



16 May 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Subject: ISPE Comments – FDA Guidance for Industry on Non-penicillin Beta-Lactam Risk Assessment: A CGMP Framework (Docket No. FDA-2011-D-0104)

Dear Sir/Madam:

Below please find ISPE's comments regarding the above draft guidance document. Thank you for the opportunity to provide feedback on this document.

Please feel free to contact me if you have any questions.

Yours sincerely,

Robert P. Best
President/CEO, ISPE



LINE NUMBER	CURRENT WORDING	PROPOSED CHANGE	RATIONALE
Document Title	Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework	Non-Penicillin Beta-Lactam CGMP Framework	The document is not a risk assessment; the document actually shows how risk adverse the agency is to these types of compounds
32	"drugs can initiate drug-induced..."	"drugs may initiate drug-induced..."	Not every instance will have this reaction some people are more tolerant than others.

<p>62-72</p>	<p>Completely and comprehensively separated</p>	<p>Suggest listing the required performance to meet “completely and comprehensively separated” such as:</p> <p>Separate facilities are considered to have:</p> <p>Physical separation HVAC separation Proof of containment/ analytical methods sensitivity</p>	<p>Further clarity is needed on “completely and comprehensively separated”. Does this mean that the concrete floor slab should be separated between these areas, etc.?</p> <p>The preamble to the GMPs does not use the words “completely and comprehensively separated” rather uses “effectively isolating and sealing off from one another these two types of operations.” This can be achieved via closed processing.</p> <p>Just because a facility is structurally isolated does not mean the risk of cross contamination does not exist.</p> <p>The current interpretation of this requirement is not very effective in “containing” the compound(s) at the source. There are several dedicated sites to these types of products that clearly are not controlling the release of the product outside the plant either via the HVAC system or via mechanical transfer such as on employees leaving the site, etc. They are meeting the LETTER of the law but clearly they are not meeting the INTENT of the law. By enforcing the use of closed/contained processes companies can meet both the letter and the intent of the law.</p>
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62-72	Expand to allow the use of closed systems to meet the requirement of “completely and comprehensively separated”		With the increased use of closed processing systems, is this considered acceptable if the manufacturer proves physical separation (the process is the boundary separation), air handling separation (the process is closed to the environment and provides the environmental conditions the product needs, even at cleaning so there is separation of air handling) and proves containment and the analytical methods have the appropriate sensitivity to detect the compound?
118-119			Please provide a reference for this statement
161-162			The statement says some beta-lactams have negligible cross reactivity to other beta-lactams in other classes, yet the document requires all classes be processed in separate facilities from each other. This is not risk-based.

<p>168-175</p>	<p>Specifically, FDA recommends that manufacturers establish appropriate separation and control systems designed to prevent the following types of cross - contamination:</p> <ul style="list-style-type: none"> • Non-penicillin beta-lactam contamination in a non-beta-lactam product (e.g., cefaclor in aspirin) • Non-penicillin beta-lactam contamination in another non-penicillin beta-lactam (e.g., cephalexin in imipenem) 	<p>Clarify that “Appropriate separation and control systems” can include facilities with closed systems, separate ventilation systems, and proof of containment and analytical method sensitivity.</p>	<p>With the increased use of closed processing systems, is this considered acceptable if the manufacturer proves physical separation (the process is the boundary separation), air handling separation (the process is closed to the environment and provides the environmental conditions the product needs, even at cleaning so there is separation of air handling) and proves containment and the analytical methods have the appropriate sensitivity to detect the compound?</p>
<p>182-191</p>	<p>General comment on paragraph.</p>	<p>FDA should allow manufacturers to use risk-based approaches to determine if separate (structurally and comprehensively isolated) dedicated facility is necessary to manage the risk of cross contamination or if other methods such as dedicated equipment, or closed processing in a multi-product facility can be safely used to manage the risk. Obviously if the manufacturer does not prove they can manage the risk of cross contamination adequately, a separate and dedicated facility is necessary.</p>	<p>Analytical methods have improved greatly over the last decade and reputable laboratories can detect Aztreonam and other beta-lactams below microgram levels in rinse and swab samples.</p>



184in which other products are manufactured.in which other products are manufactured although separate buildings may not be necessary.	In order to match with FDA's clarification in the line 64
185-186	The area in which any class of sensitizing beta-lactam is manufactured should be separated from areas	The area in which any class of sensitizing beta-lactam is manufactured should be structurally isolated (i.e., completely and comprehensively separated) from the areas	In order to match with FDA's clarification in the line 66, and the line 183