December 28, 2017

Scott Gottlieb, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD  20993

Submitted electronically via www.reglations.gov

Re: FDA-2017-N-5608 — Opioid Policy Steering Committee; Establishment of a Public Docket; Request for Comments

Dear Commissioner Gottlieb:

On behalf of the more than 5,000 members of the American Academy of Hospice and Palliative Medicine (AAHPM), thank you for the opportunity to provide input related to focus of the Food and Drug Administration’s (FDA) newly established Opioid Policy Steering Committee (OPSC), particularly with regard to how the agency’s authorities should be used to address unprecedented rates of opioid use disorder and overdose deaths.

AAHPM is the professional organization for physicians specializing in Hospice and Palliative Medicine. Our membership also includes nurses and other health and spiritual care providers deeply committed to improving quality of life for patients facing serious or life-threatening conditions, as well as their families and caregivers. The timely and effective management of pain and other distressing symptoms is central to providing these patients with high-quality palliative care, and opioid analgesics are a critical tool in alleviating that suffering.

With that in mind, AAHPM is concerned with how best to balance the growing challenges related to managing pain with opioids with the need for ready access to appropriate pain medications for patients with serious or complex chronic illness and those at the end of life — patients for whom high-dose opioids may be necessary and medically appropriate. The Academy recognizes there is an indisputable public health imperative to curb opioid abuse, misuse, and diversion, and is deeply committed to both providing continuing education that results in optimal pain management and optimal care for all patients as well as to collaborating with professional, regulatory and industry stakeholders to maximize individual and public safety. At the same time, AAHPM believes public policies must recognize there is an equally important public health imperative to ensure that our sickest, most vulnerable patients have access to timely, effective treatment of their pain and suffering. We have growing concerns regarding policies that aim to limit opioid production, availability, and/or dosage and duration of prescriptions and would impede the individualization of treatment to patient needs. These efforts serve to paint all pain as the same and threaten access to appropriate care for patients with serious illness.
AAHPM appreciates FDA’s attention to these challenges and applauds the agency for reaching out to stakeholders for information that may be useful in guiding the important work of the OPSC. Our Academy’s feedback on FDA’s specific questions follows below.

I. Assessing Benefit and Risk in the Opioids Setting

In its request for comments, FDA references a July 2017 article in the Journal of the American Medical Association in which the agency explained its approach to assessing the benefits and risks of drug products, which includes risks related to the potential misuse and abuse of these products, and ongoing efforts to incorporate the effects of decisions on public health into its benefit-risk framework in a more quantitative manner. FDA further notes it is reviewing recommendations emanating from a study commissioned from the National Academies of Sciences, Engineering, and Medicine to outline the state of the science regarding prescription opioid abuse and misuse, the evolving role that opioid analgesics play in pain management, and additional actions FDA should consider to address the opioid crisis with particular emphasis on strengthening its benefit-risk framework for opioids. The agency is soliciting additional feedback to supplement those recommendations.

How should FDA tailor, or otherwise amend, its assessment of benefit and risk in the context of opioid drugs to ensure that the Agency is giving adequate consideration to the risks associated with the labeled indication of these drugs and the risks associated with the potential abuse and misuse of these products?

As FDA’s question focuses primarily on ensuring the risks associated with opioid use are adequately considered, AAHPM is compelled to urge the agency to give due weight to the proper indications and potential benefits of these medications. Moreover, such risk-benefit analysis cannot be uniform across patient populations. For patients with serious and life-limiting illness — such as cancer, AIDS, chronic obstructive pulmonary disease, end stage renal disease, heart failure, hemophilia, and sickle cell disease — whole-person care would dictate that FDA weigh the risks of not managing pain and other distressing symptoms. Overall analysis should take into account the burden of suffering and expected duration of therapy, where the benefits of using opioids are likely to exceed the risks the shorter the duration of treatment.

Further, a prescription for a high dose of opioids should not be considered an automatic risk factor for misuse or abuse without significant high-quality evidence showing that it is an independent risk factor regardless of individual patient characteristics. Patients with serious illness or at the end of the life often require high doses of opioid analgesics to adequately manage severe pain, and considering high doses an independent risk factor can impact patient access to appropriate care, discouraging patients from asking for help in treating their pain or providers from prescribing necessary and effective analgesia.

We point FDA to a 2001 joint statement by Drug Enforcement Administration (DEA) Administrator Asa Hutchinson and 21 health organizations — including AAHPM — titled Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act. This statement called for a balance in policy between ensuring legitimate patient care and preventing diversion and abuse, warning that focusing only on the abuse potential of a drug could erroneously lead to the conclusion that these medications should be avoided when medically indicated — generating a sense of fear rather than respect for their legitimate properties.
Finally, upon adoption of any new policies, we urge FDA conduct ongoing analyses of the outcomes, to ensure they do not unintentionally set up barriers to pain treatment for patients who can benefit from high-dose opioids and be safely managed while taking them.

- **Are there specific public health considerations other than misuse and abuse that FDA should incorporate into its current framework for benefit and risk assessment as a way to reduce the opioid addiction epidemic?** That framework includes, but is not limited to, how FDA makes regulatory decisions to approve new opioids, evaluates their use in the postmarket setting, or limits or influences their prescribing through product labeling or other risk management measures.

AAHPM again suggests that FDA balance the public health imperative to stem the tide of opioid misuse and abuse and with the public health imperative to manage untreated pain. Setting aside its financial costs, unrelieved pain causes inordinate human suffering resulting in longer hospital stays, increased readmissions and outpatient visits, and decreased ability to function or enjoy quality of life.

In terms of new drug approvals, AAHPM would support incentivizing abuse deterrent formulations and encouraging manufacturers to also contribute to options for take-back and disposal. Our serious concerns related to product labeling are discussed at length below. Otherwise, we believe postmarket analysis can yield important data if structured appropriately. To that end, AAHPM urges FDA to identify evidence-based risk factors for misuse and abuse and evaluate the extent to which they are evident in patients being legitimately treated with opioids, rather than just those misusing a prescription or obtaining the drug through other means. Postmarket evaluation must also be nuanced such that it tracks more than a simple change in the total amount of opioids available or number of prescriptions written for opioids that results from a change in policy. Instead, such analysis must consider whether there has been a change in inappropriate prescribing or use, or whether a reduction in the use of opioids is in part the result of a chilling effect on proper prescribing or other barriers to access by patients with legitimate need.

### II. Steps to Promote Proper Prescribing and Dispensing

FDA states that proper prescribing and dispensing are critical to successfully reducing opioid misuse and abuse and cites the Centers for Disease Control and Prevention (CDC) 2016 **Guideline for Prescribing Opioids for Chronic Pain** in discussing FDA’s consideration of when a clinical situation may require a supply of opioid analgesics that exceeds current CDC guidelines, when a shorter course of therapy would be more appropriate, or when a non-opioid pain treatment would be adequate. The agency notes that “without specific requirements, variance in prescribing habits are likely to persist.”

AAHPM is concerned that the FDA broadly demonizes variation in prescribing habits when, in fact, patient-centered care would recognize that pain will not only differ by condition but by the individual (different patients have different pain thresholds) and his or her history and circumstances (e.g. complications in treatment). Patients with pain are not all the same, so managing pain effectively and safely requires an individualized approach based on many factors, including pain syndrome, patient risk factors, underlying illnesses, life expectancy, clinical expertise, degree of control and monitoring available to the treatment team, and appropriate goals of treatment (for many patients not just relief of pain, but also optimal physical and mental function, preserved work and family role, quality of life and survival).

Especially when taking care of individuals with serious and life-limiting illness, we must be able to carefully titrate interventions to the circumstance unique to that patient. The primary goal should be ensuring a patient’s pain and other distressing symptoms are adequately controlled.
Should FDA consider adding a recommended duration of treatment for specific types of patient needs (e.g., for specific types of surgical procedures) to opioid analgesic product labeling? Or, should FDA work with prescriber groups that could, in turn, develop expert guidelines on proper prescribing by indication?

To date, there is no scientific basis to support calls to restrict the dosage and duration of treatment for pain, and AAHPM objects to such considerations as they would unduly burden patients with serious and life-threatening illness. As a population, these patients need higher doses of opioids for a longer duration than most any other group.

For example, many palliative and hospice patients have acute symptoms from non-cancer terminal illnesses and require more than 100 mg of morphine equivalents per day for sufficient pain and symptom control and, depending on the underlying mechanism of pain and degree of development of opioid tolerance, some require much higher doses. Likewise, many palliative and hospice patients with non-cancer-related pain and other symptoms from their serious or terminal illness experience these symptoms for periods of time much longer than, say, an arbitrary 90-day maximum. If there is a 90-day limit for non-cancer opioid pain management, would we have to stop opioids for the last ten days of life for a dying multiple sclerosis patient who happens to live 100 days from the start of care?

Palliative and hospice care appropriately emphasize individualization of treatment, including analgesia for pain, and AAHPM would oppose any recommendation that would preclude an individualized approach to palliative care patients’ legitimate needs. Dosing and duration limits for opioids would cause unnecessary suffering for hundreds of thousands of patients and paradoxically sacrifice patients’ safety by leaving them in terrible pain.

AAHPM is similarly concerned about discussions focused on opioid labeling. Consider, for example, dyspnea, which is a subjective experience of difficult or distressed breathing and common in patients with cancer, AIDS, emphysema, and other terminal illnesses. One study noted that family physicians find dyspnea to be the most distressing symptom in dying patients. Dyspnea is often alleviated by titration of an opioid. Prescribing opioids is now the standard of care for management of refractory dyspnea even though these medications have not been approved for such treatment. In fact, if Hospice and Palliative Medicine specialists were to prescribe for only FDA-approved indications, we’d have to throw out practically the entire pharmacopeia used in the field. You can see, then, how a requirement to adhere only to labels and approved indications would be catastrophic for seriously ill people in the U.S.

Further restricting how opioids are labeled with regard to indications for pain is also likely to adversely impact patient access to appropriate treatment. Non-experts are liable to look to the label as reflecting a standard of care and withhold therapy from patients who could benefit. In addition, some payers may choose not to cover treatment newly considered “off-label,” and the costs of treatment will be imposed on patients, creating further barriers to adequate pain care, particularly for those with limited financial means.

Should FDA move forward with developing guidelines, AAHPM would urge the agency to do so in transparent fashion and to work closely with prescriber groups to tailor these recommendations as well define exceptions. Training in Hospice and Palliative Medicine includes specialized education in assessment and management of pain, and prescribers in our field are best suited to develop guidance for treatment of patients with serious and life-threatening illness. Otherwise, arbitrary regulations put real people at risk, and don’t allow us to focus on generating the right data needed to understand how to best care for a particular patient with the right intervention at the right time, including using opioid analgesics as needed.
If opioid product labeling contained recommended duration of treatment for certain common types of patient needs, how should this information be used by FDA, other state and Federal health agencies, providers, and other intermediaries, such as health plans and pharmacy benefit managers, as the basis for making sure that opioid drug dispensing more appropriately and consistently aligns with the type of patient need for which a prescription is being written?

Again, recommendations that aim to limit the duration of prescriptions can inflict terrible suffering in a seriously-ill patient each day that he or she lives past an arbitrary cutoff of their medication. Those that limit allowable daily dosages can result in uncontrollable pain and symptom crises for these patients that could otherwise be managed by an amount of medicine that is arbitrarily discouraged. Moreover, while it would be ideal if label recommendations were one of a number of rational considerations that prescribers use to guide treatment, along with evidence for best practices and an individual’s unique circumstances and goals of care, we expect it is more likely that any suggested restrictions would be adopted as rules. We see this now with implementation of the CDC Guideline. While the CDC’s recommendations are meant to apply to primary care outside of cancer, palliative and end-of-life care, health systems, pharmacy benefit managers and payers are using the Guideline to impose limits on opioid prescriptions regardless of a patient’s diagnosis or goals. AAHPM therefore strongly cautions FDA against moving forward with such labeling restrictions.

Are there steps FDA should take with respect to dispensing and packaging (e.g., unit of use) to facilitate consistency of and promote appropriate prescribing practice?

Severe limits on the duration of prescriptions, such as those being considered or enacted across many states, are particularly burdensome for seriously ill individuals being treated in an outpatient setting. Patients suffering moderate-to-severe chronic pain are often those least capable of meeting the increased hurdles that Schedule II drugs carry. These patients frequently have limited mobility and must be accompanied by caregivers. Requiring office visits with greater frequency simply to obtain a prescription is an even greater hurdle for those living in rural or underserved areas as their healthcare provider may be hours away. Furthermore, and perhaps most critical, access to these medications often has substantial bearing on these patients’ quality and length of life, as it allows them to complete their disease-directed treatments, sleep through the night, or continue to work and otherwise engage in daily activities.

AAHPM believes a better solution is to encourage prescribers and pharmacists to embrace partial fill policies for their patients. Such action would better target the proliferation of large amounts of unused medications which are a key contributor to the opioid crisis. To wit, in a letter sent last week to the DEA’s acting administrator, U.S. Sen. Chuck Grassley urged the agency to update its regulations and guidance related to the partial filling of Schedule II controlled substances.

In addition, FDA could consider having opioids commonly prescribed for acute indications (e.g. post-procedure, post-operatively, post-acute injury) packaged in a 3 to 5 day blister pack (similar to a Z-pak or Medrol dosepak) to facilitate dosing that is in line with the typical needed duration.

III. Requirements for Prescriber Education

In its request for comments, FDA discusses the option of mandating education for healthcare professionals who prescribe opioid medications, noting some states are considering or already require such prescriber education.
● Are there circumstances under which FDA should require some form of mandatory education for health care professionals to ensure that prescribing professionals are informed about appropriate prescribing and pain management recommendations, understand how to identify the risk of abuse in individual patients, know how to get patients with a substance use disorder into treatment, and know how to prescribe treatment for—and properly manage—patients with substance use disorders, among other educational goals? Are there other steps FDA could take to educate health care professionals to ensure that prescribing professionals are informed about appropriate prescribing and pain management recommendations?

AAHPM believes it is critical to elevate the knowledge of appropriate prescribing of controlled substances across various providers and medical specialties, as well as ensure prescribers are appropriately trained to manage risks for opioid misuse and diversion and knowledgeable in safe storage and disposal. Our Academy is deeply committed to providing continuing education that results in optimal pain management and the best care and safety for all patients.

To that end, AAHPM is a founding member of the Collaborative for Relevant Education, or CO*RE, which was initially formed to develop and disseminate REMS-compliant training in safe prescribing of long-acting/extended-release opioids and has since updated its curriculum to address the CDC Guideline and include immediate-release opioids in anticipation of the FDA adding them to the REMS blueprint. A recording of AAHPM’s “Opioid Prescribing: Safe Practice, Changing Lives” webinar is offered free on the Academy website. A volume of AAHPM’s Essential Practices in Hospice and Palliative Medicine is also focused on Pain Assessment and Management. This book presents the latest in assessing malignant and non-malignant pain, total pain, nociceptive and neuropathic pain, opioid conversions, common side effects of pain treatment, and non-opioid adjuvant medications. In addition, our annual conference routinely features sessions on topics such as managing pain in opioid-dependent patients and guidelines for methadone safety and effectiveness in hospice and palliative care, with recordings available after the meeting for those unable to attend in person. Through the American Medical Association (AMA) Opioid Task Force – of which AAHPM is a member – our Academy was also invited to assist the AMA in developing a new, interactive CME product on pain management. (This activity is funded by a Substance Abuse and Mental Health Services Administration grant supporting the Prescriber Clinical Support System for Opioid Therapies administered by the American Academy of Addiction Psychiatry.)

Despite this commitment to prescriber education, AAHPM remains opposed to mandated CME, particularly as the effectiveness of mandates has not been well established. Today, practitioners may face multiple state requirements for continuing education covering such topics as suicide or domestic violence screening, infectious disease, and cultural competence, and as such end up less engaged and simply “checking the boxes” to obtain the required credits. Before FDA considers adding to such requirements, we believe more research is needed to determine the actual impact of mandated CME on provider behaviors, treatment access, and patient outcomes.

We’re also concerned that as more training and practice burden is placed on practitioners, it is unknown what effects these mandates, coupled with new guidelines and payer policies, will have on clinician interest or feasibility to care for the complex population of patients with pain, particularly those on opioids. Numerous overlapping policies and guidance for practitioners that aim to stem the crisis of opioid abuse and overdose death have already had a cooling effect on prescribing by primary care providers, with these practitioners confused and in fear of retribution for prescribing opioid analgesics. In fact, we have seen such unintended consequences as physicians trying to get their non-terminal patients into hospice so the hospice can take over prescribing of opioids and overall pain management.
To ensure there are no such further unintended outcomes, prescriber education must be properly targeted and incentivized so practitioners actually learn when opioids are appropriate along with best practices for prescribing them, rather than opt out of doing so altogether.

- How might FDA operationalize such a requirement if it were to pursue this policy goal? For example, should mandatory education apply to all prescribing health care professionals, or only a subset of prescribing health care professionals? If only a subset, how would FDA construct a framework that focuses mandatory education on only that subset—for example, by requiring mandatory education only for those writing prescriptions for longer durations as opposed to those for very short-term use?

Should FDA decide to establish requirements for provider education, AAHPM believes they must target all prescribing healthcare professionals and would best be operationalized by requiring any practitioners who request DEA registration to prescribe controlled substances to be trained on responsible opioid prescribing practices as a precondition of registration.

In addition, while we recognize the need for simplification of prescriber education to fit within limited time resources, AAHPM believes it is still important to ensure that any basic curriculum addresses differences in the care of special populations such as: patients with limited prognosis; patients with very severe or escalating acute pain requiring rapid titration of opioids (including LA/ER formulations in combination with normal-release products); patients with chronic pain residing in long term care facilities, and patients with chronic pain who have cognitive impairment. Not to do so would be a disservice to these groups and may cause unnecessary barriers to access of opioids for these patients, especially as these special populations are frequently managed by practitioners who are not specialists.

With regard to specialist-level training, should FDA mandate education for all opioid prescribers we’d ask the agency to consider how to fashion the requirement in a manner that acknowledges certain specialties already require substantial training in assessing and managing pain, and thus allow for those specialists to meet the requirement in a way that will add meaningfully to their knowledge and skills (for example, via options for individualized education on topics such as substance use disorder screening and referral to treatment or overdose reversal agents).

- What steps should FDA take to make implementing such mandatory education efficient and more feasible? For example, should FDA work collaboratively with state public health agencies, state licensing boards, provider organizations, such as medical specialty societies and health plans, or with other stakeholders, such as pharmacy benefit managers, to integrate or avoid duplicating their educational programs or requirements? What other steps might FDA consider to make implementation less burdensome and more effective?

If FDA were to mandate prescriber education, AAHPM urges the agency to collaborate with state licensing boards to identify ways to avoid multiple, overlapping requirements at the state and federal levels, as well as to work closely with medical specialty societies who may have already developed comprehensive education and training resources.

IV. Additional Matters for Consideration

In its request for comments, FDA ask about other steps the agency could take to operationalize the above described goals or additional policy steps FDA should consider relating to the OPSC that are not identified in its notice. AAHPM believes there are a variety of issues that FDA and the Steering Committee could examine.
With regard to the factors contributing to the staggering rates of opioid use disorder and overdose death, the FDA must better identify, characterize and address emerging public health risks outside of prescription drug misuse and diversion, such as the role of illegal fentanyl and heroin. A majority of opioid deaths now involve these illegal drugs, and these deaths are unlikely to be affected by further regulation of physician prescribing. In fact, a CDC report found that illicitly manufactured fentanyl was involved in more than half of opioid overdose deaths studied in 2016, with the authors noting that “illicitly manufactured fentanyl is now a major driver of opioid overdose deaths in multiple states, with a variety of fentanyl analogs increasingly involved, if not solely implicated, in these deaths.”

There is also an acute need for more research on safe and effective treatments for chronic pain, including non-pharmacologic and non-interventional treatments. Moreover, if these treatments are to become mainstream and accessible, they must be covered by payers. When insurers typically cover medications but not non-pharmacologic approaches (such as cognitive behavioral therapy), or if complementary and alternative therapies that research has shown to be effective are not reimbursed under Medicare, this limits the availability of effective and safe non-opioid therapies. We urge FDA to work with other policymakers to encourage insurers to cover multi-modal and non-pharmacological pain treatment where these are options, otherwise prescribers will necessarily default to treatments, like opioids, that are reimbursed in order to ensure their patient’s pain is managed. Finally, FDA could also prioritize and accelerate approval of adjuvant analgesics to decrease the need for opioids as well as ease barriers to medical research on cannabinoids.

The Steering Committee should also prioritize a multi-level focus on improving training and access to evidence-based treatment for opioid use disorder and work with policymakers and payers to expand mental health resources, including access to addiction treatment. This focus should also include how best to increase the number of trained practitioners allowed to prescribe methadone and buprenorphine, so both primary care providers and specialists outside addiction medicine can provide maintenance therapy for patients with opioid use disorder who also have pain.

To the degree FDA can help develop better, expanded options for safe disposal, we’d encourage the agency to do so. We’d also ask the Steering Committee to work with the DEA to examine that agency’s regulations which, since 2014, prohibit hospice and home care providers from taking possession of unused pharmaceutical controlled substances following a patient’s death, unless authorized under state law to dispose of a decedent’s property. We see hospices stepping up efforts to educate and assist families with disposal and, through the AMA Opioid Task Force, AAHPM helped develop a backgrounder on these issues for providers. Still, since the Office of National Drug Control Policy has found that more than 70 percent of people using opioid analgesics for nonmedical reasons get them from family or friends, this is an important gap that is being left to the states to address (see H. 3132 enacted this year in South Carolina and S.978 pending in Pennsylvania). Otherwise, FDA might also consider limiting direct to consumer advertising for opioids and opioid related medications.

Finally, AAHPM would be remiss if we did not urge FDA to work with Congress to enact the Palliative Care and Hospice Education and Training Act (PCHETA). This legislation, developed by AAHPM, enjoys broad bipartisan support in both the House (H.R. 1676) and Senate (S. 693). While there is little curricula on managing pain in medical and nursing schools today, PCHETA would expose students (medical students, nursing students, pharmacy students, social work students, etc.) to palliative care education and training early on (before they choose the area in which they will practice) so they develop skills in assessing and managing pain, leading to more effective, evidence-based prescribing. Palliative care also focuses on care coordination (across providers, pharmacists, etc.), so expanding these skills can further play a role in
stemming opioid misuse. The bill would also ensure we have trained faculty in medical, nursing, and other health professions schools who can incorporate appropriate pain management education into their teaching. Finally, the legislation directs greater investment in evidence-based research to better understand the mechanisms of pain, as well as identify effective options for pain and symptom management, including non-pharmacological and multimodal approaches. Currently a fraction of one percent of National Institutes of Health funds are spent in this area which holds great potential to strengthen clinical practice and healthcare delivery.

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Thank you again for the opportunity to provide input regarding the critical issues FDA has addressed in its request for comments. AAHPM is proud of its efforts to address the opioid crisis. Our Academy has helped develop the CO*RE curriculum and delivered this and other opioid-related education to its members and other practitioners; contributed to the development of the National Conference of Insurance Legislators’ Best Practices to Address Opioid Abuse, Misuse, and Diversion; and developed guidelines for effective prescription drug monitoring programs that we’ve promoted among our membership as we encourage them to register with their state PDMP. AAHPM also chairs the AMA’s Pain and Palliative Medicine Section Council, helping to lead policy development for the House of Medicine, and is an active member of the AMA’s Opioid Task Force, working to identify strategies and tools that empower physicians to take the lead in stemming opioid use disorder and overdose death. We believe these efforts have equipped our leaders with important knowledge and experience that serve to guide the feedback we’ve provided here.

To reiterate, AAHPM recognizes the public health imperative to diminish abuse, misuse and diversion of opioids and applauds the FDA’s efforts to closely examine how best to achieve this goal. We are committed to partnering with the FDA and other federal agencies in efforts designed to enhance prescribers’ knowledge and skills to improve care and outcomes for patients and improve public health and safety while at the same time ensuring seriously ill patients’ continued, legitimate access to medications essential to their care. This will require additional research; extensive, honest dialogue; and recalibration as unintended consequences become clear. Above all, it will require recognition that overdose deaths and untreated suffering are both unacceptable.

We would welcome any opportunity to provide additional information regarding this request for comments or any other agency initiatives, particularly with regard to the unique and important needs of patients with serious or life-threatening conditions. Please address questions to Jacqueline M. Kocinski, MPP, AAHPM Director of Health Policy and Government Relations, at jkocinski@aahpm.org or 847-375-4841.

Sincerely,

Janet Bull, MD MBA HMDC FAAHPM
President
American Academy of Hospice and Palliative Medicine