



November 18, 2019

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-2514: Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) appreciates the opportunity to provide input and recommendations to the FDA on the docket titled Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO and our member companies are committed to taking all appropriate measures in conjunction with the FDA, for assuring safety, especially redressing serious problems with safety, abuse, and addiction relating to extant opioid analgesics, and pursuing innovation to reduce or eliminate these risks attendant to this class of therapy. BIO agrees with the Agency that opioid analgesics are clinically significant therapies that nevertheless bear meaningful risks of addiction, overdose, and death. These risks are serious challenges that must be managed effectively by Sponsors, providers, and patients, including through compliance with the risk evaluation and mitigation strategy (REMS) required of opioid analgesic drugs intended for inpatient and outpatient use.

BIO also believes that risks associated with opioid therapies can be surmounted through further innovation on safe and effective analgesics with lower risks, thus the focus of BIO's comments included in this letter will specifically address question 9 posed by the FDA in the docket, incentives needed to better support and encourage development of therapeutics intended to treat pain or addiction.

Current Investment Trends and Pipeline for Pain and Addiction Therapies

In February of 2018, BIO released a report entitled, *The State of Innovation in Highly Prevalent Chronic Diseases Volume II: Pain and Addiction*¹. The report examined current

¹ [The State of Innovation in Highly Prevalent Chronic Diseases Volume II: Pain and Addiction](#).



investment trends and the pipeline for pain and addiction therapies. Key takeaways from that report include:

- Pain therapies have only a 2% probability of obtaining FDA approval from phase I, compared to an overall 10% success rate across all other therapeutic areas. Due to the low number of active clinical programs over the past decade, BIO was not able to calculate success rates for addiction therapies.
- Private company investment, as measured by venture capital into US companies with lead stage programs in pain, is 3.6% of total drug development venture funding. For venture funding of novel research and development (R&D), pain has received 17 times less venture capital than oncology over the last decade.
- Investment trends for addiction therapies indicate that over the last 10 years, only \$16 million has been invested across two addiction-focused companies.

Additionally, chronic pain affects as many as 100 million people in the US alone.² The total economic and direct healthcare costs for treating pain in the US have been estimated to be as high as \$635 billion annually, higher than the costs for cancer, Alzheimer's, or cardiovascular disease.³ Substance use disorder affects more than 23 million Americans and continues to rise, in part due to abuses of pain medications.⁴ The total economic and direct healthcare costs for substance abuse is approximately \$700 billion per year.⁵

Following the release of the report, BIO established a working group, which today consists of representatives from more than 30 of BIO's member companies. Over the course of 2017 and 2018, the Working Group worked to identify barriers and potential solutions for the lack of investment into R&D for pain and addiction therapies. BIO's comments, detailed in this letter, were developed from conversations with BIO member companies and focus on ways in which the FDA can help support investment in Research and Development to develop of novel and safer pain and addiction therapies. BIO has previously also submitted comments to the FDA on the FDA's Opioid Policy Steering Committee.⁶

I. FDA Should Ensure that the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP, formally the FDA Division of Anesthesia, Analgesia, and Addiction Products; DAAAP) is Appropriately Resourced

² Medical Expenditures Panel Survey (MEPS), (2008).

³ Gaskins, D., Richard, P. Relieving Pain in America: A blueprint for Transferring Prevention, Care, Education, and Research. The Economic Costs of Pain in the United States. Institute of Medicine (US) Committee on Advancing Pain Research, Care and Education. Washington DC: National Academies Press (2011).

⁴ Defining the Addiction Treatment Gap. Open Society Foundations (2010).

⁵ National Institute on Drug Abuse, Trends and Statistics. <http://www.drugabuse.gov/related-topics/trends-statistics>.

⁶ BIO's Comments to the FDA's Docket on the FDA Opioid Policy Steering Committee.



Given the low clinical trial success rates and the public health impact of the current opioid crisis, it is essential that Sponsors working to develop novel and safer pain treatments have the opportunity to engage in discussions with the Agency on their drug development programs, in a timely manner, and that appropriate information is provided to Sponsors via guidance documents. Some of BIO's member companies indicate significant delays in the ability to meet with DAAP on their drug development programs, even for products in expedited programs. Additionally, the FDA has indicated they plan to develop guidance to assist Sponsors developing pain and addiction therapies. We appreciate the Division's candor about their workload and resource constraints that may prevent them from meeting with Sponsors and issuing guidance in a timely manner. To address this issue and signal to investors and drug developers that the FDA is committed to encouraging development of novel and safer pain and addiction therapies, BIO requests that the Agency prioritize fully staffing the Division. Prioritizing DAAP staffing may include possible near-term approach to re-allocation of existing resources, so that DAAP can engage Sponsors, review applications, and develop guidance in a timely manner. BIO also believes the FDA should develop and execute a plan for explicitly utilizing the new hiring and compensation authorities made available under 21st Century Cures to recruit top external talent in the development of pain or addiction treatments to complement FDA's existing regulatory expertise and institutional knowledge.

BIO also asks the FDA to consider implementation of regulatory 'best practices' utilized successfully by other review divisions to speed development and evaluation of products for areas of high unmet medical need. BIO also recommends that the FDA ensure that 'best practices' are adopted by all FDA divisions responsible for reviewing treatments for pain or addiction such that, for example, a Sponsor that receives Breakthrough Therapy designation should receive appropriate FDA support that is consistent across review divisions. BIO encourages the FDA to consider enhanced communication or the establishment of standardized communication plans between the FDA and Sponsors for pain and addiction programs, beyond those established for an example in the context of Breakthrough Therapy designation.

II. Clarification of the Qualification of Pain and Addiction Therapies for Expedited Programs

Expedited programs (e.g., Breakthrough Therapy designation, Fast Track designation, priority review and accelerated approval) and other incentives have proven effective in encouraging innovation and investment in other areas that are in urgent need of treatments. BIO commends the FDA for recent statements and testimony recognizing the importance of expedited pathways to accelerate the development of advanced therapies for unmet medical needs, including opioid addiction. However, BIO member experience suggests that FDA could be more proactive in how it approaches expedited pathways for such treatments and work more closely with Sponsors to accelerate clinical development programs. For example, FDA denied 10 out of 13 Breakthrough Therapy designation requests for analgesics received in the first four years of the program. In contrast, FDA granted 64 out of the 122 oncology Breakthrough Therapy designation requests during



the same period.⁷ Given the national urgency of the opioid crisis, BIO asks the FDA to promote the use of Breakthrough Therapy designations and other expedited approval pathways for novel treatments for both pain and addiction. BIO also emphasizes the need for Sponsors that receive expedited program designation to receive appropriate FDA support that is consistent with the intent of these programs as outlined in the Guidance to Industry on expedited programs. To this end, we request that FDA 1) adequately resource to support the expectations for enhanced communication between Sponsors and FDA in expediting clinical development in pain and addiction therapies and 2) CDER oversight to ensure that the review and determination for qualifying for programs are applied consistently across Divisions. BIO also calls the FDA to consider the use of priority review to more quickly bring novel and safer pain and addiction therapies to patients.

While the FDA has recognized pain as an unmet need, evidenced by the FDA granting Fast Track designation for various pain treatments, to more proactively apply its expedited programs, FDA could make a formal policy declaration that opioid addiction is a serious and life-threatening condition and an unmet medical need, and therefore, novel and safer therapies for treating pain and all therapies for treating addiction and opioid overdose are eligible for expedited pathways. This could be a way to reignite dwindling research and development in the space of novel, safer mechanisms for chronic pain and treatments that have lower or no abuse liability. BIO also requests that the FDA develop or update guidance documents to explicitly indicate that pain and addiction therapies are eligible for expedited pathways (e.g., Breakthrough Therapy designation, Fast Track designation, priority review and accelerated approval). Specifically, BIO requests the FDA reference in the guidance:

1. Serious Condition : Due to the current public health crisis, pain or addiction should be considered serious conditions and therapies aimed at addressing pain and addiction should be eligible for expedited approval pathways. BIO requests that the FDA explicitly state this in guidance.
2. Unmet Medical Need : As the FDA indicates, "an unmet medical need exists when the treatment of a serious condition "is not addressed adequately by available therapy." When no available therapy exists, a new treatment for a serious condition clearly addresses an unmet medical need. When available therapy exists, a new treatment for a serious condition may address an unmet medical need if it provides some advantage over the available therapy such as improved safety profile or lower abuse potential. Where opioids are deemed an available therapy, the FDA should indicate that treatments that mitigate risks to patients and the broader public of opioid misuse and abuse are considered to address an unmet medical need and therefore qualify for expedited approval pathways. BIO requests that the FDA explicitly state this in guidance.

⁷ Conrad, R., et al., Breakthrough Therapy Designation: CDER Analysis of Requests 4 Years into the Program, Therapeutic Innovation & Regulatory Science, 2017; 51(4): 509-515.



3. Substantial Improvement over Available Therapy: Given the current public health crisis, placebo-controlled data demonstrating that the novel pain therapy with an improved safety profile or lower abuse potential is effective at relieving pain should be sufficient to merit qualification for expedited approval pathways. Similarly, if a Sponsor has demonstrated safety and efficacy of a therapy in patients who have failed other therapies, the FDA should consider that data as a demonstration of benefit over available therapies for purposes of qualifying for expedited pathways. BIO requests that the FDA explicitly state this in guidance.
4. Breakthrough Therapy Designation and Acute Pain Therapies: Unfortunately, because acute pain programs proceed rapidly, the increased engagement with the FDA that is associated with Breakthrough Therapy designation comes relatively late in development, hindering Sponsors from taking full advantage of the features associated with Breakthrough Therapy designation. BIO thus, requests that the Agency consider extending the benefits associated with Breakthrough Therapy designation (e.g., enhanced communication with the Agency) for promising pain alternatives earlier in the drug development process.

III. Development and Updating of FDA Guidance for Pain

Because the FDA recently withdrew the 2014 draft guidance on *Analgesic Indications: Developing Drug and Biological Products*, BIO requests that the FDA organize a public meeting to hear from various stakeholders regarding the content prior to issuing updated guidance(s). We suggest that FDA revisit this guidance to provide recommendations to FDA reviewers and Sponsors on clinical trial strategies that will expedite the development of novel, safer analgesics. In order to provide regulatory clarity for Sponsors currently developing pain therapies and those who may develop pain therapies in the future, BIO requests that the FDA work to rapidly issue an updated guidance following the public meeting. BIO also requests that the FDA organize stakeholder meetings to discuss the additional topics listed below.

1. Opioid Sparing and Opioid Free: BIO recognizes and appreciates that the FDA held an advisory committee meeting in November 2018 to discuss the inclusion of opioid sparing in labeling for acute and chronic pain products. Given that additional discussion is needed, BIO requests that the FDA organize a stakeholder meeting to further discuss the ability of acute and chronic pain products to reference opioid sparing and opioid free in labeling, as well as the achievable evidence required by the Agency for inclusion of opioid sparing and opioid free in labeling to specifically address the length, appropriate design, outcome measures and targets for clinical trials to demonstrate opioid sparing and opioid free labeling. For the FDA's reference, attached to the appendix of this letter, BIO has included a consensus slide deck that was developed on this topic.
2. Benefit-Risk Assessment of Novel and Safer Treatments: In order to successfully mitigate the opioid crisis, urgency in action must be shared at all levels of the Agency and be reflected in the FDA's benefit-risk determinations across the lifecycle of product development. As such, BIO recommends that when assessing



the benefits and risks of a novel and safer pain or addiction therapy, FDA continue to evaluate the entire benefit-risk profile of a given product (e.g., analysis of conditions, including special populations, taking into account the current opioid crisis, current treatment options taking into account the risks of available therapies, the benefits of abuse deterrent formulations of conventional opioids, non-opioid treatments, and innovative treatments that have, in general, lower or no abuse liability should contribute to the benefit section of the assessment).

BIO encourages FDA to utilize a benefit-risk framework that weighs the public health impact for regulatory decisions related to both innovative opioid products *and* non-opioid pain therapies. One approach to consider is to develop a "template" of a benefit-risk framework for non-opioid therapies similar to the recently published benefit-risk framework for new opioid therapies. The "template" could include discussion of the broader impact of the opioid crisis in the "Analysis of Condition" and "Current Treatment Options" domains of the benefit-risk framework, adding potential special population needs. Reviewers may then draw from that standardized template to help inform non-opioid product-specific benefit-risk decision-making. Furthermore, this standardized benefit-risk framework should be considered at all stages of FDA decision-making, including milestone meetings, requests for preclinical and clinical data, expedited program designations, and post-market safety decisions, rather than just at the point of review/approval.

Additionally, BIO recommends that the FDA utilize its Patient-Focused Drug Development and Structured Benefit-Risk Assessment Framework programs to more systematically evaluate the toll that opioid addiction and dependence has on patients suffering from chronic pain and the families who have lost a loved one to addiction or overdose in assessing the potential benefit of new treatment options. This highlights the importance of considering multiple populations when assessing the benefits and risks of a potential treatment- the population that the drug was intended for (patients living with pain) and the unintended population which may be susceptible to abusing prescription opioids for nonmedical purposes. The benefit-risk assessment of novel and safer treatments should take into account weighting the risk (e.g., likelihood of death/overdose, addictive properties, abuse potential, and serious adverse events leading to morbidity/mortality) against severity and natural progression/outcome of the chronic pain condition.

3. Mechanisms for Measuring and Evaluating Pain: BIO requests that the FDA organize a public meeting in order to discuss issues pertaining to current mechanisms for evaluating chronic and acute pain both in the clinic and the clinical trials setting. Current methods for measuring or evaluating pain often do not take into account acute versus chronic pain, the neurobiological and/or psychosocial mechanisms underlying the pain, individual differences in pain perception, and distinctions between somatic and psychic pain. Furthermore, the



impact on different pain states on patient reported outcome measures. Following the public meeting the FDA should develop or update guidance as appropriate.

4. Innovative Clinical Trial and Statistical Designs: BIO recognizes and appreciates that the FDA is working with Sponsors on a master protocol for pain under the Complex Innovative Clinical Trial program. To springboard these efforts, BIO requests that the FDA provide information via guidance about how the utilization of novel clinical trial designs, such as master protocols, basket trials, and platform trials, including outcome measures and targets considered for demonstrating efficacy on pain and other domains influenced by pain. Furthermore, provide guidance on the regulatory mechanisms that address populations, including special populations, with severe pain or who are at risk for progressing to severe chronic pain, could be applied to the development of treatments for these conditions. To this end, BIO asks the FDA to consider holding a public meeting to discuss among stakeholders the topics below and develop or update guidance as appropriate:
 - a. A need and opportunity to clarify expectations regarding trial size, duration of effect, and exposure required to demonstrate efficacy and safety for both chronic and acute pain indications. Such guidelines should reduce uncertainty when designing development programs while still accommodating regulatory flexibility and clinical innovation;
 - b. Meeting requirements to study several different clinical pain indications in order to gain approval for broad chronic pain indications has the unintended effect of slowing and discouraging the development of next generation therapies and is an inefficient approach, especially when the mechanism of action of the class of molecules is well understood and efficacy previously shown. We suggest that FDA permit valid extrapolation and interpolation across indications where scientifically justified, among other possible methods, including real-world evidence, and reconsider the number of clinical investigations required for a broad chronic pain indication.
 - c. With respect to safety data reporting, new opportunities are emerging to better leverage active post-market surveillance and the Sentinel Network to generate evidence necessary to further refine the benefit-risk profile of products and maximize their safe use. Through an integrated lifecycle approach to evidence generation that further reduces residual uncertainty in the post-market real-world setting, we can streamline pre-market data collection requirements for new pain medications that have negatively impacted R&D investment in this area.

5. Endpoints/biomarkers: BIO is pleased to see FDA's participation in the National Institutes of Health's private-public partnership to better understand the underlying science and to develop new endpoints for assessing pain and addiction in clinical trials. BIO encourages the FDA to remain thoroughly engaged in these efforts, as it will be important for these consortia that there be a clear roadmap for taking these new endpoints from proof-of-concept to regulatory validation or qualification.



To better assist with the development of endpoints and biomarkers for pain, BIO recommends that FDA leverage its authorities under FDASIA (Sec. 901 – Endpoint Awareness Efforts) and 21st Century Cures (Sec. 3011 - Biomarker Qualification), to proactively and systematically engage with the research community and other partners to encourage the qualification of identified endpoints for regulatory purposes (including endpoint targets considered to be clinically meaningful for approval), or for the basis of Accelerated Approval. FDA should also work toward the development of qualified patient reported outcomes for chronic pain. FDA could consider issuing letters of support under the Drug Development Tools (DDT) qualification process to sustain momentum for these efforts. BIO believes that given the urgency of the opioid emergency, novel endpoint and DDT development for chronic pain studies should not be a passive process, but an active and collaborative exercise to recruit the best proposals from the scientific community. BIO requests that the FDA consider holding a public meeting with stakeholders to discuss issues pertaining to endpoints and biomarkers for pain.

IV. Development and Update of FDA Guidance for Addiction

BIO appreciates and supports the FDA’s development of the draft guidance on *Opioid use Disorder: Demonstrating Effectiveness for Drugs for Medication-Assisted Treatment* and BIO submitted comments to the docket on the Draft Guidance.⁸ In order to provide regulatory clarity for Sponsors currently developing therapies for treating opioid-use disorder, and those who may develop such therapies in the future, BIO requests that the FDA work to rapidly issue the final version of the guidance taking into consideration the previously submitted comments.

BIO also requests that the FDA organize a series of collaborative stakeholder meetings to inform its development of forthcoming guidance pertaining to addiction therapies, including the following topics:

1. Innovative Clinical Trial and Statistical Designs: BIO requests that the FDA organize stakeholder discussions to discuss how the utilization of novel clinical trial designs and data sources can be applied to the development of treatments for opioid use disorder. BIO also asks that the FDA consider other modern approaches and tools, such as real-world evidence and patient experience data, to meet safety and efficacy standards for addiction treatments.
2. Endpoints: BIO appreciates the efforts of the FDA to hold a Voice of the Patient meeting on opioid use disorder. We encourage the Agency to continue to work on translating what is important to individuals suffering from opioid use disorder into endpoints for the development of therapies to treat opioid use disorder. To

⁸ [BIO Comment Letter in Response to the FDA’s Draft Guidance on Opioid Use Disorder: Demonstrating Effectiveness for Drugs for Medication-Assisted Treatment.](#)



this end, BIO requests that the FDA hold a stakeholder meeting to discuss novel endpoints in the context of opioid use disorder. Such novel endpoints may include the reduction of opioid use and/or reduction in drug craving. BIO also requests that the FDA leverage its authorities under FDASIA (Sec. 901 – Endpoint Awareness Efforts) and 21st Century Cures (Sec. 3011 - Biomarker Qualification), to proactively and systematically engage with the research community and other partners to encourage the qualification of identified endpoints for regulatory purposes or for the basis of Accelerated Approval.

V. Greater Engagement with the Federal Agencies and the National Institutes of Health (NIH) Helping to End Addiction Long-Term (HEAL) Initiative

BIO appreciates that the FDA participates as a member of the HEAL Initiative Partnership Committee. We believe that the FDA has an important and integral role to play in providing input on the Early Phase Pain Investigation Clinical Network (EPPIC-Net) Program and other NIH HEAL Initiative activities. In particular, the EPPIC-Net program seeks to enhance the treatment of acute and chronic pain and reduce reliance on current opioids by accelerating early phase clinical trials of non-addictive pain therapeutics, including drugs and devices through the testing of new pain treatments in early phase trials funded by the NIH. For this program in particular, the FDA has the regulatory expertise and opportunity to advise the NIH and Sponsors who have been selected to participate in the EPPIC-NET program on elements such as the clinical trial design and selection of endpoints. To date, it had been unclear as to how and to what degree the FDA is engaging in HEAL Initiative activities, specifically the EPPIC-Net program. A clear, public commitment from the FDA regarding the FDA's as well as the type of FDA engagement that a Sponsor may expect if selected for the EPPIC-Net program would serve as an incentive for companies to apply for and participate in the EPPIC-NET program.

Finally, providing patients with access to novel and safer treatments for pain and addiction is critical to preventing future addiction and to helping those that are currently struggling with addiction. Unfortunately, many patients do not have access to these novel and safer treatments due to coverage barriers employed by insurers, such as utilization of management tools that require patients to 'fail treatment' with non-abuse deterrent options or require providers to fulfill substantial prior-authorization steps. Additionally, payers often do not reimburse for non-opioid pharmacologic therapies that are more expensive than opioids.⁹

Another potential coverage barrier is related to how opioid products are labeled. The requirement for opioid class labeling may provide a disadvantage to the development of novel therapies if there are limitations as to how the product's differentiated safety or

⁹ Department of Health and Human Services Interagency Taskforce Report.



efficacy profile can be reflected in the label. BIO encourages the FDA to carefully consider the appropriate use of opioid class labeling when approving innovative therapies, such as those with potentially low abuse potential or other reductions in safety risks to ensure that the improved safety profiles can be prominent in labeling.

These coverage barriers disrupt the patient-provider decision-making process, impacting patient access to the most timely and appropriate course of treatment. BIO recommends that the FDA collaborate with other federal agencies within the Department of Health and Human Services, such as the Centers for Medicare and Medicaid Services, to support access to the most appropriate course of treatment at the right time, incentivizing payers and prescribers to utilize abuse deterrent formulations, non-opioids, and medication assisted treatment for addiction, and to adopt and implement relevant recommendations in the final Pain Management Taskforce Report. The FDA should consider this a public health imperative, because this collaboration has the potential to help remove barriers to patient access and support the integration of these drug products into treatments for patients with pain or addiction.

VI. Conclusion

We thank the FDA for the opportunity to provide recommendations to FDA's docket on Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction. BIO shares the Agency's commitment to combatting the public health emergency of opioid addiction by speeding the development of new treatment modalities for both pain and addiction. Through the development of innovative, novel and safer therapies for pain and addiction, we can help to provide a viable alternative for pain and addiction treatment, reduce medical exposure to prescription opioids, and decrease the incidence of addiction in America.

Sincerely,

/S/

Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization



VII. Appendix : BIO Consensus Work on Opioid Sparing

Consensus Thinking on Opioid Sparing: The Biotechnology Innovation Organization



Purpose of this Slide Deck

- BIO believes that reference to opioid sparing in labeling is needed to best inform pain management decision-making by patients and providers.
- Guidance is needed to inform Sponsors on the FDA's expectations, including:
 - Trial designs that would demonstrate opioid sparing and result in a label claim
 - How a Sponsor can demonstrate a “clinically meaningful” reduction in opioid use
 - Evidence required to demonstrate that a patient population is opioid free

Purpose of this Slide Deck

- While this slide deck outlines industry consensus thinking, BIO requests that the FDA hold a public meeting to discuss among stakeholders the issues outlined on the previous slide.
 - While the FDA has indicated that guidance on opioid sparing is being developed, BIO requests that if the guidance is not ready to be released as draft guidance, the Agency release the document as a discussion guide for a public meeting on the topic.
- Guidance for Sponsors on opioid sparing and flexibility from the Agency on trial design for opioid sparing will encourage Sponsors to collect this data to inform patients and providers.

Benefits of Reductions in Opioid Prescribing

Opioid Sparing Therapies Benefit Both The Individual Patient and Public Health

- Benefits of reductions in opioid use via novel and safer alternatives should be considered both within the context of:
 - The individual patient suffering from pain
 - Overall benefit to public health
- Reductions in opioid use via novel and safer alternatives has the potential to:
 - Reduce the risk for the individual patient to develop addiction or experience other opioid-related adverse events
 - Reduce the risk of addiction or other opioid-related adverse events in populations other than the specific patient treated with a pain therapy by reducing the volume of opioids available for misuse

Reductions in Opioid Use Benefit The Individual Patient and Public Health

- Reductions in opioid Use:
 - Reduce risk of death by overdose
 - Reduced the risk for developing addiction or dependence
 - Patients who use 1 day of opioids versus at least 7 days have a 2x increased risk of using opioids chronically, 1 year after surgery.¹
 - Decrease length of hospital stay²⁻⁴
- 53% of misused pain treatments are bought from, given by, or taken from a friend or relative⁵
 - 60% of Americans have unused prescription opioids in the home.⁷
 - Individuals who abuse or are dependent on opioids are 40 times more likely to abuse or be dependent on heroin⁶
 - Decreasing prescription opioid analgesics, through use of opioid sparing alternatives may have a significant impact on opioid misuse in U.S. population

Reductions in Opioid Use Benefit The Individual Patient and Public Health

- Referencing opioid sparing, or other appropriate terminology, in labeling provides important information to patients and providers regarding the ability of a pain therapy to reduce the use/exposure/or escalation of opioids for treating pain and, importantly, guides prescribing practices.

Definitions Related to Opioid Sparing

Definitions Related to Opioid Sparing (continued)

- There is a need to clearly outline definitions and terminologies that describe and differentiate:
 - Opioid free: Refers to the ability of a pain therapy to eliminate the need for a patient to use opioids for pain management
 - Opioid Sparing: Refers to the ability of a pain therapy to reduce the use of opioids for pain management

Definitions Related to Opioid Sparing (continued)

- A reduction in use of opioids may be reflected by:
 - Prevention of initiation of opioids
 - Reduction in total opioid dose
 - Reduction in opioid utilization
 - Reduction in the number of times an opioid is used as a rescue

- As discussed at the November 18, 2018 Advisory Committee Meeting, it may also be beneficial to identify an alternative term for “opioid sparing” that may be more easily understood by patients and physicians.

Definitions Related to Opioid Products

Definitions Related to Opioid Products

- There is a need to clearly outline definitions and terminologies that describe and differentiate:
 - Opioids (e.g., abuse deterrent formulations, implants, topicals) that reduce the use of opioids for pain management (e.g. reduce overall opioid burden, use of opioid rescue medication, dose escalation, etc.)

Universally Accepted Opioid Conversion Method

Need for a Universally Accepted Opioid Conversion Method

- The current system for converting opioid dosage, the Milligram Morphine Equivalent (MME) fails to consider:
 - Pharmacogenomics
 - Organ dysfunction
 - Drug tolerance
 - Drug-drug interactions
 - Patient-age
 - Body surface area
- MME has been shown to be highly variable when calculated across physicians
- An FDA-accepted and more accurate method for converting opioid dosages is needed in order to advance conversations around opioid sparing.

Demonstrating Opioid Sparing in Acute and Chronic Pain

Demonstrating Opioid Sparing/Opioid Free in Clinical Trials: Regulatory Requirements

- When demonstrating opioid sparing/opioid free in the context of a pain clinical trial, a sponsor may be required to demonstrate:
 1. Adequate pain relief is accomplished;
 2. Reduction in patient use of opioids (opioid sparing) or that the patient did not administer opioids (opioid free); and
 3. Clinically meaningful reduction in opioid use

Demonstration that Adequate Pain Relief has been Accomplished

- To demonstrate that adequate pain relief is accomplished by the therapy under investigation, a sponsor may demonstrate superiority to placebo.
- However, the use of non-opioid pain alternative may allow patients to ambulate or resume function more quickly, and as a result, patients may experience some degree of pain that is higher than patients who are treated with opioids and who are not ambulating or resuming function.
 - To demonstrate that adequate pain relief is accomplished, BIO requests that the FDA consider allowing Sponsors to use a composite score that considers a patient's pain score in relation to a functional measure.

Demonstration of a Reduction in use of Opioids

- To demonstrate a reduction in patient use of opioids, a sponsor may demonstrate that the therapy under investigation results in:
 - Prevention of initiation of opioids
 - Reduction in total opioid dose
 - Reduction in opioid utilization
 - Reduction in the number of times an opioid is used as a rescue
- Adequate pain management should accompany any reduction in opioid use

Demonstration of Opioid Free

- There are a multitude of ways in which a Sponsor may demonstrate that a patient remained opioid free because of the therapy under investigation. Such demonstrates by be evidenced by:
 - No treatment of the patient with opioids during the duration of the hospital visit; or
 - No prescription for an opioid for the patient following the hospital visit through the duration of the pain trial; or
 - The patient not fulfilling a prescription for an opioid during the duration of the pain trial; or

Demonstration of a Clinically Meaningful Outcome Resulting from a Reduction in Opioid Use

- What is considered a clinically meaningful reduction in opioid use will likely depend upon the indication under study.
 - BIO requests that the FDA provide flexibility regarding what outcomes will be considered clinically meaningful in the context of opioid sparing. Examples provided in guidance will assist Sponsors when designing such studies.
 - In addition to other clinically meaningful outcomes, a Sponsor may use a reduction of opioid-related adverse events as a clinically meaningful outcome, which may include nausea/vomiting, sexual dysfunction, opioid-induced depression and/or anxiety, hyperalgesia, pruritus, constipation, somnolence, sedation, fatigue, dizziness, hypotension, respiratory depression, adrenal insufficiency, hypogonadism

Timeline for Evaluation of Opioid Sparing/ Opioid Free Outcomes in Clinical Trials

- In order to demonstrate opioid sparing in the context of an acute or chronic pain clinical trial, a Sponsor may be required to demonstrate a reduction of opioid use (or no opioid use) and clinically meaningful outcome associated with the reduction in use, for no longer than the duration of the pain trial.
- In order to demonstrate that a patient is “opioid free” in the context of an acute or chronic pain clinical trial, a Sponsor may be required to demonstrate that a patient remained “opioid free” for no longer than the duration of the pain trial.

Chronic Pain and Opioid Taper

- It is estimated that 3% to 4% of US adults use opioids long-term to help manage chronic pain; however, rapidly decreasing or abruptly discontinuing long-term opioid analgesics can significantly increase the risk of adverse consequences.⁸
 - >50% of patients who discontinued long-term, high-dose prescription opioids, were discontinued rapidly, among those that discontinued, 49% subsequently had an adverse opioid-related health care event⁹
- In April 2019, FDA issued a Drug Safety Communication regarding sudden discontinuation or rapid dose decrease of opioid pain medicines
 - FDA requires label changes to guide prescribers on gradual, individualized tapering to avoid serious withdrawal symptoms, worsening of the patient's pain, or psychological distress

Chronic Pain and Opioid Taper

- In the context of chronic pain, demonstration of opioid sparing would also require a Sponsor to use a taper to safely reduced the amount of opioids used for pain management
- BIO requests that the FDA develop guidance addressing issues pertaining to opioid taper, including:
 - Appropriate speed at which to taper opioid use in patients
 - Considerations for safety
 - Possible study designs
 - Considerations and recommendations for taper endpoints

References

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