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Sent Electronically to: P65Public.comments@oehha.ca.gov

SUBJECT: CLEAR AND REASONABLE WARNING REGULATIONS

Dear Ms. Vela:

On behalf of the Advanced Medical Technology Association (AdvaMed), thank you for the opportunity to submit comments regarding the Office of Environmental Health Hazard Assessment's ("OEHHA") Notice of Proposed Rulemaking to Article 6 in Title 27 of the California Code of Regulations pursuant to the Safe Drinking Water and Toxic Enforcement Act ("Proposition 65").

AdvaMed is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. In 94 facilities located throughout the state, our member companies contribute over 84,000 jobs to California. Our member companies range from the largest to the smallest medical technology innovators and manufacturers and actively engage in policy discussions that are critical to the growth and development of the medical technology industry.

As we have articulated in previous comments, we do not believe it is feasible or an effective communication option to include a Proposition 65 warning on medical devices and that they should be given a safe harbor similar to prescription drugs. We believe the main components within Proposition 65 - right to know and consent of the consumer - are properly achieved as devices are dispensed via prescription and by medically licensed personnel (and such accreditation and mechanisms are recognized and controlled by the State of California). Further, the risk to reward resulting from the use of any devices that may contain any Proposition 65 chemicals has been discussed with a patient (consumer) and consent would have to be obtained prior to any surgical intervention. As such, we maintain devices that are subject to the jurisdiction of the U.S. Food and Drug Administration (FDA) and approved for use by the Agency should be exempted.

Furthermore, the Medical Device Amendments ("MDA")¹, to the Food, Drug and Cosmetic Act ("FDCA")², establish a scheme for comprehensive federal regulation of prescription and other medical devices, while also protecting life-saving innovations in device technology from being stifled by unnecessary restrictions. Congress sought "national uniformity in product regulation" in

¹ 21 U.S.C. § 360c, *et. seq.*

² 21 U.S.C. § 301, *et seq.*

enacting the MDA.

In order to legally market a FDA approved medical device, the manufacturer must provide FDA with “reasonable assurance” that the device is both safe and effective.³ For Class III devices, this is initially accomplished by completing a thorough review process known as Pre-Market Approval (“PMA”). Devices that are substantially equivalent to a PMA device can then provide FDA with reasonable assurance of safety and efficacy through the 510(k) clearance process.⁴

Furthermore, FDA has established specific requirements pertaining to device labeling. The FDCA is the law under which the FDA takes action against regulated products related to labeling requirements. Labeling regulations related to medical devices are found in the following Parts of Title 21 of the Code of Federal Regulations (CFR):

- General Device Labeling -21 CFR Part 801
- In Vitro Diagnostic Products - 21 CFR Part 809
- Investigational Device Exemptions - 21 CFR Part 812
- Good Manufacturing Practices - 21 CFR Part 820
- General Electronic Products - 21 CFR Part 1010

FDA regulates the marketing and sale of medical devices and it expressly preempts state law requirements governing medical devices:

[N]o state or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement –

- (1) which is different from, or in addition to, any requirement applicable under [the FDCA] to the device, and
- (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this Act.⁵

The basis of preemption is found in the Supremacy Clause of the United States Constitution which provides that the “Laws of the United States . . . shall be the supreme Law of the Land.”

It has been established that Cal Proposition 65 conflicts with Federal law insofar as Cal Prop 65 requires a warning label to appear on products sold in California if they contain chemicals on the Prop 65 list of hazardous substances. The warning label shall state:

WARNING: This product contains chemicals known to the State of California to cause cancer and birth defects or other reproductive harm.

Fundamentally, the conflict arises between the FDCA and Cal Prop 65 requirements because of this warning. On one hand, you have a device manufacturer who has provided FDA with evidence that the device is both safe and effective (either through the PMA or 510(k) process), thus allowing the

³ 21 U.S.C. § 360e(d)(2).

⁴ See 21 C.F.R. §§ 21 C.F.R. 807 *et seq.*, 862.9, 864.9.

⁵ 21 U.S.C. § 360k(a).

device to be legally marketed in interstate commerce and on the other, a statute that requires you to label the same device with a warning indicating something to the contrary.

Medical devices can be and have been determined to be not substantially equivalent due to labeling issues. For example, recent premarket notification submissions to the FDA have received additional information requests from FDA's CDRH Office of Device Evaluation stating:

"Your package labels include several symbols. Please be advised that the current practice is that the Office of Device Evaluation does not recognize symbols in device labeling, other than the symbol "Rx only". As outlined in 21 CFR 807.87(e), proposed labels and labeling shall be sufficient to describe the directions for use of the device and Section 502(f) of the Act requires adequate directions for use. Also, as outlined in 21 CFR 801.15 (c)(1) all words, statements, and other information required by or under authority of the act to appear on the label or labeling shall appear thereon in the English language. Therefore, please provide revised package labels in which a definition is provided adjacent to each symbol on the label.

As such, we maintain devices that are subject to the jurisdiction of the U.S. Food and Drug Administration (FDA) and approved for use by the Agency should be exempted. That said, and in light of OEHHA's option to not explicitly provide a safe harbor for medical devices in the current proposed regulations, we offer the following comments:

Section 25600 – General

The proposed regulation does not retain the explanation for "clear and reasonable" language in warnings. Guidance will likely be sought through costly mechanisms or end in litigation. The language will be left for businesses to individually interpret and could result in leaving some out of compliance.

The proposed warning regulations will become effective two years after adoption, however, numerous medical devices circulate over several years through various distribution and commerce cycles. Two years is not sufficient could prove too costly to implement for device manufacturers and potentially leave them with excess inventory. As such, we suggest at least three years is needed for implementation.

Furthermore, we recommend more clarification surrounding grandfathering as the current language addressing settlements is too vague. Warnings which were previously approved by courts should stand and remain reliable.

Section 25600.1 – Definitions

"Knowingly" -- Proposition 65 requires California businesses with 10 or more employees to provide a clear and reasonable warning before "knowingly and intentionally" exposing individual to chemicals known to cause cancer and/or reproductive toxicity. Businesses often provide warnings on their products or facilities out of an abundance of caution and to avoid lawsuits, even if no chemical exposure is present or if the chemical exposure is occurring below specified threshold (safe harbor) levels. The Office of Environmental Health Hazard Assessment (OEHHA) should support efforts to further clarify the term "knowingly" in order to reduce the chances of a company being sued over whether they "knew" a chemical could cause exposure or not.

Section 25600.2 – Responsibility to Provide Product Exposure Warnings

Proposition 65 focuses more on content than exposure, and as such does not appropriately take into account the location of a substance within a product, the likelihood of a consumer actually coming into contact with the substance during conventional use, and the potential duration and route of exposure. These are all very important factors in assessing whether a true hazard exists. OEHHA should establish safe harbor levels for chemicals based on content (in parts per million) rather than exposure rates. Manufacturers should then only be required to provide additional information to consumers on how they will be exposed to those chemicals if the content threshold is exceeded and the consumer can come into contact with the chemical in a form that can enter the body through inhalation, ingestion or through the skin, thereby potentially causing harm to the consumer. A concentration of a chemical in a product should not be of concern if that chemical is not in a form that would facilitate it being absorbed into one’s body (e.g., the chemical is contained within an internal component of the product for which the consumer will not come into contact with the chemical through conventional use of the product).

Should OEHHA not provide a content-based exposure threshold, the clear and reasonable warning requirements should, at a minimum, clarify that exposure is said not to occur if the substance *“is not accessible to an individual through normal and foreseeable use and abuse of such product or component part, nor is it in a chemical state that could cause it to be absorbed into the body.”* Under this approach, OEHHA should also clarify the level of proof/evidence needed to show no significant exposure because the chemical is not accessible to the consumer. OEHHA should also require use of the word *“contains”* rather than the phrase *“can expose”* in the clear and reasonable warning and require manufacturers to explain how that content could become a hazard – such as identifying the routes for potential exposure to the Proposition 65 chemical.

Finally, chemicals should not be added to the Proposition 65 list until a method is developed to properly test for the chemical. Such test methods must maintain a consistent understanding of product usage to determine whether or not contact with the Proposition 65 chemical is even possible. The medical device industry has significant experience in developing proper test procedures to ensure that test results are consistent across manufacturers and that consumers can accurately compare products based on similar test methods. Lack of such testing leads to inconsistency in interpretation of the nature and degree of any hazard that may exist, which in turn leads to many frivolous lawsuits.

Section 25602 – Chemicals Included in the Text of a Warning

We have significant concerns about the fluidity of the list of chemicals to be included in the text of a warning. Companies need predictability and would potentially need to keep finances aside to update and possibly expand warnings to remain in compliance. Additionally, there are no criteria established for identification or to update the list of chemicals and we believe OEHHA may be overstepping its authority to create and impose this list (Gov’t Code Section. 11342.2.).

Furthermore, we have concerns with the vague grouping of phthalates as part of the “dirty dozen” list of chemicals in this section. Phthalates are a family of chemicals that includes hundreds of chemicals – most of which are not currently listed under Proposition 65. Some of the most common phthalates include:

Name	Abbreviation	<u>Structural formula</u>	<u>CAS No.</u>
<u>Dimethyl phthalate</u>	DMP	$C_6H_4(COOCH_3)_2$	131-11-3
<u>Diethyl phthalate</u>	DEP	$C_6H_4(COOC_2H_5)_2$	84-66-2

Diallyl phthalate	DAP	$C_6H_4(COOCH_2CH=CH_2)_2$	131-17-9
Di-n-propyl phthalate	DPP	$C_6H_4[COO(CH_2)_2CH_3]_2$	131-16-8
Di-n-butyl phthalate	DBP	$C_6H_4[COO(CH_2)_3CH_3]_2$	84-74-2
Diisobutyl phthalate	DIBP	$C_6H_4[COOCH_2CH(CH_3)_2]_2$	84-69-5
Butyl cyclohexyl phthalate	BCP	$CH_3(CH_2)_3OOC C_6H_4COOC_6H_{11}$	84-64-0
Di-n-pentyl phthalate	DNPP	$C_6H_4[COO(CH_2)_4CH_3]_2$	131-18-0
Dicyclohexyl phthalate	DCP	$C_6H_4[COOC_6H_{11}]_2$	84-61-7
Butyl benzyl phthalate	BBP	$CH_3(CH_2)_3OOC C_6H_4COOCH_2C_6H_5$	85-68-7
Di-n-hexyl phthalate	DNHP	$C_6H_4[COO(CH_2)_5CH_3]_2$	84-75-3
Diisohexyl phthalate	DIHxP	$C_6H_4[COO(CH_2)_3CH(CH_3)_2]_2$	146-50-9
Diisohexyl phthalate	DIHpP	$C_6H_4[COO(CH_2)_4CH(CH_3)_2]_2$	41451-28-9
Butyl decyl phthalate	BDP	$CH_3(CH_2)_3OOC C_6H_4COO(CH_2)_9CH_3$	89-19-0
Di(2-ethylhexyl) phthalate	DEHP, DOP	$C_6H_4[COOCH_2CH(C_2H_5)(CH_2)_3CH_3]_2$	117-81-7
Di(n-octyl) phthalate	DNOP	$C_6H_4[COO(CH_2)_7CH_3]_2$	117-84-0
Diisooctyl phthalate	DIOP	$C_6H_4[COO(CH_2)_5CH(CH_3)_2]_2$	27554-26-3
n-Octyl n-decyl phthalate	ODP	$CH_3(CH_2)_7OOC C_6H_4COO(CH_2)_9CH_3$	119-07-3
Diisononyl phthalate	DINP	$C_6H_4[COO(CH_2)_6CH(CH_3)_2]_2$	28553-12-0
Di(2-propylheptyl) phthalate	DPHP	$C_6H_4[COOCH_2CH(CH_2CH_2CH_3)(CH_2)_4CH_3]_2$	53306-54-0
Diisodecyl phthalate	DIDP	$C_6H_4[COO(CH_2)_7CH(CH_3)_2]_2$	26761-40-0
Diundecyl phthalate	DUP	$C_6H_4[COO(CH_2)_{10}CH_3]_2$	3648-20-2
Diisoundecyl phthalate	DIUP	$C_6H_4[COO(CH_2)_8CH(CH_3)_2]_2$	85507-79-5
Ditridecyl phthalate	DTDP	$C_6H_4[COO(CH_2)_{12}CH_3]_2$	119-06-2
Diisotridecyl phthalate	DIUP	$C_6H_4[COO(CH_2)_{10}CH(CH_3)_2]_2$	68515-47-9

Some phthalates are specifically regulated across the globe. For example, pursuant to the [Phthalates Regulations](#) within the Canada Consumer Product Safety Act “phthalate” means di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) or di-n-octyl phthalate (DNOP). Similarly, the *EU Directive 2005/84/EC* since replaced by the REACH regulation identifies the specific phthalate chemical entities subject to the Directive. These include the following 6 substances:

- Di-2-ethylhexyl phthalate(DEHP)
- Diisononyl phthalate (DINP)
- Dibutyl phthalate (DBP)
- Di-n-octyl phthalate (DNOP)
- Benzylbutyl phthalate(BBP)
- Diisodecyl phthalate (DIDP)

OEHHA should list all the specific phthalates they want raised to the level of disclosure.

Section 25603 – Product Exposure Warnings – Methods of Transmission

The issue of whether a warning can be placed in owner’s manuals, instructions for use (IFUs) and/or accompanying documents to satisfy a manufacturer’s labeling obligation under Proposition 65 is not clearly addressed in the proposed rule and may not even be allowed as currently drafted. The existing regulation states a warning may be provided “*on a product’s label or other labeling.*” The term *labeling*” in the existing regulation includes communication accompanying a product (e.g., owner’s manuals, IFUs), while the term “*label*” does not. In the proposed rule, the term “*label*” is defined as “*affixed to a product or its immediate container or wrapper*”, while the term “*labeling*” is defined to include a “*communication that accompanies a product.*” In the proposed rule, Section 25603(3) regarding the methods of transmitting a warning includes “*A label on the product that includes all the elements specified in Section 25604.*” It does not include the term “*labeling*” in this subparagraph, as is the case in the current regulation. To ensure that the current policy of providing warnings in the owner’s manual where other warnings and information are contained (e.g., electric and drinking water safety) does not change, we strongly recommend the following revision to the proposed rule before it is finalized:

Section 25603(a)(3) A label on the product OR OTHER LABELING that includes all the elements specified in Section 25604.

It is critical for medical device manufacturers to be allowed to continue to provide required warnings in owner’s manuals, IFUs and/or accompanying documents, rather than directly on product labels that are typically numerous, limited in size, and already highly populated with other state and/or federal consumer and medical device disclosure requirements. Furthermore, changes to labels for medical devices often require review and approval by the U.S. Food and Drug Administration (FDA) – an often costly process that can also significantly slow the time for newly labeled products to reach the marketplace.

Section 25603(d) states, “*If any label, labeling or sign about a product is provided in a language or languages other than or in addition to English, then a warning for that product meets the requirements of this Article only if the warning is also provided in the same language or languages on the label, labeling or sign.*” This is concerning for multi-language (e.g., in French and English for Canada) medical device labels and owner’s manuals, IFUs and/or accompanying documents, essentially requiring any related Proposition 65 warning to also be in multiple languages. We believe OEHHA is overstepping their boundary in requiring translation of a warning only applicable to the State of California.

Section 25604 – Product Exposure Warnings – Content

Subsection (a)(1) indicates that one element that a warning must contain in order to meet the requirements of the product exposure warning is “*A symbol consisting of a black exclamation point in a yellow equilateral triangle with a bold black outline*”. This pictogram requirement should be removed from the proposed rule before it is finalized because it is misleading. In ANSI Z535.4-2011 4.11, this particular symbol configuration means danger, warning or caution and states, “*Safety alert symbol: A symbol that indicates a hazard. The safety alert symbol is only used on hazard alerting signs. It is not used on safety notice and safety instruction signs.*”

Medical device manufacturers typically label their products uniformly in order to be sold in most all markets. Labeling our products with the same pictogram that ANSI defines will give consumers who don't live in California an inconsistent message and the universal impression of immediate hazard. OEHHA must recognize this and think more broadly on what the proposed pictogram means to consumers outside of California. No other state or country recognizes California's Proposition 65 law or list of chemicals, and as such, OEHHA should not require manufacturers to label their products with a pictogram that says the chemical is "known to the State of California to cause cancer" where elsewhere in the U.S., and throughout the world, the pictogram means something completely different.

FDA states that Warnings:

Describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.

Include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition and such usage is associated with a serious risk or hazard.

Appendix E of FDA's Guidance on Medical Device Patient Labeling⁶ provides specific information on what warnings are, their purpose and the appropriate content of a warning. This includes the following:

Warnings and precautions:

The purpose of this section is to:

- define and explain the terms **warnings** and **precautions**,
- discuss their use in medical device labeling,
- recommend approaches to effective presentation based on literature and research findings, and
- present some of the common issues associated with warnings and precautions.

Note: *Labeling a device with warnings and precautions is the least preferable method of controlling accidents and injuries. You should make every effort to design the device so that the hazard is eliminated. Only when this is clearly impossible should you resort to a warning or precaution in the labeling. For instance, if the device may be made without toxic substances, this would be the preferred alternative.*

⁶ <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm#>

What are warnings and precautions?

Warnings and *precautions* are written, pictorial, and/or audible alerts to a hazard. The term used to identify the particular hazard presents the reader with a cue to the seriousness of the hazard.

A warning alerts the reader about a situation which, if not avoided, could result in death or serious injury. [ANSI Z535.4-1998] It may also describe potential serious adverse reactions and safety hazards. The designation of a hazard alert as a "warning" is reserved for the most significant problems. The term **WARNING** is generally used as the signal word for this type of hazard alert. If a problem may lead to death or serious injury, FDA may expect you to highlight the warning by placing it in a box.

The term precaution is used for the statement of a hazard alert that warns the reader of a potentially hazardous situation which, if not avoided, may result in minor or moderate injury to the user or patient or damage to the equipment or other property. [ANSI Z535.4-1998] It may also be used to alert against unsafe practices. This includes the special care necessary for the safe and effective use of the device and the care necessary to avoid damage to a device that may occur as a result of use or misuse. The word **CAUTION** is generally used as the signal word for a precaution statement.

The distinction between warnings and precautions is a matter of degree of likelihood and seriousness of the hazard. The target audience for medical device labeling (health care practitioners and lay users of home use devices) generally recognize a hierarchy of hazard alerts, with warnings being those of a more serious nature and precautions being of a less serious, but important, nature.

What is the purpose of warnings and precautions in medical device labeling?

The basic purpose of a warning or precaution is twofold:

- to inform users of potential personal and environmental hazards, and
- to persuade them to modify their behavior to avoid injury or device damage.

For a warning or precaution to be effective, readers must:

- perceive the threat to be both severe and relevant to them,
- believe that they can perform the recommended response, and
- believe that response will be effective in avoiding the hazard.

Effective warnings and precautions capture the reader's attention, are understood, are consistent enough with the reader's beliefs and attitudes to be accepted, and are persuasive enough to motivate the reader to comply. They invoke an appropriate level of fear arousal, conveying the nature and extent of the hazard, without being so strong that they backfire, causing the reader to select an alternative action or no action.

What is appropriate content of an effective warning or precaution?

There are four elements generally recognized by the courts and research (See References – Warnings and Precautions) as necessary for an effective warning or precaution:



- **a signal word (WARNING, CAUTION)** to alert the reader that what follows is important hazard information. A symbol or icon may emphasize the effect of the signal word. Additional enhancement, such as bolding, larger type, underlining, italics, or color may help the information stand out from the rest of the text. However, studies have demonstrated that a large difference in font size between the signal word and the text may de-emphasize the importance of the text and therefore reduce the likelihood that the text will be read.
- **a hazard avoidance directive** in the form: **Do Not, Never, Avoid...**" (or **Do**, if more appropriate) followed by the action to avoid (or perform). The objective of this directive is to give clear instructions to the user on how to avoid the hazard.
- **a clear statement of the nature of the hazard** associated with the warning (e.g., allergic reaction to material, strong magnetic field) or precaution (e.g., environmental effect, damage from resterilization) that characterizes the severity and the likelihood.
- the **consequences**, specifying the serious adverse events, potential safety hazards and limitations in device use that result if users do not follow instructions. The purpose is to give them a clear idea of the risk, which is likely to increase compliance. Hazard alert research has shown that this element has a significant effect on readers. If the consequences are not included, the alert is likely to be less effective.

The elements contained within the proposed OEHHA's CLEAR AND REASONABLE WARNING REGULATIONS drift significantly from the requirements specified by FDA for medical devices and impose an undue, unnecessary burden on medical device manufactures.

Again, medical device labels and labeling are specifically regulated by the FDA as outlined in Title 21- Part 801 Labeling and other parts of the FD&C Act. Symbols without the use of accompanying English text are not permitted by the FDA. To do so clearly invokes a requirement that is different than, and in addition to, that governed by the Federal regulatory scheme.

Closing

In closing, these comments reflect the specific medical device industry concerns with the proposed regulations, however, we also echo the broader concerns voiced by the CA Chamber of Commerce in their formal comments.

Thank you for your consideration of our comments. Please don't hesitate to contact me if additional information or clarification is needed.

Sincerely,

Carrie A. Hartgen