Bristol-Myers Squibb
Pharmaceutical Research Institute

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October 30, 2003

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0382; *Draft* Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principle businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We have a worldwide network of pharmaceutical production facilities, several of which manufacture products by aseptic processes.

For this reason we are impacted by the draft guideline, which will update the *1987 Industry Guideline on Sterile Drug Products Produced by Aseptic Processing,* and welcome the opportunity to comment on this FDA proposal.

We commend the FDA for having provided industry with the opportunity to view the Concept Paper before the issuance of the draft and for utilizing the Pharmaceutical Quality Research Institute (PQRI) as a forum to review and provide comment to the agency. The input of the PQRI recommendations to the Concept Paper representing views from the FDA, academia and industry made for a better document and one which respects the needs of each of the participants.

There are several aspects of the proposed guidance we would like to comment on to further enhance and clarify the document. These have been cited in the attached tables in two categories: "Major Concerns" and "Concerns for Wording Clarification."

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information or discussion as may be requested.

Sincerely,

Thomas M. Primm
President
Worldwide Medicines Group
Technical Operations

Laurie F. Smaldone, MD
Senior Vice President
Global Regulatory Sciences

CC: Neil Koller
President PDA

MAJOR CONCERNS

LINE	*COMMENT*	*RECOMMENDATION*
142-154	Considering further Harmonization besides the ISO designations for clean room classifications	Consideration should be given for incorporating the EU system of Grade A-D
215	This section indicates that every count should be investigated.	"Contamination *above Alert/Action Levels* in this environment should receive investigative attention. *Contamination below these levels should receive consideration for investigative attention depending on frequency, location and count.*"
280	Testing filters periodically during use adds to the aseptic manipulations required and potential for contaminating these units.	"Filters also should be integrity tested upon installation and *at a minimum at the end of use.*"
327, 332	Periodic/regular monitoring of filter air velocity is intrusive to the control of the environment.	Monitoring pressure differential across the filter face could also provide information on the proper functioning of the filter.
411 459	Perturbing or disrupting airflow is inevitable.	"... it's design should not *disrupt unidirectional airflow.*" "Personnel should *avoid disrupting* the path of unidirectional airflow in the aseptic processing zone, *especially the flow of air to exposed product or containers.*"
456	For example, in rooms or areas with 100 % HEPA filter coverage, keeping the entire body out of the path of unidirectional air may be impractical.	"*Minimizing disruption of airflow in the aseptic processing zone.*"
574 etc.	The term "pyrogen-free" should be avoided.	Use the term "*non-pyrogenic*", meaning that the quantity is below the threshold which would produce a pyrogenic response in a human.
709	Process simulations of aseptic API operations may not be able to utilize a nutrient growth medium in place of the product.	The medium (or placebo) does not necessarily need to promote growth in a bulk aseptic simulation. The medium should not inhibit the survival of microbes that could potentially be present.
723-724, 784 and 824	Avoid the use of the term "worst case"	"...operations as closely as possible, *taking into consideration activities which provide a challenge to the aseptic operations...*"

		"...overall study design should adequately *incorporate challenge conditions* and cover ..." "...evaluate a single *challenging* line speed...".
823	It is not necessary to fill media to the product fill volume.	There are other ways to simulate exposure of filling.
935-944	The actions for addressing one contaminated unit differ between the 5,000-10,000 unit fill and the >10,000 unit fill. Also are these considered failures?	There is an established acceptance criterion in the EU GMPs (Annex 1) of 0.1% contamination at a 95% confidence level, which is now in use worldwide. Consideration should be given to harmonizing with this acceptance criterion.
1395	Processing interventions/excursions are validated through media fills. It should not be necessary to take sterility samples at the time of any occurrence. This can be a cumbersome process as a set number of samples are tested, and additional samples would need to supersede the normal sampling plan.	Eliminate the suggestion to take additional sterility samples at the time of interventions or excursions.
183-184, 361-368, 1297-1298, 1425-1426, (no text) 1352	It is our concern that in several places there are recommendations and opinions that may be interpreted as requirements in the future.	Avoid recommendations and opinions unless it is clear to the field that they are not required.
1019-20	In sterile API campaigns these filters may not be replaced each batch.	Several API batches may be run with a single filter. Integrity testing should still be done before initiation of the first batch and after the campaign ends.
1235	The term "sporeforming organisms" includes fungi as well as bacteria. The presence of fungi would not necessarily require the use of a "sporicidal" agent, as these are geared towards the destruction of bacterial spores.	Replace "sporeforming organisms" with either "*bacterial spores*" or "*sporeforming bacteria.*"

CONCERNS FOR WORDING CLARIFICATION

LINE	*RECOMMENDATION*
73, 83	There is no definition of "high-quality" and "extremely high-quality"
74	"...to minimize the microbial *and particulate* content..."
192	"....to which the product is *exposed such as with equipment running but no product powder being filled.*"
243-244	Monitoring can also be on an exception basis, recording only results out of limit, depending on the validated monitoring system.
289	Replace "aseptic processing room." with "*Class 100 areas.*"
493	"Semi-annual or yearly qualification is sufficient *under most conditions.*"
878	"...education, training, and *experience in detection of microbial contamination.*"
1051	Variable load configurations can also be validated and used.