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Dockets Management Branch (HFA-305)

Food And Drug Administration

5630 Fishers Lane, rm.

1061, Rockville, MD 20852.

Dear Sir:

Referring to the Draft Guidance for Industry on **" Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment"** **[Docket No. 2003D-0493]** . Published on the 27th of October 2003 .

And considering that this guidance document is being distributed for comment purposes, we would like to send you some comments and suggestions regarding this draft.

These comments are sent by

Name: **Seetaraju Gembali**

Organization: **Hikma Pharmaceuticals – The Hashemite Kingdom Of Jordan.**

Position: **The vice president of research and development department.**

Academic Degrees: A bachelor degree in pharmacy and a master degree in pharmaceutics form college of pharmaceutical science, Kasturba medical college. Also a diploma in marketing management and a diploma in pharmaceutical management.

Previous experience before joining Hikma: worked in a variety of positions in the pharmaceutical industry in India with internationally affiliated or multinational companies for 15 years. Involved in product development process validation and regulatory submission of ANDA's. Also worked as senior lecturer in a pharmaceutical college.

Hopefully our comments will be taken positively.

Seetaraju Gembali

G. SeetaRaju 11/12/03

Vice President of Research & Development

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Date: December 11, 2003

2003D-0493 C1

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[Docket No. 2003D-0493]

Draft Guidance for Industry on Powder blends and finished dosage units – stratified in-process dosage unit sampling and assessment; Comments

1. **Section IV.B: CORRELATION OF IN-PROCESSS STRATIFIED SAMPLING WITH POWDER MIX AND FINISHED PRODUCT,** ***correlation of powder mix uniformity with stratified in-process dosage unit data:***

1.1. The compression or filling processes in this guidance are divided into a minimum of 20 sampling locations with at least 7 samples taken from each location. This is applied for process development batches and validation batches. The point that I would like to mention here is that during a validation batch with a batch size of for example 1,000,000 units and machine speed of 60,000 units per hour, the compression or filling cycle could take up to 1000 minutes to be completed, this may give sufficient time to take samples as per this guidance, i.e. taking samples every 50 minutes.

1.2. While in the exhibit batches, usually the batch size is one tenth of the validation batch size, this sampling intervals may not be convenient.

1.3. Based on the above example the batch size of the exhibit batch is 100,000 units and the compression or filling cycle will be completed in about 100 minutes, i.e. the samples will be taken every 5 minutes which is not convenient and appropriate.

1.4. **It is mentioned in the same section that this 20 locations strategy with 7 samples each should be used for process development batches, validation batches and routine manufacturing batches for approved products.**

1.5. While in section VI.D **"VERIFICATION OF MANUFACTURING CRITERIA,** ***sample locations for routine manufacturing"*** the guidance recommended that during routine manufacturing at least 10 sampling locations during capsule filling or tablet compression should be identified to represent the entire routine manufacturing batch.

1.6. I feel that this point is not clear and that the number of sampling locations should be the same in both sections for routine manufacturing batches.

1.7. Our suggestion for that point is as follows: Provided that the manufacturing process is fully and successfully validated, and knowing that validation assures the product quality and calls for reduced sampling during routine manufacturing, we recommend to follow the sampling strategy described in section VI.D rather than that mentioned in Section IV.B for routine manufacturing batches of approved products.

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2. **Section VI: VERFICATION OF MANUFACTURING CRITERIA – B. criteria to meet the readily pass classification, and C. criteria to meet the marginally pass classification.**

2.1. The third criteria in both sections is : *"all individual results are within the range of 75.0% to 125.0 % of target strength"*, in fact our comment on this point is that in general this range seems to be wider than enough and a more narrow range will be appropriate.

2.2. Another point considering this criteria is that when it is correlated with the first criteria in the readily pass classification which is: *"for all individual results (for each batch $n \geq 60$) the RSD ≤ 4.0 %"*, These two criteria are contradicted, I mean that assuming that our 60 samples reading are all the same for example 100 % and we only have one point equals 75 % and another point equals 125%, still the RSD value will be more than 4.0% (equals 4.6%), in spite of meeting the second and third criteria. See example in attachment # (1) .

2.3. On the other hand the RSD value criteria can be better achieved (3.68) if the individual results range was more narrow than the one mentioned in the draft, for example to be from 80% to 120%. See the example in attachment # (2) .

2.4. Based on the above discussion and examples we comment that the RSD value for readily pass criteria can be increased to $\leq$ 5.0 %. And the range of individual results for both readily pass classification and marginally pass classification can be tightened to 80.0% to 120 % range (instead of 75% to 125%).

Hope you consider these comments positively and it will be highly appreciated if you can acknowledge these comments and send us your feedback.

Seetaraju Gembali

Vice President of Research and Development

Hikma Pharmaceuticals

Date: December 11, 2003

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Attachment # (1)

Location	Sample1	Sample2	Sample3	AV.	SD	RSD
1	100	100	100	**100.00**	0.00	0.00
2	125	100	100	**108.33**	14.43	13.32
3	75	100	100	**91.67**	14.43	15.75
4	100	100	100	**100.00**	0.00	0.00
5	100	100	100	**100.00**	0.00	0.00
6	100	100	100	**100.00**	0.00	0.00
7	100	100	100	**100.00**	0.00	0.00
8	100	100	100	**100.00**	0.00	0.00
9	100	100	100	**100.00**	0.00	0.00
10	100	100	100	**100.00**	0.00	0.00
11	100	100	100	**100.00**	0.00	0.00
12	100	100	100	**100.00**	0.00	0.00
13	100	100	100	**100.00**	0.00	0.00
14	100	100	100	**100.00**	0.00	0.00
15	100	100	100	**100.00**	0.00	0.00
16	100	100	100	**100.00**	0.00	0.00
17	100	100	100	**100.00**	0.00	0.00
18	100	100	100	**100.00**	0.00	0.00
19	100	100	100	**100.00**	0.00	0.00
20	100	100	100	**100.00**	0.00	0.00
Min	**75**					
Max	**125**					
Average of 60	100.00					
RSD of 60	**4.60**					

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Attachment # (2)

Location	Sample1	Sample2	Sample3	AV.	SD	RSD
1	100	100	100	**100.00**	0.00	0.00
2	120	100	100	**106.67**	11.55	10.83
3	80	100	100	**93.33**	11.55	12.37
4	100	100	100	**100.00**	0.00	0.00
5	100	100	100	**100.00**	0.00	0.00
6	100	100	100	**100.00**	0.00	0.00
7	100	100	100	**100.00**	0.00	0.00
8	100	100	100	**100.00**	0.00	0.00
9	100	100	100	**100.00**	0.00	0.00
10	100	100	100	**100.00**	0.00	0.00
11	100	100	100	**100.00**	0.00	0.00
12	100	100	100	**100.00**	0.00	0.00
13	100	100	100	**100.00**	0.00	0.00
14	100	100	100	**100.00**	0.00	0.00
15	100	100	100	**100.00**	0.00	0.00
16	100	100	100	**100.00**	0.00	0.00
17	100	100	100	**100.00**	0.00	0.00
18	100	100	100	**100.00**	0.00	0.00
19	100	100	100	**100.00**	0.00	0.00
20	100	100	100	**100.00**	0.00	0.00
Min	**80**					
Max	**120**					
Average of 60	100.00					
RSD of 60	**3.68**					