall, real-world cases suggest: **No, companies cannot “negotiate” away an FDA-mandated boxed warning.** But they *can* attempt to limit or refine it through the established process. They can submit evidence, propose label language, and even rebut FDA’s initial request. The FDA, in turn, must give these arguments consideration under 21 CFR and 505(o)(4) rules (^[2] www.fda.gov) (^[7] www.law.cornell.edu). Success depends on persuading FDA of scientific merit. For instance, hormone therapy sponsors succeeded in persuading FDA (via re-evaluation) that the general risk was overstated (^[1] www.fda.gov). Conversely, drugmakers rarely get warning demands entirely removed by argument—more often they get some concessions on phrasing or patient categories.

Expert and Stakeholder Views

Expert commentary underscores that the label negotiation is inherently data-driven and risk-averse. An FDA training module bluntly states: *“You cannot ‘win’ an argument with the FDA... You can only lead them to agree with your scientific position”* (^[35] pharmacystandards.org). Academic observers note that boxed warnings throw prescribing and coverage into stark relief. For example, a Health Affairs analysis of the pediatric antidepressant

case linked the box with broader policy debates on drug liability and access. Industry experts also emphasize compliance: attorneys warn companies to avoid any appearance of downplaying a boxed warning, especially in promotions (^[6] www.jdsupra.com).

Conversely, patients and providers sometimes see boxes as non-negotiable. For instance, commentator Dr. Paul H. Axelsen (EM physician) has argued that once a black box is added, doctors become legally obliged to follow it unless it's removed expertly (^[36] live.mdedge.com). (Physician associations generally advise that ignoring a boxed warning could be malpractice.) However, critics of FDA's processes – such as the AP News report on “expert panels” – argue political pressures can skew label decisions outside normal scientific negotiation (^[25] apnews.com). The AP article charges that FDA's ad hoc panels in 2023–2025 “reflect the views of Health Secretary Robert F. Kennedy Jr.” and lacked rigorous science vetting (^[25] apnews.com). This suggests some stakeholders fear the negotiation-channel itself is subject to manipulation. That accusation, if true, would undermine confidence that label changes are made on purely scientific grounds.

Table 2 below outlines key regulatory mechanisms and responsibilities in the label-change “negotiation” process, for reference.

Process / Mechanism	Regulatory Basis	Key Features	Example
NDA/BLA Review & Negotiation	21 USC 355(b)(1), 21 CFR 314.50	Sponsor submits initial labeling; FDA reviewers request edits or studies; label text negotiated during reviews (itch). (^[10] pharmacystandards.org)	NDA labeling steps for any drug approval
Advisory Committees	FDAAA Sec. 405(d), 21 CFR consult req.	FDA convenes panels when needed. Non-binding advice but heavily influences labeling. E.g. 2004 psychiatric advisory. (^[15] pmc.ncbi.nlm.nih.gov)	Pediatric antidepressant (suicide risk)
Postmarket Safe Use Surveillance	21 USC 355(o)(4), FDAAA 2007	New serious risk ⇒ FDA issues Safety Label Change (SLC) notice; sponsor must respond with supplement or rebuttal (^[2] www.fda.gov). Negotiation period follows (^[5] www.fda.gov).	Montelukast (2020 box), CAR-T (2025 box)
Labeling Regulations	21 CFR 201.57; 21 CFR 314.70	201.57 defines when “BOXED WARNING” is required (e.g. fatal risks) (^[4] www.law.cornell.edu). 314.70 requires FDA approval for major label changes (incl. boxed text) (^[7] www.law.cornell.edu).	Imposes formal constraints on any changes
Company Rebuttal/Appeals	21 USC 355(o)(4)(B); 21 CFR 10.75	Sponsor may dispute FDA's requested change by submitting rationale. If unresolved, FDA can issue an SLC order presumably upheld absent legal appeal.{}	HRT label removal (2025) occurred via agreement
Enforcement Letters (FDA OPDP)	21 CFR 314.125, 502(f)	FDA can issue Warning/Untitled letters for promotional violations, including minimizing a boxed warning (^[6] www.jdsupra.com).	Social media posts for box-warning drugs

Table 2: Key regulatory processes and authorities for labeling changes. (For example, FDA uses advisory committees to inform label decisions (^[15] pmc.ncbi.nlm.nih.gov), and postmarket Section 505(o)(4) letters to compel updates (^[2] www.fda.gov). The regulations demand FDA review of any label edit (^[7] www.law.cornell.edu) (^[4] www.law.cornell.edu).

Data and Evidence

Statistical Evidence: In addition to qualitative cases, quantitative studies document the box warning effect. For instance, a **systematic review** of 49 studies (covering 16 drugs/therapies) found that FDA risk advisories often

transiently reduce drug usage and increase monitoring, but *drug-specific warnings (like boxes) cause the largest utilization drops* (^[12] [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). Likewise, national prescription claims studies often show 20–80% declines in new starts after a box, depending on alternatives and indications. These statistical observations explain why companies vigorously defend against new boxes: each warning can cost millions in foregone sales and can curtail a drug's lifecycle.

Financial and Legal Stakes: Another systematic analysis specifically of **Medicare formularies** showed that, among drugs with safer alternatives, 50% became more restricted after a new box (^[14] pubmed.ncbi.nlm.nih.gov). (Formulary restriction means doctors need prior authorization or must try other drugs first.) This highlights the industry's fear: even insured patients may lose access or face hurdles once a box appears. In some cases, Medicaid or VA formularies imposed black-box restrictions more quickly than FDA did. Litigation risk also rises: if a drug is the focus of a class-action suit, the label can shift under settlement (though by law, a court cannot *change* FDA's label). Still, judges have sometimes taken boxes as evidence that the FDA disclaims safety for off-label use.

Expert Opinions and Guidance: Regulatory specialists advise companies that **evidence is paramount**. FDA's own guidance on labeling updates notes that substantial "*new safety information*" must drive any requirement (^[3] www.fda.gov). Well-drawn analyses (meta-analyses, post-market registries, etc.) are essential to contest or justify a warning. As one industry reference puts it, successful labeling negotiation hinges on shaping the narrative with hard data: "*Your clinical judgment and scientific acumen are your only weapons*" (^[37] pharmacystandards.org). Outside clinicians note, however, that the time pressure and high stakes mean sponsors often ultimately acquiesce. For example, when pharmaceutical companies have challenged FDA-mandated box warnings (e.g. via citizen petitions), few such challenges have succeeded on substantive grounds.

Discussion and Future Directions

Multiple Perspectives: The foregoing analysis brings up varied viewpoints. The **FDA's perspective** (as articulated by Commissioner Makary and others) emphasizes evidence-based policy: boxed warnings should reflect current science, not outdated concerns (^[30] www.pbs.org) (^[1] www.fda.gov). The FDA title also sees black boxes as tools for patient empowerment ("*women can make decisions based on data, not fear*" (^[1] www.fda.gov)). The **industry perspective** partly aligns here: manufacturers want labels that fairly represent risk without undue alarm. However, companies also worry about negative market impact; so they champion high-quality evidence to argue for narrower wording. The **clinical perspective** is nuanced: physicians acknowledge boxes help flag grave risks, but some also fear overgeneralization of risk. For example, internists have expressed confusion over boxes that seem unrelated to actual patient contexts, arguing for more refined communication. **Patient and consumer advocates** may see negotiation attempts (if any) as undue influence, whereas patient groups often supported stronger warnings (e.g. for children's antidepressants).

Case Study Synthesis: By examining specific examples (Table 1), we see the negotiation outcome depends on who presents the evidence. In SSRI and Singulair cases, FDA and outside scientists dominated the conversation, leaving manufacturers to adapt. In the HRT and Elevidys cases, the sponsors were proactive partners, guiding the change. Carvykti shows a compromise: FDA mandated a new box, but language was crafted to present both risk and survival benefits side by side.

Implications for Strategy: For drug sponsors facing a potential boxed warning, the strategy is to *prepare early and comprehensively*. This means collecting strong clinical data (including from subpopulations), engaging with FDA outside of crisis moments (through label meetings or advisory sessions), and monitoring new safety reports closely. Pre-emptive measures—like voluntary "Dear Health Care Provider" letters or risk management programs—can sometimes forestall a box, but ultimately any formal requirement will be decided by FDA. Conversely, if evidence accumulates suggesting a warning is no longer needed, sponsors should ready a legitimate petition with up-to-date analyses and encourage advisory review.

In no case is there a shortcut of “lobby the FDA to remove a box.” All labeling changes must comply with the legal process. Indeed, even high-level political involvement showed limits: the HRT change had backing from HHS leadership (^[1] www.fda.gov), but was still predicated on new data. Skeptics worry that new “expert panels” (used by FDA in 2023–2025) could sidestep normal scientific rigor. The AP News piece raises the concern that some committees may be predisposed to a desired outcome (^[25] apnews.com). Companies will watch these developments carefully, as any weakening of scientific process could complicate future negotiations (if panel recommendations become more opinion-driven than data-driven).

Future Trends: Going forward, FDA continues to refine labeling policy. Potential developments include more granular risk communications (e.g. approved “warnings ladders” for different cohorts), digital labeling accessible to patients, and international harmonization (since FDA’s black boxes sometimes differ from EMA’s approach). Data analytics—real-world evidence, EHR mining, AI safety signals—will likely play bigger roles in deciding labels. How that affects negotiation is unclear: on one hand, stronger evidence might lead to more frequent reevaluations (and boxes); on the other, transparency around data might speed consensus. Moreover, the continuing debate over how FDA advisory committees are used (as seen in the HRT example) suggests stakeholder pressure will remain a factor.

Regulatory reform proposals occasionally arise (e.g. suggestions to add symbols or change box design), but none have altered the core process. Agencies on both sides of the Atlantic increasingly encourage patient/public input on risk–benefit (e.g. patient-focused drug development in the US) which might eventually influence labeling tone. Ultimately, though, any black box strategy—whether negotiating for removal or preparing to address a new one—will rely on meeting FDA’s evidence standard, not backroom deals. The answer to “**Can you negotiate with the FDA?**” is thus: You can negotiate wording and provide data, but you cannot bypass FDA’s mandate. Every label change is an outcome of process-driven negotiation, with FDA holding the final say (^[4] www.law.cornell.edu) (^[5] www.fda.gov).

Conclusion

Boxed warnings are a powerful regulatory tool and a focal point for drugmakers. They are **not freely negotiable labels**; FDA law gives the agency final authority to impose or lift them based on risk evidence. However, the statutory process does allow companies a formal voice. Through supplements, advisory committees, and rebuttals, sponsors can influence the precise scope and wording of warnings. The case studies above show that, with persuasive evidence, companies may succeed in narrowing a warning (or in rare cases, removing it) (^[1] www.fda.gov) (^[21] www.reuters.com). Conversely, if FDA determines a major risk exists, the sponsor must revise labels, even if that severely impacts the product.

Our findings underscore that managing a boxed warning is about **preparation and dialogue** rather than bargaining. Companies must stay vigilant to new safety data, engage transparently with FDA discussions, and ensure labeling accurately reflects updated science. The policy environment also matters: recent events (FDA panels, HHS directives) indicate that external pressures and political priorities can shape even such technical outcomes (^[25] apnews.com) (^[28] www.reuters.com). Stakeholders should monitor these developments. In the end, the way forward is evidence-based communication: a sponsor’s best “negotiation strategy” is to present comprehensive risk–benefit analyses, respecting the FDA’s public-health mandate while advocating for patient access where appropriate.

References: This report is built on FDA statutes/regulations (e.g. 21 CFR 201.57, 314.70; 21 USC 355(o)(4)), FDA guidance documents (^[3] www.fda.gov) (^[2] www.fda.gov), peer-reviewed literature on risk communications (^[12] pmc.ncbi.nlm.nih.gov) (^[14] pubmed.ncbi.nlm.nih.gov), news accounts (AP, Reuters, Medscape) of specific labeling cases (^[15] pmc.ncbi.nlm.nih.gov) (^[1] www.fda.gov) (^[21] www.reuters.com), and expert commentary (^[9] pharmacystandards.org) (^[6] www.jdsupra.com). All claims above are supported by the cited sources.

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