Point32Health, parent company of
Harvard Pilgrim Health Care & Tufts Health Plan
ETHICS ADVISORY GROUP (EAG) Deliberation

Deliberation Report
'Paying for hope? Considerations for payer communication at the intersection of uncertainty and costs'
29 July 2024

Purpose
To seek input from the multi-stakeholder Ethics Advisory Group (EAG) on considerations for payers about communicating with stakeholders about uncertainty of evidence underlying approvals of new treatments.

Customers for the Ethics Advisory Group and Expert Guests
The Point32Health customer for the EAG deliberation was Gail Ryan, BS, PharmD, Director of Pharmaceutical Transformation. Melanie Wyne, JD, Chief Policy Officer, National Breast Cancer Coalition, offered expert remarks.

Background[a]
FDA approvals over time
The United States Food and Drug Administration (FDA) was once considered an agency that set the most stringent standards globally for evaluating and approving safe and effective new products.[1] In the past 30 years, "repeated regulatory failures and a shift in the FDA's mission from protecting public health to speeding drugs and devices to market has tarnished the agency's reputation and, more importantly, harmed patients."[2] In 1992, the Prescription Drug User Fee Act made the FDA dependent on fees paid by the pharmaceutical firms whom it is supposed to regulate. FDA regulation has since shifted from requiring assessments of safety and efficacy before its approval of products to facilitating expedited development and earlier approvals of drugs and relying on studies of safety and effectiveness after those approvals (see Appendix, page 7). This shift in regulation, combined with the challenges of removing approvals post-marketing, has resulted in products being introduced to the market with uncertain benefits and harms and in products with known lack of benefit and known harms being prescribed, used, and paid for by insurers, employers, and government programs. Since there is no price regulation in the US, new products are priced at "what the market bears". For example, 3 therapies marketed by Sarepta for a rare, severe, progressive genetic disease in children, approved without documentation to date that they work, have accumulated $4 billion in sales for the company since 2016, not including revenue from a $3M/patient gene therapy (Elevidys) for the disease also lacking evidence of benefit.[3,4] Gregg Gonsalves, an advocate for speedier FDA approvals in the wake of the HIV epidemic

[a] **This background relies on PharmedOut's March 2024 report 'What Needs to Change at the FDA? Protecting and Advancing Public Health', written by Sharon Batt, PhD, Judy Butler, MS, and Adriane Fugh-Berman, MD. PharmedOut is a project at Georgetown University Medical Center that advances evidence-based prescribing and educates health care professionals and students about pharmaceutical and medical device marketing practices.**

of the 1980s now says, "[w]e get drugs more quickly onto the market in the US than ever before, faster than many peer regulatory agencies in other nations, but at the same time, we know less and less about what we put in our bodies and often pay more and more for drugs with dubious, unproven efficacy."[5,6] A recent analysis has identified 4 problems at the FDA that characterize recent drug approvals, with downstream implications for payers, providers, and patients: transparency and accountability, innovation, pre- and post-market standards of evidence, and value in health care.[2]

Transparency

Internal controversies, disregard of expert advisory committee votes,[7] and impacts of testimonies by industry-sponsored patient advocates[8] have given rise to concerns about conflicts of interest in FDA approval processes.

Innovation

"FDA is responsible for advancing the public health by helping to speed innovations."[9] Pressure to approve more "innovative" drugs faster has resulted in the designation as "innovation" of virtually any newly approved drug, when few are innovative in the sense that they make people live better or longer compared to what is already available. Regulatory terms for expedited development and approval, such as "breakthrough therapy" and "accelerated approval", misleadingly imply that an approved product has added benefits when there is no evidence of such benefits at the time of approval.[2,10]

Evidence

"The FDA has decreased regulatory standards and compromised public health with its shift away from approving drugs and devices based on rigorous tests of safety and efficacy, towards faster approvals based on preliminary evidence."[2] Drugs may be approved after only 2 phases of testing, clinical trials increasingly involve small, non-representative groups of patients and usually omit comparisons to established standards of care, and study designs that minimize the influence of extraneous factors (e.g. randomized controlled trials) are no longer the norm. [11,12,13,14,15] Although regulators stipulate that evidence of clinically meaningful benefits be shown after marketing, this often does not happen. [11,16,17] When lack of effectiveness is shown post marketing, pressure by industry, Congress, and patient advocacy groups makes it difficult for FDA to withdraw approvals, and products often remain on the market. Consequently, faster FDA approvals result in more new drugs available with uncertain benefits or with known lack of clinical benefit. Of 55 drugs newly approved in 2023,[18] 65% (36) were approved using at least one of the FDA's expedited development and review pathways (fast track designation, breakthrough therapy designation, priority review designation, and accelerated approval. See Appendix for a summary of expedited development and approval programs).

Value

FDA's expedited approval pathways have created costs for payers and patients when approvals are withdrawn for products shown to lack benefit or for which harms outweigh benefits. Cell- and gene-therapies, currently still mostly indicated for rare diseases, lack data at approval to document longer-term effects and have several million-dollar price tags per patient, rationalized by promises of curing severe illnesses. Payers are concerned about the costs of these newly-approved treatments that lack evidence of benefit,[19] while FDA decision makers believe that their promise to cure fatal or debilitating illnesses justifies the risks of approvals based on limited benefit evidence.[20,21]

<u>Information about uncertainty</u>

The FDA plays a crucial role in providing information to patients and physicians about the benefits of

medications. It is responsible for "advancing the public health …. by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health."[9] The FDA mandates that all approved drugs have labeling that includes important information for healthcare providers and patients. However, drug labels are lengthy, complex, and do not sufficiently inform,[22] especially about the uncertainty of benefits given limited evidence for approvals based on accelerated approval and other expedited regulatory pathways. Medication information primarily focuses on explaining how to use a drug, what to use it for, and potential side effects. Studies indicate that the information sources currently available to people are not considered helpful[23] and that individuals seek more balanced and comprehensive information[24] in order to make informed decisions about their healthcare. Informed decisions require understanding a drug's potential benefits and the likelihood or uncertainties of those benefits. Regulators rarely and inconsistently communicate uncertainty of benefits of new drugs to prescribers and not at all to patients,[25,26] increasing the information asymmetry inherent in health care.

Information asymmetry

The information status quo creates problems for patients, clinicians, payers, and society at large. There is a discrepancy between what physicians and patients assume about new drugs and the actual evidence base that is known to manufacturers and regulators. This information asymmetry generates unjustified trust in the benefits of new drugs, which leads to increasing use and spending based on those assumptions.

Physicians commonly lack familiarity with FDA drug regulatory practices and are under the impression that the data supporting FDA drug approvals are more rigorous than they often are. Patients[27] and physicians[28] often overestimate the benefits of approved drugs, wrongly assuming they work better than they do. At the same time, they underestimate potential harms and side effects.[29] In a national survey, almost 40% of US adults mistakenly believed that the FDA approves only "extremely effective drugs" and 25% that FDA-approved drugs lack serious side effects.[30] Almost three-quarters of physicians reported they believe that FDA approval means a clinically important benefit.[31] Among a randomly selected national sample of internists, cardiologists, and oncologists, 65% of physicians recently reported they believe that FDA approval requires evidence from randomized controlled trials (Table 1).[32] The survey also documented that nearly all physicians thought that randomized, blinded trials that met primary endpoints should be very important factors required to secure regulatory approval and that the FDA should revoke approval for drugs or devices that did not show benefit in post-approval studies.

Table 1. US physicians' limited understanding of FDA drug approvals[32]

	N (%)
Perception of newly FDA-approved products (multiple responses allowed)	
More effective than other available treatments for same condition	190 (39)
More effective than placebo	446 (91)
Safer than other available treatments for same condition	153 (31)
Perceived evidence requirement for FDA approval	
2 or more randomized controlled trials	156 (32)
A single randomized controlled trial	319 (65)

Registries or other nonrandomized studies	14 (3)

Source: Dhruva SS et al, *Health Affairs* 2024[32]

Both patients and physicians receive information about new drugs from pharmaceutical companies, including through extensive marketing that is intended to increase product use.[33,34,35] For example, a recent press announcement by Sarepta for Elevidys states: "Confirming the functional benefits, the FDA granted traditional approval for ambulatory patients.**"**[36] The company information does not acknowledge that there are no data that Elevidys has clinical benefits or that children 8 years old and older were excluded from the trials, misleading those without regulatory science knowledge. Marketing of drugs with uncertain benefits contributes to unjustified beliefs in the benefits of a new drug which may be of particular concern for patients whose remaining life is measured in weeks.[37,38,39] Use of some cancer drugs in seriously ill cancer patients has been termed "desperation oncology".[40] It has raised concerns about quality of care at the end of life,[39] and may waste individual and societal resources, along with precious remaining time that patients may otherwise choose to spend outside of clinical settings.[41]

Implications of information asymmetry for payers

The limitations of the information landscape also contribute to high demand and public and private coverage for new drugs. Payers are expected to cover FDA-approved drugs. There is no clear association between the clinical benefits, certainty of evidence, and prices of new treatments.[42,43] For many approved highly priced drugs and gene and cell therapies, payers may have no or limited leverage to negotiate prices, or to delay or deny coverage. Therefore, payers ultimately pay high prices for therapies with marginal clinical benefits and important harms.[44,45,46,47] Such payments, likely unknowingly to patients and providers, may contribute to harmful waste of limited resources in the health care system and society.[48]

Ethical considerations for payer communication about benefit uncertainty of FDA-approved treatments

Arguably, payers have resources and responsibilities to help mitigate the information imbalance regarding what is known and what is not known about approved treatments that they pay for. Although payers too are restricted to publicly available information, they review manufacturer and FDA approval information about a new drug when they bring new therapies to Pharmacy & Therapeutics committees or similar medical advisory committees for clinical assessment, formulary recommendations, and coverage policy design.

In 2023, FDA issued guidance for firms to help FDA assess whether a new treatment's benefits outweigh its risks.[49,50] Pharmaceutical firms are asked to generate information for benefit-risk assessments throughout the drug development process. Benefit risk assessments detail evidence on benefits, risks, and the uncertainties of benefits and risks. They are part of FDA's review prior to approval of a new treatment as well as post-marketing. Benefit risk assessments are available in FDA review documents.[b] However, they are unlikely to be accessed by providers or patients.

Payers' "location" in the drug information landscape provides them access to information that pharmaceutical firms and FDA have, and that patients need and cannot easily access. In this context, do payers have responsibilities to mitigate the information imbalance about clinical benefits of newly approved treatments?

[b] For example, the benefit-risk assessment for Elevidys is available on pages 91ff of the FDA Integrated Clinical and Clinical Pharmacology Review Memorandum.

Possible answers to this question could consider *potential "down-stream" impacts on individual members, their providers, and on insured populations,* and *potential "upstream" impacts in society*. Down-stream, the principle of *transparency* would suggest that payers may have an obligation to support patient-provider *shared decision-making* with as much information as possible, including information about uncertainties of benefits and risks. *Transparency* would also support payers' sharing information about benefit uncertainties in relationship to quality of care and costs of new treatments and the down-stream impacts of higher health care spending on premiums, affordability of health insurance, and wages (as discussed in prior EAG deliberations, please see below). In this way, payers' information sharing could enhance their credibility in facilitating quality, high value care.
Upstream, payers' sharing evidence of benefits and risks and uncertainties around both might *support ongoing efforts for better information about and calls for better evidence for approved treatments*. In 2023, the FDA proposed to broaden the provision of Medication Guides by requiring 'Patient Medication Information' for all outpatient drugs.[51] While a step in the right direction, experts highlight that the proposed formats focus on indication and safety information and do not include information about the evidence supporting expected drug benefits.[52] Another opportunity is including summary information on new drug approvals on the FDA website, similar to an approach of the European Medicines Agency for more than two decades. There are also long-documented important opportunities for improving the FDA-approved labelling for physicians, [53,54] which currently summarize benefit and risk information inconsistently and without accessible information about uncertainties.[25] Ideally, in the longer-term, payers mitigating the imbalanced information landscape might contribute to pharmaceutical firms developing and FDA approving better drugs that meet patients' needs for better quality and longer duration of their lives. In this way, payers would support calls for reforming FDA evidence standards, including a call by the National Breast Cancer Coalition.[55]
Considerations against payers providing information to patients, providers, and/or the public about uncertainty of benefits and risks of FDA-approved treatments also exist. At the individual level, concerns could include payers *interfering in patient-provider relationships* and *impacts on individuals' and their families' "hope" for cures*. More broadly, there may be *reputational risks* for the payer to the extent that media and patient organizations' portrayal of payers discussing limited evidence of benefits (and possibly limiting coverage for drugs lacking clinical evidence) may be viewed as self-serving and not in the patients' or society's interest.[56,57,58] Further, one could argue that informing stakeholders about evidence underlying drug approvals is not payers' responsibility and efforts a payer invests in educating patients, providers, and the public would again contribute to higher insurance costs, higher premiums, and well-known down-stream effects of those.

Related Prior Ethics Advisory Group (EAG) Deliberations

Since 1998, more than 10 EAG deliberations have focused on pharmaceuticals. Until 2017, the deliberations mostly addressed questions of how the health plan should best balance its responsibility to cover costly drugs for individual members against its responsibility to ensure sustainably affordable coverage for all its members. Deliberations addressed ethical questions around incentives for members and prescribers toward most cost-effective alternatives. In 2017, in a deliberation[c] on the increasing proportion of (specialty) pharmaceutical spending of the health plan,[59] participants discussed, for the first time, questions around not covering a drug based on costs. In 2021, following FDA accelerated approval of a highly priced drug lacking evidence of benefit (aducanumab, which the health plan did not

[c] A Framework of Values for Dealing with High Drug Prices. Consultation report of the Harvard Pilgrim Health Care Ethics Advisory Group deliberation. October 17, 2017. Available from anita_wagner@hms.harvard.edu.

cover), EAG participants acknowledged that a payer should provide member and clinician education about evidence of benefits and risks of rapidly approved drugs lacking evidence of benefit and publicly advocate for system change. *"In this way, a payer demonstrates consistently its efforts as an "honest broker" in a complex system."*[d] In 2023, EAG participants discussed affordability of new therapies and suggested "*a need for and responsibility of the health plan to engage with all its stakeholders proactively and visibly about the trade-offs that are required, locally and nationally, by increasing pharmaceutical spending*."[e] In all EAG deliberations on pharmaceuticals and other highly priced technologies, participants advised the health plan to provide physicians and members with information about drug prices. They also suggested that the health plan work with other stakeholders to promote public understanding of (a) the fact that health care costs trade off against other desirable social goals and (b) the health plan's responsibility to manage care and costs and to do so fairly for all its members. Provider, member, and public education by the health plan were seen as necessary to support reforms of the pharmaceutical system.

Questions for the Point32Health Ethics Advisory Group Deliberation

FDA approves more treatments with uncertain clinical benefits, and FDA-regulated drug information does not adequately communicate the uncertainty of benefits of approved treatments. Providers and patients tend to overestimate benefits and underestimate harms. High and increasing prices of new treatments, the approval of more therapies with clinical uncertainty, and the imbalanced information landscape impact individuals and society.

On July 29, 2024, the EAG was asked to reflect on the following questions: In the imbalanced drug information landscape,

1. What, if any, is the responsibility of payers to communicate uncertainty of benefits of FDA-approved treatments they cover?
2. If payers should communicate uncertainty of benefits of covered treatments, how should they do so?
    a. With whom should payers communicate about uncertainty of benefits? Does the responsibility differ for providers vs patients? What would be the goals of communications? What are concerns about communicating with providers and patients?
    b. Which communications should payers prioritize?

Summary of the Point32Health Ethics Advisory Group Deliberation

Almost 50 individuals joined the deliberation. At the outset, adding to the information in the preceding pages of this document, the Point32Health customer, invited expert, and participants highlighted the following points:

- There is a mismatch of FDA goals and the responsibilities of a health plan: Peter Marks, director of the FDA Center for Biologics Evaluation and Research, justified the accelerated approval pathway in

[d] Accelerated Drug Approvals: Roles and Responsibilities of a Health Insurer. Consultation report of the Point32Health Ethics Advisory Group deliberation. October 15, 2021. Available from anita_wagner@hms.harvard.edu.

[e] Affordability of New Therapies - Principles for Health Plan Communication. Consultation report of the Point32Health Ethics Advisory Group deliberation. January 9, 2023. Available from anita_wagner@hms.harvard.edu.

support of industry saying "[t]he wherewithal to do a three-year study or a four-year study without having a revenue stream, it's just beyond many companies that are startups. So having the accelerated approval process is a way to get there."[20] This rationale suggests an FDA focus on the financial sustainability of biotech companies, rather than a focus on public health and affordability of care, and an expectation that payers (and thus society) pay for post-approval evidence generation.[60]

- Because FDA has shifted requirements for generating evidence of benefit to the time after many drugs are approved, and for some drugs does not require post-approval evidence, there is a lack of science-based information about newly FDA-approved, used, and reimbursed drugs.
- The combination of clinical uncertainty and rising costs leads to lower quality health care.
- "Patients want drugs that work, not just more drugs faster." For this reason, the National Breast Cancer Coalition has established Project LEAD, a science training program partnering advocates with researchers. It enables training patients for advocacy based on science, "marked by transparency, innovation and a peer relationship among scientists, researchers, policymakers and consumers nationwide".[61]
- The June 2024 Supreme Court ruling on the so-called Chevron doctrine[62] undercuts longstanding authority of federal agencies and is expected to further complicate FDA decisions on behalf of US consumers. The Chevron doctrine had laid out that courts should generally defer to federal agencies' reasonable interpretations of their authority.

The majority (79%) of EAG participants responding to poll questions agreed that payers should communicate about uncertainty of benefits of FDA-approved drugs they cover (Table 2, question #1). Specifically, most (79%) endorsed health plan communication with prescribers who prescribe the drugs in question. More than a third of respondents stated that payers should communicate with members and about a third that payers should communicate with the public (Table 2, question #2).

Table 2. EAG participants' responses to poll questions about payer communication of uncertain drug benefits

Question #1. Do you think payers should communicate about uncertainty of benefits of FDA-approved treatments they cover? (n=33)		Question #2. If payers were to communicate about uncertainty of benefits of FDA-approved drugs they cover, whom should they communicate with? (n=28, multiple responses allowed)	
Yes, n (%)	26 (79)	1. Prescribers who prescribe the treatments in question, n (%)	22 (79)
Not sure, n (%)	6 (18)	2. All prescribers, n (%)	13 (46)
No, n (%)	1 (3)	3. Members who receive the treatments in question, n (%)	12 (43)
		4. All members, n (%)	10 (36)
		5. The public, n (%)	9 (32)
		6. Others, n (%)	3 (11)
		7. None of the above, n (%)	0 (0)

EAG participants offered the following rationales *in favor of* payer communication about uncertainty of benefits of FDA-approved drugs.

- FDA regulation of drug information has not kept pace with FDA regulation of drug approvals, leading to a lack of information on benefit and risk uncertainty of approved drugs, and misconceptions. In

this gap, it may be a responsibility, and possibly an ethical obligation, of payers to provide missing information. Reasons include to:

- Help equip health care consumer with all available evidence (about efficacy, risks, uncertainties, and trade-offs) to make informed decisions, in communication with their clinicians.
- Meet a responsibility to patients whom health plans are serving because communicating uncertainty helps prevent therapeutic misconceptions about efficacy and safety of approved and covered drugs and makes it clear that health plans are concerned about evidence.
- Clarify a potential misconception that reimbursement of prescription drugs means that drugs are effective.
- Fill a gap that many patient organizations, due to financial ties to pharmaceutical companies, cannot easily fill.[63]
- Help underscore the need for better information on the part of FDA.

EAG participants offered the following rationales *against* payer communication about uncertainty of benefits of FDA-approved drugs.

- While education and better information about efficacy and safety of newly FDA-approved drugs are needed, payers may not be the best providers of this information because:
  - Payers are not trusted as neutral providers of information.
  - Information about evidence of efficacy and risk of newly approved drugs is complex, highly specialized, and constantly changing. Payers may not be able to analyze, synthesize, and communicate this information appropriately.
  - Communication about "uncertainty of benefit" requires a definition of "uncertainty" and nuanced communication, especially in clinical areas with limited therapeutic options, such as pediatric oncology, where off-label medication use is common and payer communication with patients about uncertainty of benefit and risk evidence could interfere with patient/parent-clinician communication.

If payers were to communicate about uncertainty of benefits and risks of FDA-approved drugs, EAG participants suggested the following strategies:

- Identify Target Audience(s): Most EAG participants endorsed communication targeting prescribers who should be the primary source of information for their patients. EAG participants also mentioned the importance of information being available to all health care consumers.
- Partnerships: "It can't just be the health plan's voice" because "acting alone creates suspicion about motivation". Given that the level of trust in health plans is low and that health plan communication about uncertainty will likely be viewed as self-serving, that is, "putting payments over patients", health plans should partner with neutral, independent organizations such as ICER (Institute for Clinical and Economic Review). Partnerships with select patient advocacy organizations could potentially be explored. For oncology drugs, a recently established group of oncologists, Common Sense Oncology,[64] may be of interest.
- Separating Coverage and Communication: Health plans should distinguish between coverage of drugs with uncertain benefits for individual members and communicating about drugs with uncertain benefits to diverse stakeholders. The latter would be intended to fill gaps in the drug information landscape for multiple audiences, including to inform individual clinician-patient decision making.
- Assuming Coordinator and Facilitator Roles, Creating Tools: Health plans could provide resources and tools for members, providers, and others to access information about benefit and risk

uncertainty, for example in the form of a webpage. Web-based tools could refer to the FDA Drug Trials Snapshots and augment the information with data on evidence of clinical benefits, risks, and uncertainties. Patients could use the information provided in conversations with their clinicians.

- Emphasizing Changing Evidence: It would be crucial to highlight that any information provided will change as new data becomes available and to ensure that information is up to date.

In summary, most, however not all, EAG participants agreed that there is an ethical obligation for payers to communicate uncertainties in the evidence underlying newly approved covered drugs. There are substantial challenges in meeting this obligation. Approaches would need to be nuanced, considering the complex technical and rapidly evolving nature of the information, and multi-modal, accounting for different needs of different stakeholders.

This report is respectfully submitted, with gratitude to Point32Health leaders, the expert guest, and all who generously shared their perspectives, for making this important and timely Point32Health EAG conversation possible. Thanks also go to Alyssa Halbisen, Kelsey Berry, and Caitlyn Tabor for supporting this EAG deliberation.

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Appendix: FDA programs to expedite drug development and approvals (copied from Batt et al [2])

Orphan Drug Act (1983)

- Goal: to facilitate development of therapies for rare diseases
- Pathways:
  - Federal research grants
  - 50% tax credit for clinical testing expenses (reduced to 25% in 2017)
  - 7 years of market exclusivity to delay approval of competitor drugs
  - Flexibility in conduct of clinical trials

Expanded Access for Serious Illnesses (1987)

- Goal: Provide patients with unmet medical needs access to experimental therapies
- Pathway:
  - Patients can access experimental therapies before FDA approval

"Fast-track" regulations (1988)

- Goal: Speed evaluation and approval after Phase II trials of treatments for patients with unmet medical needs
- Pathways:
  - Early meetings with the FDA
  - Timely communication to promote efficient trial design
  - Involvement of senior FDA officials

Accelerated approval (1992)

- Goal: Reduce the duration of pre-market clinical studies for drugs intended to treat serious illnesses
- Pathway:
  - Reliance on surrogate markers is encouraged, e.g., reduction in tumor size

"Priority Review" of Applications (1992)

- Goal: For specific conditions, speed approval of drugs that appear to offer improvement over current treatments in safety, efficacy, or convenience
- Pathways:
  - FDA issues vouchers under certain conditions listed below that commit the agency to a review period 6 months earlier than the standard 12 months (later reduced to 10 months). The company receiving the voucher can use it or sell it to another company
  - Neglected Tropical Disease Priority Review voucher, introduced in 2007 in the FDAAA, section 1102
  - Rare Pediatric Disease Priority Review voucher, introduced in 2012 under the FDASIA to encourage the development of therapies for rare pediatric subsets of other diseases.

Breakthrough Therapy Program (Section 902 of FDASIA, 2012)

- Goal: Reduce clinical trial burden for treatments intended to treat serious conditions that, based on preliminary evidence, may provide a substantial improvement over existing treatment.
- Pathways
  - Encourages use of historical controls or other alternatives to concurrent control groups
  - Encourages smaller trials that take less time to complete
  - Early meetings with the FDA
  - Timely communication to promote efficient trial design
  - Involvement of senior FDA officials.

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