Resolution #43 (16) –2016 Annual Leadership Forum

TITLE: Expiration Dates on Epinephrine Auto-Injectors

SPONSORED BY: Section on Allergy/Immunology
Section on Pediatric Pulmonology and Sleep Medicine

DATE: December 1, 2015

DISPOSITION: ADOPTED

Whereas, children with severe food and venom allergies are required to have two epinephrine auto-injectors on hand at all times; and

Whereas, many children are cared for in multiple locations, requiring several auto-injectors; and

Whereas, the cost of these auto-injectors has risen by 200% or more over the last four years, now exceeding $500 in some locations; and

Whereas, these devices are marketed with an expiration date that is only slightly more, and sometimes less, than one year from the time of purchase, and schools require unexpired products, therefore be it

RESOLVED, that the Academy request the Food and Drug Administration (FDA) to explain why the expiration date for epinephrine auto-injectors such as Epipen is so short (resulting in need to re-purchase the device repeatedly), and if it is due to lack of scientific data, ask that the FDA require the device companies to produce such data.

FISCAL NOTE:

REFER TO: 2016 Annual Leadership Forum

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BACKGROUND INFORMATION:

Background Information from the Author

The FDA requires medication manufacturers to place a date on their products that indicate the medication is guaranteed to be effective and usable up to that date. There is usually very little information in the literature on whether these medications are effective or usable after that date. One exception, however, is the

epinephrine auto-injector made by Mylan, where the research indicates that these devices retain some potency for up to 5 years after that date. This places an exceptional financial burden on families, who are forced to purchase new auto-injectors every year to satisfy school requirements. If these devices do retain some potency for a much longer period of time, why is the expiration period so short? Health care providers need to know the basis for these expiration dates, and have the FDA establish rules for transparent, realistic information on the shelf-life of this and other medications.

Background Information from the Committee on Drugs

At this time, the Committee on Drugs is not addressing the issue(s) raised in the resolved portion(s) of this resolution. However, the following is current information related to the topic:

Title 21 CFR Part 211 of the Code of Federal Regulations - Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMPs), establish requirements concerning expiration dating and stability testing to assure the appropriateness of that date. Each drug product may be considered by FDA as a unique article because of, for instance, differences in (1) chemical and physical properties of the active ingredients or the excipients, (2) manufacturing procedures, (3) formulations, (4) containers and closures, (5) proposed storage conditions, and (6) the stability of the article to maintain its quality or purity through the use of antioxidants or preservatives. Because of the uniqueness of each drug product, FDA acknowledges that it is virtually impossible to provide one set of rules that can apply to all situations. CGMP provisions were purposely written broadly to allow for such unique differences.

21 CFR 211.137 – Expiration Dating

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.
(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in 211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.
(d) Expiration dates shall appear on labeling in accordance with the requirements of 201.17 of this chapter.

21 CFR 211.166 – Stability Testing

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:
(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
(2) Storage conditions for samples retained for testing;
(3) Reliable, meaningful, and specific test methods;
(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;
(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

Additionally, an adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

FDA Guidance

FDA has published several guidance documents related to stability testing. While guidance is not legally enforceable, it does provide the agency's current thinking on a topic and includes recommendations. For example, the objective of FDA's *Q1A Stability Testing of New Drug Substances and Products* is to define

what stability data for a new drug substance or drug product is sufficient for a registration application within the three regions of the European Union (EU), Japan, and the United States. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

FDA has also published – *Guidance for Industry and Staff: Technical Considerations for Pen, Jet, and Related Injectors for Use with Drugs and Biological Products*. This guidance focuses on the scientific and technical considerations that a manufacturer should consider when developing a pen, jet, or related injector and submitting a marketing application. Injectors are subject to different regulatory requirements depending, for example, on their intended use, technological characteristics, proposed labeling, and packaging. Per the guidance:

Applications for injectors intended for use with a specific drug/biologic product or for a drug/biological class/family or product line should include stability data to establish the shelf-life and expiration dating of the relevant fully assembled injector-drug/biological product. For example, as appropriate, tests may assess the shelf life of the assembled product in storage conditions before use. They may also assess stability and expiration dating of the final to-be-marketed configuration under expected in-use conditions (e.g., rugged use, different environmental conditions). Where applicable, the tests should evaluate the product after reconstitution. They should assess any injectate that remains in the fluid path after injection; e.g., to determine if it degrades or contributes to the denaturing of the drug/biological product. As applicable, the in-use life testing should include data to demonstrate that the method of injection (e.g., rate, shear force, injection pressure) does not affect stability, safety, or effectiveness of the drug or biological product(s).

When conducting stability and expiration dating tests, the entire injector system should be tested; i.e., the drug/biological product in its direct container closure (cartridge) plus any surrounding injector materials and packaging. Bench testing for container

closure and packaging ruggedness should include, but is not limited to, mechanical reliability (release specifications), accelerated testing, temperature cycling, temperature extremes, pressure changes, vibration, etc.

Background Information from the Committee on Federal Government Affairs

Food and Drug Administration (FDA) regulations require drug products to carry expiration dates to assure that they meet "applicable standards of identity, strength, quality, and purity at the time of use" (21 CFR 211.137). Manufacturers are required to conduct stability testing of their products (under 21 CFR 211.166) and the results of such stability testing is required to "be used in determining appropriate storage conditions and expiration date." In practice, expiration dates tend to be a date at which manufacturers still guarantee continued effectiveness of a drug product, but not necessarily the date at which a drug is no longer effective. FDA regulations do not prohibit use of drugs after their expiration date. The Committee on Federal Government Affairs has not at this time addressed the issue of epinephrine auto-injector expiration dates.

RESPONSE INFORMATION: ***Response from the Section on Allergy and Immunology**