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March 16, 2017

IPAC-RS Comments on Draft FDA Guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA."[1]

Docket FDA-2016-D-4412

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS[2]) commends the FDA CDER effort to define clear approaches for establishing substitutability of devices in drug-device combination ANDA products, as evidenced by the Draft Guidance "*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*"[1] ("Draft Guidance").

As an association of generic and innovator companies[3] that develop, manufacture and market drug-device combination products for drug delivery to the respiratory tract, IPAC-RS has significant experience with these product types, and welcomes the opportunity to provide feedback on the Draft Guidance[1] in these Comments. In addition, IPAC-RS would be willing to

[1] FDA. CDER. Draft Guidance for Industry. Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA. 2017. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery Docket FDA-2016-D-4412

[2] IPAC-RS seeks to support the regulatory science of orally inhaled and nasal drug products (OINDPs) by collecting and analyzing data, conducting joint research projects, and engaging with the wider regulatory and scientific community on topics of importance to the stakeholders interested in the development and availability of high quality, safe and efficacious OINDPs. See IPAC-RS Homepage at http://ipacrs.org/.

[3] IPAC-RS Member Companies: http://ipacrs.org/about/list-of-member-companies/

meet with the Agency to discuss these issues further in an appropriate setting, including a public workshop.

The Draft Guidance[1] addresses the management of user-interface-related risks that are unique to generic drug-device combination products, specifically with regard to substitutability. Clarifying the regulatory thinking in this area is much appreciated because the terms applied until now (that devices be "similar" or "equivalent") were not always sufficient to assess specific ANDA situations.

IPAC-RS welcomes the Draft Guidance and the introduction of the concept of a comparative task analysis, including a comparison of labeling (Instructions for Use). The Agency's elaboration on these topics will inform the Usability and Human Factors Engineering in developing generic devices. IPAC-RS also agrees with the importance of the definition of substitutability, which is very helpful.

IPAC-RS wishes to express its fundamental concern, however, that this Draft Guidance recommends a prescriptive quantitative approach to Human Factors (HF) for design differences that fall under the category "other than minor". A quantitative approach to HF studies is inappropriate in light of the essentially qualitative nature of HF studies; appears contrary to the established Human Factors practices, existing guidances and standards[4,5,6,7]; is new/unproven; and would be impractical and burdensome to implement, while adding little to no value to the safety, efficacy or substitutability determination of a combination generic product. IPAC-RS

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[4] FDA. CDRH. Final Guidance for Industry and Food and Drug Administration Staff. . Applying Human Factors and Usability Engineering to Medical Devices. 2016. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf

[5] FDA. CDRH, CDER, CBER, OCP. Draft Guidance for Industry and FDA Staff. Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. 2016 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

[6] ISO. IEC 62366-1:2015. Medical devices -- Part 1: Application of usability engineering to medical devices. http://www.iso.org/iso/catalogue_detail.htm?csnumber=63179

[7] ANSI/AAMI. HE75:2009/(R)2013. Human factors engineering – Design of medical devices. A preview pdf available at http://my.aami.org/aamiresources/previewfiles/HE75_1311_preview.pdf

recommends, therefore, that formative and validation Human Factors studies, appropriately designed with special considerations for the results of comparative risk analyses, be recognized as the most effective and efficient means to achieve the FDA's mission of maximizing the likelihood that generic drug-device combination products are safe, effective and substitutable with regard to intended users, uses, and use environments.

This key IPAC-RS concern is explained in further detail below, followed by a table of specific line-by-line comments. IPAC-RS would be willing to meet with the Agency for a scientific discussion, and/or a public workshop, and/or consider collaborative research through appropriate mechanisms, in order to explore these topics further.

Explanation of the Key Concern

The Nature of Human Factors Studies is Essentially Qualitative

By nature, Human Factors studies are inherently non-quantitative. The primary objective of Human Factors Engineering is to minimize use-related risk. Human Factors studies are conducted in a simulated use environment and focus directly on the users' interaction with the device: how they handle it, what errors occur and why. These assessments are made across the target patient population profiles, with consideration of age, co-morbidities, caregivers, and use environment. The HF data are fundamentally qualitative because the nature of use errors and their root causes matter far more than the count of observed errors. In a Human Factors study, each observed error is assessed for its impact on user safety and on dose delivery. A quantitative comparison is, therefore, fundamentally inapplicable to Human Factors studies, since they are aimed at understanding Human-Device interactions, while the simple counting of errors offers little insight for that understanding, and could even be misleading. **In Human Factors studies, the criticality of errors, their root-cause and their consequences, are more important than the number of errors.** One critical error is not "less" than ten non-critical errors even though 1<10. In addition, some errors are attributable to the product design while others to a specific user's habits, and this understanding can only be obtained qualitatively.

The prescriptive quantitative approach in the Draft Guidance treats all "other than minor" differences as equally important, whereas in Human-Device interactions, some tasks (and differences in those tasks) are critical to safe and effective use, while others are not.

Moreover, the task criticality cannot be assessed in the abstract but has to be determined in the context of a deep understanding of a particular device. RLD and generic devices may have nearly-identical user interfaces while the internal mechanisms may be different, such that use errors potentially critical for one device may be

inconsequential for another. For example, an incomplete advancement of the lever on a dry powder inhaler might still deliver the full dose in one device, while in another device such incomplete movement might result in partial dosing, inconsistent dosing, or even mechanism's jamming and complete device failure. A simple counting of task failures, therefore, is meaningless and misleading without the context of a deep understanding of potential risks associated with a particular device. In many cases, it may be impractical or even impossible for a sponsor company to gain the in-depth understanding of an RLD device that is necessary to accurately and comprehensively judge the criticality of specific user actions.

The focus on specific use errors which occur with rates that are high enough to make the quantitative approach practical is also at odds with the risk-focused nature of medical device HF. Specifically, HF is particularly concerned with the minimization of the likelihood of any use errors that have the potential to cause SERIOUS harm to users. These types of errors should, by definition, be extremely rare events. They will have rates of occurrence too low for practical investigation using the method suggested by the Draft Guidance. The suggested method will, therefore, direct attention onto use errors that, by definition, are not critical from a safety perspective. This is not to say they are unimportant, but that it is not warranted on a risk basis to make them central to the discussion of the HF of a generic drug delivery device.

Also importantly for substitutable products (which are developed after the RLD), the strictly quantitative approach does not account for improvements that might be made in the generic version (e.g., improvements based on known issues with the RLD and/or changes in available technology, user expectations or use environment), improving on the risk-benefit profile without the need for users' re-training.

It is possible that a generic could be developed that is both substitutable and an improvement on an RLD. For example, in an RLD device, removing a cap could be critical to receiving a dose upon actuation; but in a generic device with a similar interface, an internal mechanism could be added that prevents the device from being actuated at all if the cap is not removed, leading to the user's immediate self-correction. Such a change

could serve to reduce the criticality of this use error without jeopardizing the ability of the user population to operate the device without additional training.

The quantitative non-inferiority approach described in the Draft Guidance is similar to methods used in drug clinical trials. Such a statistical methodology is appropriate for numerical, uniform, continuous variables, such as those measured in clinical trials. By contrast, Human Factors information is acquired through human observation of human behavior. Human Factors studies are based on visual observations and interviews, subjective interpretations and judgements, risk assessment and root-cause analysis. As such, Human Factors data are qualitative in nature and therefore must be evaluated qualitatively.

IPAC-RS supports the first part of the Draft Guidance, which recommends analyzing differences qualitatively, using risk-based approaches; however, the second part of the Draft Guidance – evaluating those differences – is quantitative and not appropriate for HF studies. IPAC-RS agrees that for devices to be substitutable, products have to be safe and effective for the intended user population without intervention of a healthcare provider, although the specific approach in the Draft Guidance requires revision.

IPAC-RS proposes that differences be evaluated via a comparative risk analysis, with those results inputting into the design of traditional HF studies, which should be at the foundation of an ANDA device development program.

Goal Should be Safe and Effective Use and Substitutability Rather Than Quantitatively Minimizing Differences

HF Studies are meant to ensure that an ANDA product is safe and effective for the intended user population. In addition, there is a requirement to demonstrate substitutability, i.e., that an ANDA product could be used by the target population without intervention of a healthcare provider. *Minimizing the number* of differences, by itself, is not a goal.

The existing FDA Guidelines[4,5] state that the user interface should be optimized with regard to use safety and effectiveness (rather than that differences be minimized). Users often make errors with drug-device combination products regardless of design[8]. For example, a 2014 study[9] showed that only 9% of metered dose inhaler users used their device properly, while 63% of users missed 3 or more steps. These and other similar studies illustrate the common challenge of less-than-perfect use patterns, highlighting opportunities for improvement. A comparative risk analysis, therefore, would be more appropriate than a quantitative study. Such a comparative risk analysis should include consideration of both experienced RLD users and naïve product users, since the generic product might be given to patients at the pharmacy upon their first prescription, rather than as a transfer from an earlier RLD use.

Scientific Validity of Quantitative Approach for HF Studies Not Established

The hypothesis-based comparative Human Factors analysis described in the Draft Guidance is a new, unusual concept in the field of Usability and Human Factors Engineering, and as such should not be recommended without additional confirmation on the validity of the method.

The Agency's existing Guidances on Human Factors[4,5], and indeed the current practice and history of the application of Human Factors Engineering to date, both in the medical device field and other industries, have all been centered on designing user interfaces to minimize use-error and the validation of a particular user interface.

Since the Draft Guidance[1] introduces a new concept, it should be accompanied by demonstration of, or references to published sources, related to the validity, sensitivity, and specificity of a quantitative comparative analysis program.

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[8] Sanchis J, Gich I, Pedersen S. Systematic review of errors in inhaler use: has patient technique improved over time? Chest. 2016;150(2):394-406. doi:10.1016/j.chest.2016.03.041. Available at http://journal.publications.chestnet.org/article.aspx?articleid=2514047

[9] Bonds R, "Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease", Annals of Allergy, Asthma & Immunology, January 2015.

Other Ways Exist to Ensure Appropriate Design

For the reasons summarized above, a quantitative approach to Human Factors studies is contrary to the qualitative nature of Human Factors, not justified scientifically, and would be problematic in practice. More appropriate approaches exist to ensure safe, effective, substitutable generic combination products. The previously issued FDA Guidances on Human Factors[4,5], (i.e., a simulated use study), along with a comparative risk analysis that would inform the design of formative and validation studies, should be used as a basis for HF studies in drug-device combination products submitted through an ANDA.

Line-By-Line Comments

Line	Original Language	Proposed Change and Rationale
Throughout	*"Threshold analysis"* and *""comparative use human factors study*"	Change "*threshold analysis*" to "***Comparative risk analysis***" Also, remove descriptions of "*comparative use human factors study*", since the "threshold analysis" should not serve as a trigger for such a study.
17	"*…applicants who plan to develop and submit an abbreviated new drug application (ANDA) to seek approval of a proposed combination product that includes both a drug constituent part and a <u>delivery device</u> constituent part*."	The scope should be expanded beyond "*delivery devices*" to include any device that was approved within the original marketing application, which could include, but may not be limited to devices used to prepare the medication, prepare an administration site, or digital health/software applications. The guidance should apply to all devices that allow the drug to achieve its intended use.
27-29	*"In the early stages of development, potential applicants should carefully consider the design of the user interface of a proposed generic combination product and seek to minimize differences from the user interface for the RLD."*	As explained in the main body of these Comments, minimizing differences, in itself, would not necessarily lead to a most safe and effective generic product because some differences in the generic could be addressing known use problems with the RLD. Please clarify to what extent the improvements in the generic combination product user interface can be made to reduce or eliminate user errors on critical tasks known for an RLD. In addition, the Draft Guidance should include a clear statement that design of the combination product may be changed to improve the user interface to reduce use errors but that these design changes must not change the drug product itself, the bioequivalence of the combination product, or the safe and effective use of the product without retraining.
34-41	*"Depending on the results of the threshold analyses discussed in this guidance, submission of additional data may be warranted, such as data from comparative use human factors studies, to assess the acceptability of differences identified in the user interface for the proposed generic combination product as compared to the user interface for the RLD. Applicants may consider modifying the design of the generic*	Change to: ***Formative and validation human factors studies of the proposed generic combination product should be designed to focus special attention on risks associated with differences in the user interface as identified in the comparative risk analysis***.

	combination product to minimize differences from the RLD to avoid conducting comparative use human factors studies. To the extent an applicant conducts comparative use human factors studies, this guidance provides recommendations on the design and conduct of such studies."	
37	"*Applicants may consider modifying the design of the generic combination product to minimize differences from the RLD to avoid conducting comparative use human factors studies*."	…"*modifying the design of the*" should be changed to simply "***designing***", since this statement is applicable to designs being submitted for original approval. In addition, the Draft Guidance should include a clear statement that design of the combination product may be changed to improve the user interface to reduce use errors but that these design changes must not change the drug product itself, the bioequivalence of the combination product, or the safe and effective use of the product without retraining.
78-79	*"comparative use human factors studies."*	Change to*: "**analysis of potential risks associated with user interface differences and studies designed to evaluate those potential risks**."*
83-90	*"FDA does not consider the comparative use human factors studies described in this guidance to be clinical investigations intended to demonstrate the safety or effectiveness of the proposed generic combination product. Rather, the comparative use human factors studies described in this guidance are intended to confirm that the differences in device and labeling between the generic combination product and RLD are acceptable and that the proposed generic combination product can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling."*	Change to*:* *"**The results of the comparative risk analysis should be considered in the design of formative and validation studies with special attention to risks associated with differences in the user interfaces or use environments related to generic substitutable products."***
90-92 and 126, ftnote	*"FDA intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the*	Please revise/clarify the requirement for substitutability without a health care provider's consultation. In case of an RLD-to-generic substitution, a healthcare provider's consultation and training for the patient would be a reasonable and wise activity for even minor changes, and not overly

12 and 141	*generic combination product*." *[…]* *"FDA does not necessarily expect for approval that a generic combination product can be used according to the RLD labeling per se, but rather it is critical that the generic combination product can be substituted for the RLD without additional physician intervention and/or retraining prior to use" […]* "*In general, FDA expects that end-users of generic combination products…can use the generic combination product when it is substituted for the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product*."	burdensome. Such consultation and training should not be precluded. The patient self-trains by reading the labeling. So if the labeling changes (which would be allowed), then the patient should be reasonably expected to read the new labeling (i.e. self-train) and be able to consult with their healthcare provider if they have questions or need further support. Moreover, there are two distinct user groups of a generic product: (1) those transferring from an RLD, and (2) naïve users who had no experience with an RLD. Substitutability, therefore, should not always rely on the user's previous training with an RLD. In addition, the labeling of an RLD may state that training is required for lay-users by a health care provider before first use; the labeling of the generic combination product may therefore also state that such training is required.
132-178	Section "*General Considerations*"	The Draft Guidance should add that preliminary analyses (e.g., formative studies, heuristic analysis, identification of known use problems, etc.) should be conducted as recommended in the Final Guidance "*Applying Human Factors and Usability Engineering to Medical Devices"*[4]. For example, new use-related problems may have come to light between approval of the RLD and development of the generic combination product, and should be analyzed using the established HF approaches.
136 (footnote 13)	"*If a sponsor is proposing a presentation for which the RLD is not approved (e.g., seeking approval of a generic combination product as a pre-filled syringe in instances when the RLD was approved in a vial), FDA strongly encourages the sponsor to discuss the proposed presentation with FDA via controlled correspondence and/or pre-ANDA meeting package prior to product development or submission of an ANDA*."	Since the described situation would be a new design interface, such a product should follow the HF approaches set out in the existing FDA Guidances[4,5], which should be referenced here.
138	"*FDA recognizes that a potential applicant of a proposed generic combination product may develop a user interface that has certain differences from the user interface approved for the RLD. FDA may accept such design differences if they are justified, adequately*	Please reiterate risk assessment as part of this analysis.

	analysed, scientifically and do not preclude approval in an ANDA."	
149	*"comparative use human factors studies,"*	Change to: *"**appropriately designed validation studies**,"*
161	*"comparative use human factors studies (as described further in this section)"*	Change to: "***validation studies"***
165	*"To conduct a comparative analysis of the user interface"*	Change to: "***When designing formative and validation studies**"*
166	*"and its RLD"*	Please remove "*and its RLD*" because, as explained in the main body of these Comments, an appropriate study of the generic product should follow established HF approaches, taking into consideration results of a comparative risk analysis (rather than a comparative quantitative study using an RLD).
167-176	*"external critical design attributes"* and *"critical to the use of the product"*	Change to, respectively, *"**likely external critical design attributes**"* and *"**potentially critical to the use of the product**"* Before Human Factors studies are conducted, critical use errors, critical tasks, and critical design attributes may be postulated based on the intended use of the product and experience from previous studies, but only a post-study review and root-cause analysis can bring full understanding of critical use errors committed and the design attributes that may have contributed to those critical use errors.
221	*"No design difference*."	Since, at the very least, branding would have to be changed, which may include coloring or other superficial changes, a scenario "*no design difference*" appears impossible in practice. Therefore, please remove this as a potential scenario, or provide further clarification.
222-224	*"it is likely that certain information and/or data, such as data from comparative use human factors studies, will not be necessary to support approval of the ANDA."*	Change to: ***"then there is no need in design of formative and validation studies to consider risks associated with such differences."***
245	**"***rather than a comparative use human factors study***."**	Change to: "***along with appropriately designed formative and validation studies**."*
260,	*"a comparative use human factors study"*	Change to: "***formative and validation studies**."*

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270, 273, 288, 295, and 300	"*difference that may not be minor*"	Since the Draft Guidance defined only two categories, "minor" and "other", please revise the text to clearly refer either to "minor" or "other". Please also add examples of each type, and explain when additional studies would be required. Please consider examples that account for technology advancements (e.g., types of batteries, cable connectivity, wireless transmission mechanisms), which may seem "other" (not minor) yet would have no impact on Human Factors.
280-281	*"In addition, there may be instances in which a comparative use human factors study is limited to "*	Change to: ***"Formative and validation studies should be designed with special consideration for"***
285-429	"Comparative Use Human Factors Studies" and "Appendix A"	Delete both sections, for reasons explained in the main body of these Comments. The Draft Guidance should instead recommend that properly designed formative and summative studies be conducted with an ANDA device, supplemented with a comparative risk analysis to ensure safe and effective use as well as substitutability.
End		It would be helpful if the Draft Guidance included a Glossary with all relevant terms defined, such as "External Critical Design Attribute", "Use Related Error", making sure that this Guidance's definitions align with similar concepts given in previous FDA Guidances and consensus standards related to Human Factors/Usability Engineering.

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