Comments from the European Industrial Pharmacists Group on the Revised GMP Guidelines Chapters 3, 5 and 6

General Comments:
We consider these proposals are a major improvement to the current GMP guidelines.

However, the legislation is still focused on "classical big pharma manufacturing operation" and specific activities such as radio pharmacy and early phase studies are not completely integrated into these guidelines. In future, this should be taken into account.

The following observations take into consideration the contents of the proposed Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

Observation No. 1

- *In order to accommodate a more scientific approach, Chapters 3 and 5 of the GMP guideline have been revised and refer to a "toxicological evaluation" for establishing threshold values for risk identification.*
- *According to the use of the PDE principles, it would be possible that for some substances a higher carryover would be permitted with regards to that calculated according to the current cleaning validation rules. This conclusion is against the standard principle that consolidated quality achievements cannot be worsened. Moreover, it might lead to contaminant levels that exceed values consistent with those approved for individual related substances of the subsequent product, or, even worse, they could be non-detectable under the relevant specification set.*

Observation No. 2

- *Arbitrary evaluations by different users for a same substance should be avoided by introducing standard values of the adjustment factors in establishing PDE values as required in the Guideline on setting health based exposure limits.*
- *Official valid reference sources of values for toxicity values should be introduced, at least for substances already on the market for some years.*

Observation No. 3

- *Living organisms are not reported any longer in the potentially most hazardous materials and it is not clear how the PDE approach could be applied for them.*

Observation No. 4

- *Amongst others, facilities are approved for manipulation also with some "special requirements" (e.g. hormones or substances with hormonal activity). We wonder if this approach will be maintained or transformed after adoption of the PDE principles.*

Chapter 5

Prevention of Cross-Contamination: Does this include vitamins, nutriments and cosmetics?

5.17 "Exceptional circumstances" The wording is too restrictive for Contract Manufacturing Organisations and requires clarification.
Also, the "premises used for the manufacture" has a much wider meaning compared with "equipment" and "area" at the beginning of paragraph 5.17.
Use of words such as "dedicated facilities", "premises" and "area" are used in different contexts. These should be reviewed and clarified in order not to become too restrictive.

Chapter 6

6.13 Please confirm that the last sentence means samples may not be stored outside the storage condition claimed on their labels.

6.20 The words "Certified, Qualified and Verified" should be clearly defined in the document