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题目：PDA 关于 CFDA 确认和验证（征求意见稿）的建议
Ref: CFDA Draft Guidance GMPs Draft Annex 1: Qualification and Validation

亲爱的先生/女士
Dear Sir/Madam,

PDA 非常高兴能够为这个指南草稿提供建议。
The Parenteral Drug Association (PDA) is pleased to be able to provide comments to this draft guidance document.

PDA 赞同 CFDA 在这个指南草稿中有关确认和验证的观点, 该观点与全球其他卫生当局的观点是一致的。PDA 鼓励 CFDA 继续这种方式。
同时，PDA 也鼓励 CFDA 在指南中使用一致性的术语，比如引用 ICH 术语，但是也理解由于汉语和英语之间的语言及翻译的差异会有一些限制。
PDA commends the CFDA for including Qualification and Validation concepts which are harmonized with other global health authorities in this draft guidance and encourages CFDA to continue with this approach.
PDA also encourages CFDA to use harmonized terminology, such as ICH terminology, throughout the document, but understands there are limits because of language and translation differences between Chinese and English.

PDA 认识到 CFDA 未正式发布指南的英文翻译，建议谨慎使用其他组织机构的英语语言。举一个例子：“持续”这个词的英文翻译，PDA 建议使用 EMA 的“on going”，或者使用 FDA 的“continued”。PDA 建议不使用“continuous”作为“持续”这个词的翻译，因为这个术语在多种语言中不易被理解。
PDA recognizes that CFDA does not officially publish English translations, and recommends cautious use of any English language materials prepared by other organizations. One example is the word “chixu.” PDA recommends this be translated as “on going” used commonly by EMA or “continued” used by the FDA. PDA advises not to use translate chixu as “continuous” as that term is less well understood across multiple languages.
PDA 是一个非盈利的全球专家协会，拥有 10000 多名在药品、生物制品、

器械等多个领域的生产和质量科学专家。我们的建议是由在药品生产和工艺验证方面经验丰富的协会专家起草，代表了我们领导委员会、科学顾问委员会、法规事务和质量顾问委员会的意见。
PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing and process validation representing our Board of Directors, our Science Advisory Board, and our Regulatory Affairs and Quality Advisory Board.

如果有任何疑问，请联系我 Richard Johnson （Johnson@pda.org）或 李鸿阳（hongyang.li@novartis.com） PDA 会员，质量顾问委员会中国代表
If there are any questions, please do not hesitate to contact me(Johnson@pda.org) or Hongyang Li, (hongyang.li@novartis.com) member of the PDA Regulatory and Quality Advisory Board representing China.

此致
Sincerely,

Richard Johnson

PDA 主席
President, PDA

附件
Attachment

中国食品药品监督管理局
GMP 指南文件附录 2:确认与验证(征求意见稿)
2014 年 7 月
China Food and Drug Administration Draft Guidance
GMPs Draft Annex 2: Qualification and Validation
July 2014

1. 总的建议

General Comments

PDA 赞同 CFDA 在这个指南草稿中有关确认和验证的观点, 该观点与全球其他卫生当局的观点是一致的, 同时鼓励 CFDA 继续这种方式。PDA 也鼓励 CFDA 在指南中使用一致性的术语，比如引用 ICH 术语，但是也理解由于汉语和英语之间的语言及翻译的差异会有一些限制。 PDA commends the CFDA for including Qualification and Validation concepts which are harmonized with other global health authorities in this draft guidance and encourages CFDA to continue with this approach. PDA also encourages CFDA to use harmonized terminology, such as ICH terminology, throughout the document, but understands there are limits because of language and translation differences between Chinese and English.
PDA 认识到 CFDA 未正式发布指南的英文翻译，建议谨慎使用其他组织机构的英语语言。举一个例子：“持续”这个词的英文翻译，PDA 建议使用 EMA 的“on going”，或者使用 FDA 的“continued ”。PDA 建议不使用“continuous” 作为“持续”这个词的翻译，因为这个术语在多种语言中不易被理解。 PDA recognizes that CFDA does not officially publish English translations, and recommends cautious use of any English language materials prepared by other organizations. One example is the word “chixu.” PDA recommends this be translated as “on going” used commonly by EMA or “continued” used by the FDA. PDA advises not to use translate chixu as “continuous ” as that term is less well understood across multiple languages.
当对验证~~主~~总计划的具体内容信息进行描述时，PDA 建议指南允许这些信息参考其他文件，而不是直接把这些内容写到验证~~主~~总计划的内容中。不是所有的 GMP 信息都需要在验证方案中被重复描述。PDA 认为一些文件中的冗余信息会产生不一致的风险，应当在文件之间交叉引用减少这种风险。

When specifying the list of information contained in the Validation Master Plan, PDA recommends that the guidance allow for some of the information to be referenced in other documents rather than included directly in the VMP documentation. Not all GMP information should need to be repeated in the validation protocol. PDA believes redundant information in several documents poses the risk for inconsistency, which can be minimized by making cross references between documents.

2. 征求意见稿中具体内容的建议

Comments to Specific Sections of the Draft Text

章节 Chapter or Article	**原文 Current Text**	**修改意见 Proposed Change**	**理论依据 Rationale**
第三章 第四条 Chapter 3; Article 4	验证总计划应当包含以下信息： 5）计划和日程安排； The VMP should include the following information: 5) Planning and scheduling;	从内容中删除此条 Delete “planning and scheduling” from this list.	PDA 建议将此条写入其他文件，然后在 VMP 中加以引用即可。 PDA recommends that planning and scheduling be collected in other documents and referenced in the VMP.
第三章 第四条 Chapter 3; Article 4		PDA 建议在 VMP 中增加~~的~~“要求与接受标准”。 PDA recommends adding “requirements and acceptance criteria” to the VMP.	VMP 的主旨在于说明包括要求与接受标准在内的计划验证方法。将这一条列出，是符合国际标准的。 The overall goal of the VMP is to identify the planned validation

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			approach including requirements and acceptance criteria. It is consistent with other global standards to include this in the VMP.
第三章 第三条 Chapter 3; Article 3	确认与验证的关键要素都应在验 证总计划或同类文件中详细说明。 The critical aspects of qualification and validation should be specified in a validation master plan (VMP) or an equivalent document.	PDA 建议应清楚的定义“关键要素”，或提供实例。 PDA recommends that critical aspects should be clearly defined or examples provided.	“关键”一词经常用到，但是有不同的理解。PDA 建议提供几个案例以澄清“关键要素”应该包括哪些内容。 The use of the term “critical” is widely used but subject to different interpretations. PDA recommends examples be provided to clarify what is requested to be included.
第五章第 11 条 Chapter 5 Article 11	企业应当对新的厂房、设施、设备按照预定用途和本规范及相关法律法 规要求制定用户需求，并经审核、批准。 The user requirement specification (URS) for a new facility, system or equipment should be defined according	PDA 注意到，当发生变更或升级时，所有的设施都应有相同的 URS 准则要求，不仅仅是针对新设施。 PDA notes that the same principles of URS could be applied to all facilities when changes or updates are made not just new facilities.	

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	to the pre-defined usage, the requirements of this guideline and the relevant regulations and laws. The URS should be reviewed and approved.		
第五章第 16 条 Chapter 5 Article 16	运行确认完成后，应当建立必要的操作、清洁、校准和预防性维护保养 的操作规程，并对相关人员培训。 After the completion of the OQ, necessary operation, cleaning, calibration and preventive maintenance SOPs should be established, and operators shall be trained.	PDA 建议删除“清洁”一词，改成“运行确认完成后，应当建立必要的操作、校准和预防性维护保养 的操作规程，并对相关人员培训。” PDA recommends removing cleaning from this section. “After the completion of the OQ, necessary operation, ~~cleaning,~~ calibration and preventive maintenance SOPs should be established, and operators shall be trained.”	根据 PDA 的经验，如果包括清洁在内，相关的规程不会在 OQ 阶段建立。因为在这个阶段，产品通常还没有被引入。PDA 建议最终的清洁验证 SOP 应该在 PQ 阶段建立。 In PDA’s experience, procedures covering cleaning are typically not finalized at the OQ stage because product is not generally introduced at this stage. PDA recommends that <u>final</u> SOPs for cleaning validation be established during PQ.
第 19 章：工艺验证；第 28 至 31 条：工艺与	持续工艺确认 Continuous Process Verification	PDA 赞同 CFDA 将“生命周期概念”这一概念引入到“工艺验证”中，并体现在该草案里	请留意，在英语翻译方面，“on-going”一词的翻译是与 EMA 附件 15 一致的，避免与

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验证 Article 19 Process Validation; Article 28-31; also		PDA commends CFDA for inclusion of the concepts of Life Cycle Approach to Process Validation in the draft document 。	“continuous”和“continued”的混淆。 Please note that for translation in English The use of the term “on-going” is aligned with EMA Annex 15 and avoids translation confusion with the term “continuous” and “continued.”
第五章第 21 条 Chapter 5 Article 21	首次工艺验证应当涵盖该产品的所有规格及使用的生产线。企业可根据风险评估的结果采用简略的方式进行后续的… The initial process validation should cover all the strengths and the production lines used. The abbreviated approach can be applied for subsequent	请阐明，矩阵/归类法是否适用于多产品和多规格验证的情况。 Please clarify whether a matrixing and/or bracketing approach can be used when multiple products and strengths are being validated.	矩阵/归类法是一种常见的验证方法，而且受到其他一些监管机构的认可 Use of matrixing and bracketing is a common practice in validation and accepted by other regulatory agencies. 。
第 28 至 31 条，第 19 条：工艺验证 Article 28-31; also Article 19	持续工艺确认 Continuous Process Verification	PDA commends CFDA for inclusion of the concepts of Life Cycle Approach to Process Validation in the draft document PDA 赞赏 CFDA 将“生命周期”	请留意，在英语翻译方面，“on-going”一词的翻译是与 EMA 附件 15 一致的，应避免与“continuous”和“continued”

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Process Validation		这一概念引入到“工艺验证”中，并体现在该草案里。	的混淆。 PDA 注意到，CFDA 没有发布正式的英文翻译。但是，CFDA 使用的或认可的所有（该词的）翻译，都应该要么与 EMA 的“on-going”一致，要么跟 FDA 的“continued”的一致。PDA 建议不要再使用“continuous”一词。 Please note that for translation in English The use of the term “on-going” is aligned with EMA Annex 15 and avoids translation confusion with the term “continuous” and “continued.” PDA recognizes that CFDA does not officially publish an English translation. However, any translation used by CFDA or endorsed PDA recommends terminology should be aligned with the EMA term “on going” or FDA term continued. PDA advises not to use “continuous”

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第三十条 Article 30	持续工艺确认应当按照批准的方案进行，并根据获得的结果形成相应的 报告… Continuous process verification should be conducted based on an approved protocol and a corresponding report should be prepared…	应改为：“持续工艺确认应使用批准的方案、计划或规程进行，并根据获得的结果形成相应的报告…” Continuous or on-going process verification should be conducted using an approved protocol, plan, or procedure and a corresponding report should be prepared …	PDA 留意到，使用经批准的方案进行持续工艺确认限制性太强——也许使用其他的方法也可以做到，比如使用一个计划或者 SOP。随着工艺参数的积累和工艺能力的证明，这样做使对标准进行修订变得可能。 PDA notes that the use of an approved protocol for ongoing process verification is too restrictive – there may be other ways of achieving this, such as using a plan or SOP. This permits modifications in criteria as process data is accumulated and process capability is demonstrated over time.
第三十一条 Article 31	在产品质量回顾过程中应当采用持续工艺确认的方法支持产品的验 证状态，还要考虑当趋势出现渐进性变化时，应当进行评估并采取相应的措施。 Continued/on-going process	PDA 建议对该内容进行修改，以阐明持续的工艺确认应该定期进行，而不是在年度产品回顾时只进行一次。 PDA suggests that this section be revised to clarify that chixu/continued/ongoing	文中大写字母的使用，有暗示“持续性工艺确认”只在“年度产品回顾”时进行一次的意思。 The use of capital letters in the translation we have used implies that CPV is used only once per year during the Annual Product

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	verification should be used to support the validated status of the process during Product Quality Review. However, incremental changes over time should also be considered and the need for any relevant actions should be assessed and taken.	process verification should be conducted periodically and not only once per year at the annual product review.	Review. 。
第三十四条 Article 34	因同步验证批次产品的工艺和质量评价尚未全部完成产品即已上市， 企业应当增加对验证批次产品的监控。 Because concurrent validation means that the products have been put on the market before, the process and quality evaluation on the concurrent validation batches have not been completed therefore, the manufacturers should increase the monitoring and control of the products batch.	PDA 建议删除该条款的后半部分内容。 PDA recommends to delete the second part of this article. Because concurrent validation means that the products have been put on the market before, the process and quality evaluations on the concurrent validation batches have not been completed. ~~therefore, the manufacturers should increase the monitoring and control of the products batch.~~	因在进行验证批次的生产时，已经涵盖了监控和检测，而且这些监控和检测比商业产品批次要多得多，就没有必要在产品放行后再增加监控和检测了。 Because of the expanded monitoring and testing that has occurred during the production of the validation batch, which is much more than with typical commercial batches, there is no need for expanded monitoring after release.

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第四十一条 Article 41	企业在清洁验证后应当对设备的清洁效果进行持续确认 Continuous verification on the cleaning effect of equipment should be conducted by manufacturers after cleaning validation.	PDA 建议删除持续确认的要求，或者采用第 51 条中的说法 PDA recommends deleting the requirement for continuous verification or to use the language from Article 51 。	周期性评估的要求在第五十一条里已经说得很明白了。 The requirement for periodic assessment is well stated in article 51.
第四十五条 Article 45	最长时间和最大批次数量 the maximum length of a campaign (in both time and number of batches)	PDA 建议在定义“阶段性生产”的时候，应该允许一定的灵活性。 “……最长时间和（或）最大批次数量”。 PDA recommends that flexibility be allowed to define the campaign. …in ~~**both**~~ time and**/or** number of batches	根据被验证产品的性质，通过批次数量或总生产时间定义＂阶段性生产＂比较关键，取决于哪个因素存在更大的风险。 注意：工艺时间和产品残留会影响阶段性生产所期望的时间，批次之间的残留是工艺的特定内容。PDA 建议是“时间或批次数量”，使用“和”这个词是不合适的。 Depending on the nature of the product being validated, it may be more critical to define the campaign by number of batches of by total time length. Depending on which factor poses

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			the greatest risk to the validation. Comment: Process and product residues vary and the impact on campaign length with respect to time and carry-over between batches is process specific. PDA recommends that either time or number of batches and not both may be not appropriate.
第四十六条 Article 46	如多用途设备没有单一的最差条件产品时，最差条件的确定应当考虑产品毒性、允许日接触剂量和溶解度等。每个使用的清洁方法都应当进行最差条件验证 When there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider toxicity and PDE value as well as solubility. Worst case cleaning validation should be	PDA 建议澄清挑选最差条件产品的方法。 PDA suggests clarification of the approach to selection of a worst case product.	根据 PDA 的经验，对于多用途设备来说，最好的做法是根据毒性最大产品设定各种限度，并根据最难清除的（产品），比如，溶解性最小的，来进行清洁验证。 In PDA's experience, the best practice in a multi-product facility is to set limits based on the most toxic product and perform cleaning validation with the hardest to remove, for example the least soluble.

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	performed for each cleaning method used		
第四十八条 Article 48	企业应当评估设备所用各种材质进行取样的方法有效性 Any sampling method used for effectiveness/recovery should be shown to be effective for all materials used in the equipment.	PDA 建议作如下修订：“用擦拭法对材质取样的，企业应证明其取样方法对该材质是有效的。 PDA recommends the following change: Sampling effectiveness should be shown to be possible from ~~all~~ materials **that are swabbed.** ”	因为淋洗水取样的结果通常偏向于定性，而棉签擦拭法则偏向定量，因此，PDA 建议在这里不应该使用“recovery”一词，而（文中的）最后这句话应该仅限于擦拭法。 PDA recommends that recoveries should not be taken from rinse because the results are typically more qualitative. Swab results are more quantitative. The last sentence should be applied to the swab sampling method only.
第五十二条 Article 52	关键的生产工艺和操作规程应当定期进行再验证，确保其能够达到预期效果 Critical process and operational procedures should be revalidated at an appropriate frequency to confirm the expected effect to	PDA 建议删除该条。 PDA recommends deleting this article.	如果满足第五十一条和第五十四条的要求，其实已经包涵了持续性工艺验证和定期检查的意思，就可以证明工艺处于受控状态，因此再在第五十二条里单独规定再验证（的要求），就没有必要了。 By meeting the requirements of

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	be achieved.		articles 51 and 54, which already covers both the chixu/ongoing/continued process verification and periodic review, the process can be demonstrated to remain in a state of control and therefore a separate revalidation as defined in article 52 would not be necessary.
第六章 工艺验证 第二十五条 Chapter 6 Article 25	如未按照第二十四条要求进行预先的风险评估，企业应当至少进行连续三批成功的工艺验证。对产品生命周期中后续商业生产批次获得的信息和数据，进行持续的工艺确认。 If the above mentioned risk assessment is not performed following Article 24, a minimum of three	ＰＤＡ建议删除第二十五条。如果第二十四条里的质量风险管理的原则被应用的话，再在该指南中指出三批是不必要的。 PDA Recommends deleting Article 25 because specifying three batches is unnecessary if QRM principles noted in Article 24 are followed.	ＰＤＡ认为如果这个指南继续提及某个具体的批次数的话，有些企业就会继续采用这个默认的数而不会用必要的分析来确定更合适的方法。 另外，第二十五条还会被企业认为第二十四条关于质量风险管理的原则并不是强制的，从而也就没必要进行风险评估了。 PDA feels that if the guidance continues to refer to a specific number of batches some firms

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	consecutive successful batches should be produced by the manufacturer for the validation of the process. On-going process verification should be conducted based on the information and data obtained from subsequent commercial batches during the product life-cycle.		will continue to use that as a default and not perform the needed analysis to determine a more appropriate approach. Furthermore, Article 25 could be interpreted that the requirement of Risk Management Principles in Article 24 may not be mandatory, and therefore the company may not perform risk assessment.